BTS
British Transplantation Society

The Voice of Transplantation in the UK

UK Guidelines on Pancreas and Islet Transplantation

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Compiled by a Working Party of
The British Transplantation Society

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British Transplantation Society Guidelines

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1 INTRODUCTION

1.1 The Need for Guidelines

These are the first guidelines on pancreas or islet transplantation published by the British Transplantation Society. Given the complexity of these treatments, the associated risks, and the multiple treatment options available to patients with insulin-dependent diabetes, this is perhaps surprising. It is hoped that these guidelines will inform clinical teams and patients regarding treatment options, provide guidance on clinical management, and suggest possible avenues for research and audit.

Guidelines on islet transplantation have been produced alongside those on pancreas transplantation as the treatment modalities are, at present, complementary. In addition, the United Kingdom is unique in that the deceased donor islet and pancreas allocation schemes are combined. It therefore makes sense for these guidelines to cover both treatments, with the expectation that a joint approach to assessing the patient with insulin-dependent diabetes will enable closer working between islet and pancreas transplant teams and optimal patient outcomes.

The authors and editors are aware that many recommendations within this document are for improved data returns. We hope that better data collection and an increased awareness of these issues will help provide much needed evidence for future iterations of this document. We encourage other national transplant organisations around the world to improve data gathering on pancreas and islet recipients, and to publish their findings.

The authors and editors suggest that this document should be read alongside other relevant guidelines from the British Transplantation Society where more detail is required, such as the Guidelines for Living Donor Kidney Transplantation, Detection and Characterisation of Clinically Relevant Antibodies in Allotransplantation (joint with The British Society of Histocompatibility & Immunogenetics), and Transplantation from Deceased Donors after Circulatory Death.

1.2 Process of Writing and Methodology

The British Transplantation Society formed a guideline development group in January 2016, chaired by Mr Chris Callaghan and with Mr Martin Drage, Dr Pratik Choudhary, and Mr Chris Callaghan as section editors. A meeting was held in London in September 2016 to confirm topics, review draft chapters, and undertake the preliminary grading of recommendations. A further meeting was held in London in December 2017 for review and grading of the recommendations.

The guidelines were written in line with the BTS Guideline Development Policy, and the recommendations of NICE Evidence (1). A literature search was undertaken using PubMed® to identify relevant evidence, and search terms included combinations of pancreas transplantation, transplantation, islet transplantation, deceased donor, immunosuppression, islet isolation, recipient outcomes, histocompatibility, and ethics. Meeting abstracts were not considered.

The section editors reviewed preliminary versions of the guideline chapters and these were further revised by Mr Chris Callaghan. Comments on the preliminary draft were invited from patient representatives of two centres undertaking pancreas transplantation. The guidelines were edited by Dr Peter Andrews, Chair of the BTS Standards Committee, and were opened for public consultation through the website of the British Transplantation Society in July 2019. Comments from organisations and individuals representing relevant patient groups were specifically encouraged. Following revision, the final guidelines were published in September 2019, with an appendix giving a one-page summary of Outcome Measures in SPK Transplantation for use in the general clinic environment.

These guidelines will next be revised in 2024.

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All feedback on these guidelines has been appreciated. We especially thank the following for helpful comments during the web-based consultation period:

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Dr Natalia Burlinson (on behalf of the British Society for Histocompatibility & Immunogenetics)

Dr Chris Dudley (Consultant Nephrologist, Bristol)

Dr Ruth Joyce (on behalf of the Human Tissue Authority),

Dr Liset Pengel (Centre for Evidence in Transplantation, London)

Dr Rommel Ravanan (Consultant Nephrologist, Bristol)

Professor Chris Watson (Professor of Transplant Surgery, Cambridge)

1.4 Declarations of Interest

Dr Peter Andrews – none

Mr Chris Callaghan – none

Mr John Casey – none

Dr Pratik Choudhary – has received speaker fees and participated in advisory boards for Abbott, Astra Zeneca, Dexcom, Lilly, Medtronic, Novo Nordisk, Roche, and Sanofi

Mr Martin Drage – none

Dr Anneliese Flatt – none

Professor Peter Friend – none

Professor Shareen Forbes – none

Mr James Gilbert – none

Dr Guo Cai Huang – none

Dr Steven Hughes – none

Professor Paul Johnson – none

Professor Derek Manas – none

Dr Adam McLean – none

Mr Anand Muthusamy – none

Mr Gabriel Oniscu – none

Professor Vassilios Papalois – none
Mr Gavin Pettigrew – none
Professor James Shaw – none
Dr Olivia Shaw – none

1.5 Grading of Recommendations

These guidelines represent consensus opinion from experts in the field of transplantation in the United Kingdom. They represent a snapshot of evidence available at the time of writing. It is recognised that recommendations are made even when the evidence is weak. It is felt that this is helpful to clinicians in daily practice.

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 (2). The approach used in producing the present guidelines is consistent with that adopted by Kidney Disease Improving Global Outcomes (KDIGO) (3, 4). Explicit recommendations are made on the basis of the trade-offs between the benefits on one hand, and the risks, burden, and costs on the other.

For each recommendation the quality of evidence has been graded as:

A (high)
B (moderate)
C (low)
D (very low)

Grade A evidence means high quality evidence that comes from consistent results from well performed randomised controlled trials, or overwhelming evidence of another sort (such as well-executed observational studies with very strong effects).

Grade B evidence means moderate quality evidence from randomised trials that suffer from serious flaws in conduct, consistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength.

Grade C evidence means low quality evidence from observational evidence, or from controlled trials with several very serious limitations.

Grade D evidence is based only on case studies or expert opinion.

For each recommendation, the strength of recommendation has been indicated as one of:

Level 1 (we recommend)
Level 2 (we suggest)
Not graded (where there is not enough evidence to allow formal grading)

A **Level 1** recommendation is a strong recommendation to do (or not to do) something where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients.

A **Level 2** recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain.

1.6 Abbreviations

ATG	Anti-thymocyte globulin
BMI	Body mass index
BTS	British Transplantation Society
CDC	Complement-dependent cytotoxicity
CIA	Common iliac artery
CIT	Cold ischaemic time
DBD	Donation after brain death
DCD	Donation after circulatory death
DSA	Donor-specific antibody
ESRD	End-stage renal disease
FCXM	Flow cytometric crossmatching
GDA	Gastroduodenal artery
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTK	Histidine-tryptophan-ketoglutarate
IBMIR	Instant blood-mediated inflammatory reaction
IEQ	Islet equivalents

IMV	Inferior mesenteric vein
IP	Isolated pancreas (i.e. PTA or PAK transplant)
IVC	Inferior vena cava
MMTT	Mixed meal tolerance test
NHSBT	National Health Service Blood and Transplant
NORS	National Organ Retrieval Service
NPOS	National Pancreas Offering Scheme
PAK	Pancreas after kidney
PDRI	Pancreas donor risk index
PFD	Perfluorodecalin
PTA	Pancreas transplant alone
QoL	Quality of life
SaBTO	Advisory Committee on the Safety of Blood, Tissues and Organs
SCS	Static cold storage
SH	Severe hypoglycaemia
SIK	Simultaneous islet-kidney
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
SPK	Simultaneous pancreas-kidney
SUITO	Secretory Unit of Islet Transplant Objects
UK	United Kingdom
US	United States of America
UW	University of Wisconsin

1.7 Definitions and Scope

These guidelines cover solid organ pancreas transplantation (referred to as ‘pancreas transplantation’), and allogeneic islets of Langerhans transplantation (referred to as ‘islet transplantation’). These guidelines exclude islet autotransplantation.

In addition, pancreas transplantation from living donors has not been performed in the United Kingdom due to concerns about the risks of donor diabetes mellitus (5), and this topic is therefore not covered in these guidelines.

Although the anaesthesia and critical care of pancreas transplant recipients is an important part of the transplant pathway, these guidelines do not cover these topics in detail.

1.8 Disclaimer

This document provides a guide to best practice, which inevitably evolves over time. All clinicians involved in these aspects of transplantation need to undertake clinical care on an individualised basis and keep up to date with changes in the practice of clinical medicine.

These guidelines represent the collective opinions of a number of experts in the field and do not have the force of law. They contain information/guidance for use by practitioners as a best practice tool. It follows that the guidelines should be interpreted in the spirit rather than the letter of their contents. The opinions presented are subject to change and should not be used in isolation to define the management for any individual patient.

The guidelines are not designed to be prescriptive, nor to define a standard of care. The British Transplantation Society cannot attest to the accuracy, completeness or currency of the opinions contained herein and do not accept responsibility or liability for any loss or damage caused to any practitioner or any third party as a result of any reliance being placed on the guidelines or as a result of any inaccurate or misleading opinion contained in the guidelines.

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2 EXECUTIVE SUMMARY OF RECOMMENDATIONS

Chapter 3 Ethics

We recommend that

- All healthcare professionals involved in pancreas and islet transplantation must be familiar with the principal ethical considerations and the current ethical issues relating to equity, efficiency, and beneficence. (Not graded)

- Healthcare professionals must be familiar with the legal and ethical principles in relation to respecting recipient autonomy and enabling valid consent. (Not graded)

- Healthcare professionals involved in pancreas and islet transplantation must understand the current eligibility criteria as well as the processes of consent, prioritisation and organ allocation so they can advise potential transplant recipients accurately and in a timely manner. (Not graded)

- All patients who fulfill the listing criteria must have access to pancreas or islet transplantation, as appropriate. (Not graded)

Chapter 4 Organ Availability and Allocation

We recommend that

- All deceased donor pancreases and islets for transplantation in the UK must be offered through the National Pancreas Offering Scheme (NPOS). (B1)

We suggest that

- Appropriate deceased donors, including controlled donation after circulatory death donors, should be considered for donation of islets for transplantation. (D2)

Chapter 5 Donor Selection: Pancreas

We recommend that

- Pancreas donor risk indices can be used to estimate the short-term outcomes of organs but are not sufficiently accurate to inform individual clinical decisions on organs offered for transplantation. (C1)

- Peri-procurement donor insulin requirements must not influence decisions on pancreas utilisation. (C1)

- If a dual perfusion technique is used when the liver is procured from the same donor as the pancreas, portal perfusion must be via a cannula in the portal vein with the vein vented on the side of the pancreas. (D1)

- There is no clear evidence to favour using a specific cold organ preservation fluid in pancreas donation, and current National Organ Retrieval Service (NORS) standards must be followed. (B1)

Chapter 6 Donor Selection: Islets

We recommend that

- Pancreas donors for islet isolation must be managed according to existing BTS and NHSBT guidelines. (C1)

- Pancreases retrieved for islet isolation must be procured using the same high surgical standards as those retrieved for solid organ transplantation. (C1)

- There is no clear evidence to favour using a specific cold organ preservation fluid in pancreas donation for islet isolation; current NORS standards must be followed in the UK. (C1)

- Careful assessment of the procured pancreas must occur at the islet isolation centre to identify factors that are associated with reduced islet isolation outcomes. (C1)

We suggest that

- Donor peak blood glucose level, serum amylase, and hypotension influence human islet isolation and can be used to determine whether to accept or reject an organ offer. (C2)

- There is no clear evidence to favour using University of Wisconsin (UW) solution alone or the two-layer method for pancreas preservation prior to islet isolation. (C2)

Chapter 7 Recipient Selection: Pancreas

We recommend that

- Insulin-treated patients with diabetes and chronic kidney disease must be considered for simultaneous pancreas and kidney (SPK) transplantation where their predicted survival, or survival free from progression of serious diabetic complications, would be improved by SPK relative to available alternative therapies. (A1)

- Insulin-treated patients with diabetes with a functioning kidney transplant must be considered for pancreas-after-kidney (PAK) transplantation where the predicted patient or kidney-graft survival, or survival free from progression of serious diabetic complications, would be improved by PAK relative to other treatment options. (B1)

- Patients with insulin-treated diabetes and recurrent severe hypoglycaemia must be considered for solitary pancreas or islet transplantation if they have stable, preserved kidney function (eGFR >40 mL/min/1.73m^2) and failure of other approaches to control their diabetes. (B1)

- Potential pancreas transplant recipients must undergo screening for cardiovascular disease, particularly asymptomatic atheromatous coronary artery disease. (C1)

- Potential pancreas transplant recipients must be carefully counselled about the available treatment options to allow them to make an informed decision. (Not graded)

- Insulin-treated patients with diabetes and chronic kidney disease in whom SPK transplantation is considered too high-risk can now be considered for simultaneous islet and kidney (SIK) transplantation. (Not graded)

Chapter 8 Recipient Selection: Islets

We recommend that

- Potential islet transplant recipients must first be seen in a specialist hypoglycaemia clinic to optimise their medical management. (Not graded)

- Potential islet transplant recipients with problematic hypoglycaemia must follow an evidence-based approach to optimise medical management as part of their assessment process. This must include structured education (e.g. DAFNE) and sensor augmented insulin pump therapy before islet transplantation is considered. (B1)

- Islet transplantation must be considered for patients with type 1 diabetes that have on-going problematic hypoglycaemia (defined as more than two episodes of severe hypoglycaemia in the last two years and impaired awareness of hypoglycaemia) despite optimal medical management. (B1)

- Islet transplantation must be considered for patients with type 1 diabetes that have a functioning renal transplant but are unable to achieve optimal glycaemic control despite optimised conventional therapy. (B1)

Chapter 9 Pancreas Transplantation and Peri-operative Care

We recommend that

- Cold ischaemic time independently impacts on pancreas graft outcome, and must be minimised. (B1)

- Bench work preparation of the pancreas must be performed by an appropriately trained surgeon in the correct environment and with adequate organ cold preservation. (D1)

- There are a variety of surgical techniques for pancreas bench preparation and implantation, but within units we recommend that a standardised approach is used for the majority of patients. There is not enough evidence to suggest that a specific surgical approach is clearly superior. (Not graded)

- Every pancreas transplant must have a thromboprophylaxis protocol. There is not enough evidence to suggest that a specific approach is clearly superior. (Not graded)

- Early hyperglycaemia must be investigated with either cross-sectional imaging or exploration of the graft. (D1)

- Pancreas re-transplantation must be considered in all patients with original graft failure, independent of the original graft type or when the graft fails. (B1)

We suggest that

- Managing the exocrine secretions of the graft by either bladder drainage or enteric drainage must be tailored to the individual patient and be within the experience of the surgeon and transplant centre. (D2)

Chapter 10 Islet Isolation, Infusion, and Perioperative Care

We recommend that

- Cold ischaemia times from retrieval to starting isolation must not exceed national recommendations. (C1)

- Islet isolation must take place in a Human Tissue Authority licensed, Good Manufacturing Process approved laboratory. (Ungraded)

- Islets must meet the minimum release criteria for number, purity and viability. (C1)

- Maintenance of euglycaemia with the use of a variable rate insulin infusion is required for a minimum of 24 hours in the peri-operative period to prevent loss of islets through oxidative stress. (C1)

- Anti-coagulation must be used to help prevent the Instant Blood Mediated Inflammatory Reaction in the early post-transplant period. (C1)

- Use of a sealant along the percutaneous transhepatic needle track will minimise the risk of intra-operative bleeding. (C1)

Chapter 11 Histocompatibility and Immunosuppression

We recommend that

- Once a patient is listed for pancreas or islet transplantation, it is recommended that samples be obtained for HLA antibody analysis at least every three months. (B1)

- Potential sensitising events must be notified promptly to the histocompatibility and immunogenetics laboratory and samples sent for HLA antibody analysis approximately 2-4 weeks after the event. (Not graded)

- To reduce cold ischaemic times in pancreas and islet transplantation, virtual crossmatch and/or donor peripheral blood lymphocyte crossmatching techniques must be available. (C1)

We suggest that

- There is no strong evidence to support the use of depleting over non-depleting antibody induction immunosuppression in SPK transplantation. Pancreas units must assess the risks and benefits of each approach. (C2)

- The use of depleting antibody induction therapy is recommended in recipients of PTA and PAK transplants. (C2)

Chapter 12 Recipient Outcomes: Pancreas Transplantation

We recommend that

- Centres performing pancreas transplantation must submit data to the UK Transplant Registry according to NHSBT requirements. (Not graded)

- In addition to the minimum data set, additional data must be collected to allow pancreas graft function to be categorised according to the Igls criteria. (C1)

- An HbA1c of >6.5% or a rise of HbA1c by >0.5% should prompt consideration of investigations to identify an underlying cause of potential graft dysfunction. (Not graded)

Chapter 13 Recipient Outcomes: Islet Transplantation

We recommend that

- Centres performing islet transplantation must submit data to the UK Transplant Registry according to NHSBT requirements. (Not graded)

- The above should include assessment at 1, 3 and 12 months after transplantation, and yearly thereafter. The data should include:
    - Metabolic monitoring (monitoring of graft function using mixed meal tolerance tests with paired glucose and C-peptide). (B1)
    - Monitoring of clinical outcomes, including documentation of mild and severe hypoglycaemia, glycaemic control, and any anti-hyperglycaemic medication used. (B1)
    - Immunological monitoring, including measures of alloantibodies and autoantibodies. (Not graded)
    - Quality of life monitoring. (Not graded)
    - Monitoring and management of on-going complications of diabetes. (B1)
    - Monitoring and management of on-going complications of immunosuppression. (B1)

- In addition to the minimum data set required by NHSBT, additional data must be collected to allow islet graft function to be categorised according to Igls criteria and BETA-2 score calculation. (C1)

- Patients are encouraged to perform structured self-monitoring of blood glucose (i.e. fasting and post-meal glucose values) and to contact the transplant team if there are any significant changes in values. (Not graded)

3 ETHICS

Recommendations

We recommend that

- All healthcare professionals involved in pancreas and islet transplantation must be familiar with the principal ethical considerations and the current ethical issues relating to equity, efficiency, and beneficence. (Not graded)

- Healthcare professionals must be familiar with the legal and ethical principles in relation to respecting recipient autonomy and enabling valid consent. (Not graded)

- Healthcare professionals involved in pancreas and islet transplantation must understand the current eligibility criteria as well as the processes of consent, prioritisation and organ allocation so they can advise potential transplant recipients accurately and in a timely manner. (Not graded)

- All patients who fulfill the listing criteria must have access to pancreas or islet transplantation, as appropriate. (Not graded)

3.1 Definitions

Altruism: the premise that organ transplantation from deceased donors is performed as a gift from the donor, without any expectation of remuneration or reward.

Autonomy: the right of the individual to determine his/her own fate, including that of their organs after death. In the recipient's context, this represents the right of patients to make informed decisions such as to accept or to refuse an organ offer.

Dignity: the unique and precious status of a human being and the ethical requirement to treat it respectfully without inflicting harm in both life and death.

Beneficence / non-maleficence: the Hippocratic ethical principle that healthcare professionals should make every effort to serve the best interests of their patients and, equally, make every effort not to cause harm or distress to their patients.

Futility: the contentious principle that it is unethical to perform interventions that cannot benefit the individual receiving them; the controversy focusing upon what does or does not constitute benefit.

Equity: The concept of fairness or justice with respect to the way the organs donated are allocated and utilised.

3.2 Pancreas Transplantation: Introduction

Pancreas transplantation in the United Kingdom has evolved from a poorly regulated, low volume procedure with variable outcomes to a nationally delivered service with more than a thousand transplants reported to National Health Service Blood and Transplant (NHSBT).

As the number of transplants has increased over the last decade, with consistent outcomes reported across the UK, there has been an increase in the utilisation of non-standard (or expanded criteria) pancreas donors to sustain this increased transplant activity. As a consequence, pancreas transplant centres are increasingly facing ethical and legal dilemmas when considering utilising the organs offered. This chapter aims to provide a framework for the ethical principles underlying the process of pancreas transplantation and related issues.

Key principles to be considered:

1. Equity versus efficiency: Given the scarcity of transplantable organs, there is a dynamic balance between being efficient (i.e. maximising the utilisation of available resources) and equity (transplanting the patients who would benefit the most). This is addressed by the NHSBT pancreas offering scheme incorporating elements of justice (e.g. waiting time, sensitisation status, etc.) and elements of medical benefit (human leukocyte antigen (HLA) matching, measures to reduce preservation time) to provide equitable access to transplantation across the various centres.
2. Beneficence versus non-maleficence: With the continuous impetus to expand the donor pool and the increasing presence of older recipients on transplant waiting lists, transplant clinicians have the primary responsibility to ensure that the principle of beneficence is adhered to at all times.

3. Respect for donor and recipient autonomy: It is important for the transplant community to respect the wishes of the donor, as it may be argued that the donor may be harmed posthumously if their desire or interest (i.e. to donate their organs) is not respected. The transplant community must strive towards optimising the organ procurement, preservation and transplantation processes to ensure that the donor's wishes are fulfilled. With the current legislative framework (opt-in in England; deemed consent/opt out in Wales; deemed consent/opt out shortly to be introduced in Scotland), it is important that organ donation teams take all means necessary to ensure that the donor's wishes are carried out, such as consulting the National Organ Donor Register and discussing the donor's wishes with the family and/or the next-of-kin. Often, and especially in case of non-standard donor offers, this requirement conflicts with the recipient team's responsibility to respect the recipient's autonomous right to refuse an organ based on the information provided by the medical team.

   Legislation is scheduled for implementation in Spring 2020 to introduce deemed consent/opt out to England, making this the universal status throughout the United Kingdom.

4. Fairness and equity: As the majority of the pancreas transplants are performed as simultaneous pancreas-kidney (SPK) transplants, there has been a concern that this undermines the principle of equity and fairness towards patients awaiting kidney transplantation alone (1). This has been addressed by the NHSBT pancreas and kidney allocation schemes and is re-audited on a regular basis.

5. Legal aspects and obtaining consent: Transplantation of any organ carries risk. It is the responsibility of the transplant team to discuss the potential risks involved with transplantation in general, as well as any additional risks posed by the particular organ(s) being offered to the recipient (2). During the process of transplant work-up, transplant teams must discuss the specific risks posed by pancreas transplantation, as well as the additional risks and benefits in accepting organs from non-standard donors. This is designed (in light of the Montgomery ruling (3)) to provide information related to the consent process which is tailored for the specific recipient, as well as giving ample time to weigh the pros and cons of the decision. Detailed guidance is available on the Organ Donation and Transplantation website (4).

3.3 Pancreas Transplantation: The Donor Perspective

Pancreas allografts have the highest discard rate after procurement of all solid organs (5). Organs are most commonly discarded due to a combination of factors such as suboptimal appearance of the graft (e.g. fattiness) and procurement-related issues (e.g. damage). The National Organ Retrieval Service (NORS) team must optimise modifiable factors in the process of organ assessment and procurement, whilst maintaining clear communication with the recipient team about new information as it becomes available (6).

New strategies to improve organ preservation such as normothermic regional perfusion, ex vivo machine perfusion, and DCD donor optimisation strategies should be carefully considered from the ethical perspective, ensuring that the best interests of the donor (his / her willingness for donation to proceed with a successful outcome) are served.

3.4 Pancreas Transplantation: The Recipient Perspective

The transplant recipient team acts in the interests of the recipient and is required to advise the patient about the risks and benefits of pancreas transplantation, and whether there are any perceived additional risks posed by the specific organ or donor. The team has a legal responsibility to advise the patients of the risks associated with and the likely outcomes of alternative choices; recipient autonomy is paramount (3). This should be done in a comprehensive and evidence-based way.

With increasingly good medium-term results of pancreas transplantation and widespread awareness of the procedure, there is an inevitable demand to expand the recipient eligibility criteria for transplantation. This must be considered carefully from the perspective of recipient autonomy and medical benefit. The ethical debate arises in prioritising higher risk recipients. The principle of equity would suggest they should have an equal access to the pancreas donor pool as those patients listed under standard criteria. However, prioritisation by the principle of a ‘fair innings’ approach suggests that the older the patient, the lower the priority should be, as such patients have had an opportunity to live a longer life in comparison to younger patients with a similar disease burden. However, it is important to distinguish between chronological age and overall disease burden and lack of conditioning (‘physiological age’); estimates of post-transplant benefit should be individualised and not based on chronological age alone.

It remains the responsibility of the transplant team to advise potential higher risk recipients of the complexity and additional risks involved. Dedicated multi-disciplinary team clinics, seminars for patients and their families, and the use of credible e-learning material are examples of good and ethically sound practices. Education must be provided prior to wait-listing; discussion on the day of a transplant offer is not only ethically unacceptable, but is clinically counterproductive and may confer significant extra risk.

The decision to remain on the transplant waiting list must be reviewed at regular intervals to ensure that the potential recipient's risk-benefit analysis has not changed (e.g. due to increasing age, deterioration in medical condition, etc.).

3.5 Pancreas Transplantation: The Transplant Team Perspective

Transplantation is a co-ordinated procediure involving multiple sites and members of varied specialties. As communication is key in successful transplantation, it is important for all the members of the team to be aware of the importance of maintaining donor and recipient confidentiality according to NHSBT guidelines (4). The criteria for listing for pancreas transplantation must be evidence-based and not depend on the preference of individual clinicians or centres. The team also has a duty of candour to be honest and up front with the recipient about complications and/or adverse events that may come to light at any stage of the transplant process.

3.6 Islet Transplantation

The ethical principles and recommendations discussed in the context of pancreas transplantation also apply to islet transplantation. In addition, the following specific issues need to be considered:

1. The families of potential donors must be informed that the donor pancreas may be offered for islet transplantation.
2. Potential recipients must be of the likelihood of requiring more than one islet transplant.

3.7 BTS Ethics Committee

The BTS Ethics Committee is a multidisciplinary forum of healthcare professionals practicing in transplantation and its related fields. It consists of elected and appointed individuals with a specialist interest in ethical issues that are relevant to donation and transplantation. The committee encourages questions and approaches for advice on ethical dilemmas of any kind in the area of transplantation ethics and may be contacted via ethics@bts.org.uk or through the officers of the BTS.

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4 ORGAN AVAILABILITY AND ALLOCATION

Recommendations

We recommend that

- All deceased donor pancreases and islets for transplantation in the UK must be offered through the National Pancreas Offering Scheme (NPOS). (B1)

We suggest that

- Appropriate deceased donors, including controlled donation after circulatory death donors, should be considered for donation of islets for transplantation. (D2)

4.1 Pancreas and Islet Allocation Policy in the United Kingdom

Since 1st December 2010, all deceased donor pancreas and islet offers in the United Kingdom have been offered to patients via the National Pancreas Offering Scheme (NPOS) (1). Patients waiting for a solid organ pancreas transplant are therefore on the same waiting list as patients waiting for an islet transplant. A new scheme will be introduced in the UK in late 2019, re-named the National Pancreas Offering Scheme. This new name emphasises that organs are offered by NHSBT, but that transplanting centres will make decisions on offer acceptance.

Factors affecting transplant outcomes were identified using the UK transplant registry and data from the United States Organ Procurement and Transplant Network. A computer algorithm was then designed to prioritise patients according to waiting time, calculated reaction frequency (cRF) >75%, dialysis requirement, proximity to donor hospital, similarity of donor and recipient age, and HLA mismatch. In the resultant allocation programme, priority is given to patients waiting for their second or subsequent islet graft, as it is clinically preferable that such patients receive these grafts soon after their first graft. Donor BMI is also included in the allocation algorithm; low BMI donors are weighted towards becoming solid organ pancreas donors and high BMI donors are weighted towards becoming islet donors. This is because high BMI donor pancreases have worse outcomes for solid organ transplants, but improved islet yields in islet transplantation (2).

On 1st December 2010, the median waiting time for a patient on the pancreas transplant list was 402 days (NHSBT data). By 1st December 2015, after 5 years of operation of NPAS, the median waiting time had fallen to 250 days, with reduced variation between centres. It appears that the NPAS has significantly improved access to pancreas transplantation.

The waiting time for highly sensitised patients (as defined by cRF >75%) has also decreased from 714 days in 2010 to 423 days in 2015 (unpublished data, NHSBT). However, a high cRF at the time of listing reduces the chance of transplantation. In the five years of operation of the NPAS, 30% patients with a cRF >75% at the time of listing died or were removed from the list (unpublished NHSBT data). Therefore, if a pancreas from a marginal donor is offered to a patient with a high cRF, the increased risks of transplantation must be weighed against the risk of remaining on the waiting list.

Recipient blood group also affects the waiting time for transplantation. In 2015, the median waiting time for a pancreas transplant in the UK by blood group was: O - 529 days; A - 383 days; B - 297 days; and AB - 102 days (unpublished data, NHSBT). These data should be taken into account when considering the offer of a marginal pancreas to a patient on the waiting list.

A pilot study for simultaneous islet-kidney (SIK) transplantation is currently being explored in the UK. The recipient selection criteria are likely to be similar to those for SPK transplantation and the offering pathway will be part of the NPAS. As yet, it is unclear how many patients will benefit from SIK transplantation and how this might impact on the demand for organs.

4.2 Pancreas and Islet Transplantation in the UK and the use of DCD Donors

Approximately 180-200 pancreas transplants are performed per year in the UK, in eight specialist pancreas transplant centres. Approximately 10% of pancreas transplants are isolated pancreas (IP) transplants (pancreas transplantation alone (PTA) or pancreas after kidney (PAK) transplants); the remainder are simultaneous pancreas-kidney (SPK) transplants.

Since the first Maastricht category III DCD donor pancreas transplant was performed in the UK in 2005/6, there has been a rapid expansion of the controlled DCD donor

pancreas programme, which now accounts for approximately 25% of all pancreas transplants. This is one of the highest rates of DCD donor pancreas usage in the world.

Muthusamy et al compared the short-term survival of pancreas transplants from DCD versus DBD donors in the UK and found that one-year graft survival rates were similar (3). Similarly, in the United States, Siskind et al compared 320 DCD donor pancreas transplants with 20,448 DBD donor pancreas transplants between 1996 and 2012. There were no differences in graft survival at 1, 3, 5, 10 or 15 years on univariate analysis (4). However, DCD pancreas donors tend to be younger, with lower BMIs, and a large multivariate analysis from the US has identified DCD donation as a risk factor for poorer pancreas graft survival (5). Overall, these data support the transplantation of pancreases from controlled DCD donors, though it would seem prudent to minimise other donor risk factors such as age and BMI, and to keep the pancreas cold ischaemic time as short as possible (6-8).

In the UK, islet transplantation is performed 30-35 times per year in seven specialist centres. The national median waiting time for islet transplantation is 355 days (95% confidence interval 246-464 days). Approximately 10% of islet transplants come from controlled DCD donors.

The published experience of using pancreases from DCD donors for islet transplantation is limited, but early experience suggests reasonable outcomes (8). Appropriate controlled DCD donors should be considered for islet transplantation.

4.3 Rates and Causes of Organ Discard

Approximately 50% of all deceased donor pancreases procured for the purposes of either pancreas or islet transplantation are discarded each year in the UK (9). The most frequent reasons for organ discard are insufficient islet yield (19%), fatty organ (17%), miscellaneous reasons (17%), and organ damage (10%). Overall, the median pancreas donor age in the UK from 2008-2012 was 44 years (range 1-64), with the donor BMI being 23.9 (12.7-39.1) kg/m^2.

The pancreas is a challenging organ to procure, and higher rates of damage are reported than for either liver or kidney retrievals (9). The presence of a hepatic artery arising from the donor superior mesenteric artery is independently associated with an

increased risk of pancreas damage during organ retrieval. Awareness of the high rates of pancreas damage, careful training and supervision, and meticulous surgical technique are required to minimise organ damage.

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Chapter 5 DONOR SELECTION: PANCREAS

Recommendations

We recommend that

- Pancreas donor risk indices can be used to estimate the short-term outcomes of organs but are not sufficiently accurate to inform individual clinical decisions on organs offered for transplantation. (C1)

- Peri-procurement donor insulin requirements must not influence decisions on pancreas utilisation. (C1)

- If a dual perfusion technique is used when the liver is procured from the same donor as the pancreas, portal perfusion must be via a cannula in the portal vein with the vein vented on the side of the pancreas. (D1)

- There is no clear evidence to favour using a specific cold organ preservation fluid in pancreas donation, and current National Organ Retrieval Service (NORS) standards must be followed. (B1)

5.1 Introduction

As with all forms of solid organ transplantation, careful donor selection is essential to ensure acceptable post-transplant outcomes. This chapter summarises the existing evidence on donor risk factors for adverse pancreas outcomes after transplantation, as well as optimal donor management, pancreas retrieval and preservation, and organ assessment at the implanting centre. In general, the available evidence is weak and there is a paucity of randomised controlled trials in these fields.

5.2 Deceased Donor Risk Factors

5.2.1 General Approach to Donor Risk

Transplantation is associated with risk to the recipient, including the risk of poor or non-function of the graft(s), and donor-transmitted diseases. Knowledge of donor

characteristics associated with worse graft survival outcomes after pancreas transplantation is necessary in order for the transplant clinician to assess the balance of risks and benefits when considering an organ offer. Guidance on the responsibilities of clinicians when considering the acceptance of organs from deceased donors must be consulted (1). To summarise that document:

- The risks of transplantation with a higher risk organ must be balanced against the consequences of non-use and waiting for another, lower risk organ.
- It is the responsibility of the senior supervising implanting surgeon to decide whether to accept or decline the offered organ.
- The surgeon is encouraged to seek the advice of other clinicians who are aware of the clinical condition of the potential recipient. Where the organ is associated with higher risk, it is recommended that the surgeon seek advice from expert colleagues and that the discussion and rationale for transplantation is recorded in the clinical records.
- The surgeon should be aware of current guidelines for accepting / refusing a graft but has the option of deciding not to follow these where he/she considers it is in the patient's best interest. In such a case, the decision and reasons behind it must be recorded in the patient notes.
- The implanting surgeon has responsibility for ensuring that the patient has been fully informed about the risks of transplantation, including donor-related conditions that represent a higher than average risk, and that the patient has given consent according to NHSBT / BTS guidelines (2).

In the context of pancreas transplantation, the following must be taken into account:

- The risk of death without a transplant. In the UK, 4% of patients listed for a pancreas transplant have died, or have been removed from the waiting list, without transplantation at one year after registration (NHSBT Annual Report on Pancreas and Islet Transplantation 2015/2016). One-year patient survival after pancreas transplantation in the UK is 96-98% (NHSBT Annual Activity Report 2014-15). SPK transplantation is associated with a survival benefit over remaining on the waiting list (3,4).
- The expected waiting time for the potential recipient. Factors that influence recipient waiting time include blood group, ethnicity (HLA type), degree of HLA sensitisation, and transplant centre. The degree of clinical urgency will be influenced by multiple factors including concerns regarding imminent loss of

dialysis access, progression of cardiovascular disease, and the presence and frequency of severe hypoglycaemic episodes (5).

5.2.2 Specific Donor Risks

Deceased donor risk factors for pancreas graft survival or patient survival can be specific to the organ, or to the donor. For SPK recipients, consideration should also be given to risk factors for poor renal allograft outcomes, as dialysis freedom confers a strong survival benefit over remaining on dialysis (6). Renal risk factors are not considered in these guidelines.

Organ-specific risks are best considered using the concept of a donor risk index. Donor risk indexes are derived from large retrospective analyses (e.g. from national registries) enabling statistical correction for multiple donor, recipient, operative, and immunological factors. This approach leads to a more objective measure of donor risk.

There is only one pancreas donor risk index (PDRI) derived from a large national registry analysis (7). Risk factors for 'technical failure' after pancreas transplantation have also been examined but this does not encompass graft loss from immunological causes (8). The Eurotransplant Preprocurement Pancras Suitability Score (P-PASS) predicts pancreas offer acceptance or decline (9), but does not predict pancreas graft survival (10-12).

Axelrod et al examined data from the US Scientific Registry of Transplant Recipients for all patients undergoing SPK (n=6248), PTA (n=780), or PAK (n=2373) between 01 January 2000 and 31 January 2006 (7). The definition of pancreas graft failure included patient death. Donor factors that independently predicted worse one-year pancreas graft survival in SPK recipients were male gender, black or Asian race, cerebrovascular accident as cause of death, DCD donor, serum creatinine > 220 μmol/L, and short stature. The relationship between donor age and pancreas graft outcome was non-linear. The best pancreas graft outcomes were with donors aged 20 years and outcomes worsened with donor ages both younger and older than this, though donors less than 20 years were at lower risk than older donors. Likewise, donor BMI and outcome shared a non-linear relationship, with optimal donor BMI between 18-25 kg/m^2.

Of note, donor amylase, lipase, duration of loss of cardiac output ('downtime'), smoking, cocaine use, alcohol use, and hypertension were not associated with pancreas graft failure. This may reflect either a true lack of association, incomplete registry data, or limited clinical practice during the study period (i.e. the number of organs transplanted from donors with those characteristics was low and therefore the study lacked statistical power).

Axelrod's PDRI has been validated for one-year pancreas graft survival in the UK SPK transplant population, but does not appear to be valid for UK PTA and PAK cohorts (13). PDRI was able to adequately discriminate between high-risk and low-risk donors with regards to one-year graft survival, but there was little difference in graft survival between the top and bottom risk quartiles at five years.

Although Axelrod's PDRI has DCD donor status as a risk factor for pancreas graft outcome, early UK data suggest similar outcomes to transplants from DBD donors (14,15). However, DCD donors tended to be more highly selected, as donor ages and BMIs were lower in the DCD than the DBD cohort. Current UK guidelines suggest abandoning pancreas retrieval if the functional warm ischaemic time (defined as donor systolic BP <50 mmHg) is more than 30 minutes (16), though the evidence base for this threshold is limited. The time from treatment withdrawal to loss of cardiac output is unlikely to be a reliable marker of pancreatic ischaemia as it does not take physiological parameters into account (17). Pancreases from DCD donors should not be declined on their donor type alone (18), but it would seem prudent to minimise additional risk factors in such donors.

The roles of other potential donor risk factors for pancreas graft outcome have not been adequately examined, e.g. history of gestational diabetes, acute pre-morbid insulin requirement, family history of diabetes, and South Asian ethnicity. Molecular and genetic markers may be able to define further donor risk factors in future (19).

The PDRI enables a better quantification of risk, and might be used in the future to facilitate organ allocation. However, the use of the PDRI to decide whether or not to accept an individual organ offer is not advised, as its ability to predict one-year graft survival is not sufficiently strong (index of concordance 0.67), and it does not appear to be able to accurately predict medium-term graft outcomes (7,13).

The potential risk of transmission of tumours and serious viral illnesses should also be considered. In the UK, guidance from the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) should be consulted when considering donors with a history of cancer (20). SaBTO guidance also exists for donors with a history of significant infections, e.g. bacterial meningitis, viral meningo-encephalitis, and bacteraemia. Expert microbiological advice should be obtained when there is significant concern about the risk of transmission of serious infection, and the risks and benefits of accepting the organ offer should be carefully considered. Donors with negative serology for hepatitis B, hepatitis C, and HIV, but with demographic or behavioural risk factors for these pathogens may also be suitable donors for selected pancreas recipients. SaBTO guidance on the use of organs from such donors is currently lacking, though guidance from Canada has been published (21).

5.3 Deceased Donor Management

There are limited data available on the optimal management of potential pancreas donors, though it is likely that the numerous physiological changes before and after donor death have a significant impact on subsequent pancreas graft function. Specific issues to consider with respect to pancreas transplantation include the management of hyperglycaemia, fluid balance, and the use of desmopressin (DDAVP).

It is recognised that donors are likely to be hyperglycaemic due to high volumes of glucose-rich intravenous fluids, raised levels of circulating catecholamines, and the use of methylprednisolone to reduce systemic inflammation associated with brain injury. As a result, donors are often treated with sliding scale insulin infusions to maintain glucose between 4-10 mmol/L in order to avoid an osmotic diuresis and volume depletion. Although an early single-centre analysis suggested that donor hyperglycaemia is a risk factor for pancreas graft loss (22), this topic has not been studied further. Given the difficulties in avoiding hyperglycaemia in deceased donors and the absence of convincing evidence for insulin's deleterious effect on pancreas graft function, it is recommended that insulin infusions should be used to maintain permissive normoglycaemia and that peri-procurement insulin requirements must not influence decisions on pancreas utilisation.

The optimal fluid balance regimen for pancreas donors is not known. It would seem reasonable to aim for euvolaemia, maintaining a mean arterial pressure of

60 - 80 mmHg, urine output of 0.5 - 2.0 mL/kg/hour, and serum sodium <150 mmol/L, as per NHSBT guidance (23).

Desmopressin is frequently used to treat diabetes insipidus in DBD donors, in order to avoid volume depletion, hypernatraemia, and the deleterious effects of hypernatraemia on the graft survival of liver transplants. However, desmopressin is known to be pro-coagulant, and animal data suggest that administration may impair pancreas graft microcirculation after transplantation (24). In addition, a large univariate analysis of registry data found an association between donor desmopressin use and pancreas graft thrombosis (25). However, given the need to avoid donor dehydration, the absence of a multivariate analysis supporting the association between desmopressin and pancreas graft dysfunction, and that desmopressin seems to improve renal allograft survival (26), there is no strong evidence to avoid desmopressin use in potential pancreas donors.

5.4 Deceased Donor Organ Retrieval

Detailed descriptions of acceptable surgical techniques for deceased donor pancreas procurement have been published elsewhere (16,18,27). Regardless of whether the pancreas is procured for solid organ or islet transplantation, the technique is the same. The evidence base for specific surgical approaches is lacking, and relies instead on an accumulation of clinical experience. Where evidence exists for a specific approach, it is discussed below. The following principles should be adhered to during pancreas procurement.

After cessation of the donor's circulation, cold preservation fluid should be administered via a large cannula in the distal aorta or proximal common iliac artery. The optimal cold perfusate pressure and flow rate for pancreas retrieval are unknown. There is no evidence on whether the use of a thrombolytic agent in the perfusate is beneficial in DCD pancreas donors. Ice slush should be placed around the pancreas and within the lesser sac. This enables rapid cooling of the pancreas, improving islet recovery and function (28). If the liver is being procured from the same donor and a dual (aortic and portal) perfusion technique is used, portal perfusion must be via a cannula in the portal vein with transection of the vein on the side of the pancreas. This avoids the pancreatic congestion that is likely to occur if perfusion is performed via the pancreatic inflow and outflow vessels simultaneously. There is no evidence that procurement of both the liver and pancreas from the same donor compromises survival of either graft (29).

The liver and pancreas can be explanted separately or en bloc, as there does not appear to be any significant difference in the rate of pancreas damage between the two techniques (30). There is limited evidence, however, that suggests that en bloc retrieval improves the function of the transplanted liver (29). Procurement of the small bowel can also take place from pancreas donors without compromising either organ, though this is a surgically challenging procedure (31). Regardless of the approach, surgical technique must be meticulous to avoid pancreas damage, which is more common than with either kidney or liver procurement (30). Handling of the pancreas and duodenum must be minimised, and the spleen must be used as a handle to manipulate the graft. Knowledge of aberrant vascular and pancreatic anatomy is essential in order to avoid rendering the pancreas unusable (32). There is no evidence on whether the majority of the pancreas dissection should be performed in the warm or cold phases during retrieval from DBD donors.

5.5 Organ Preservation and Perfusion Technologies

There are a growing number of alternative organ preservation and machine perfusion technologies in organ transplantation. At present, the evidence for the use of these in pancreas transplantation is sparse. Conventional DCD and DBD donor retrieval techniques using a cold preservation fluid and subsequent static cold storage (SCS) of the pancreas should be viewed as standard.

The choice of pancreas cold preservation fluid for donor organ flush in situ and SCS varies between countries and units. The most widely used fluids are University of Wisconsin (UW) solution, histidine-tryptophan-ketoglutarate (HTK), and Celsior®. A recent meta-analysis found three randomised controlled trials and seven observational studies comparing these fluids in DBD donors, with the quality of evidence judged to be low or very low (33). Pancreases perfused and stored in UW solution had lower post-transplant serum peak lipase than those perfused and stored in HTK solution, but there were no statistically significant differences in peak serum amylase level, thrombotic graft loss rate, hospital length of stay, or one-month graft survival between the two fluids. The studies included within these meta-analyses had a low median donor age (26 years) and did not include DCD donors. Meta-analyses were not possible between studies comparing UW and Celsior®. UK NORS standards mandate the use of UW solution and these standards must be followed within the UK (16).

Other techniques for pancreas preservation include the two-layer method, oxygen persufflation, and hypothermic machine perfusion (34). These approaches have not been used clinically in solid organ pancreas transplantation, and are therefore not considered further here.

Warm machine perfusion techniques are of increasing interest. Studies have shown the feasibility of 'ex vivo' normothermic perfusion of the human pancreas after organ retrieval, but such transplants have not yet been performed (35,36). In 2014, the Cambridge group reported two pancreases that were successfully transplanted from DCD donors that underwent in situ normothermic regional perfusion at the time of organ retrieval, followed by SCS (37); a further 13 cases have subsequently been presented.

5.6 Organ Assessment at the Implanting Centre

In the UK a greater proportion of retrieved pancreases are discarded after back-table assessment than any other solid organ. It is likely that there is significant variation between units, and surgeons, in their assessment of the suitability of pancreases for donation. However, these variations are as yet poorly characterised.

It appears that concern regarding damage is one of the most common reasons for discard (30), with approximately half of retrieved pancreases reported as suffering damage. Other reasons for discard include poor perfusion, pancreatic fibrosis, and fat infiltration. Damage may be to vascular structures (e.g. superior mesenteric or splenic artery or portal vein), the pancreatic parenchyma, or the duodenum. Occasionally, the pancreas may be undamaged but severe atherosclerosis or damage to the donor vessels supplied for vascular reconstruction renders the organ unusable for solid organ transplantation. Excessive traction on the donor iliac vessels during organ procurement may result in a subtle tear to the bifurcation of the common iliac artery, which can result in severe bleeding if not detected prior to organ reperfusion.

Overall, the presence of pancreas damage does not seem to influence graft survival (30), though the authors of this study acknowledge that only organs with mild damage were likely to have been implanted. Pancreases transplanted after arterial damage or parenchymal damage were identified had a higher rate of graft loss than undamaged organs.

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Chapter 6 DONOR SELECTION: ISLETS

Recommendations

We recommend that

- Pancreas donors for islet isolation must be managed according to existing BTS and NHSBT guidelines. (C1)
- Pancreases retrieved for islet isolation must be procured using the same high surgical standards as those retrieved for solid organ transplantation. (C1)
- There is no clear evidence to favour using a specific cold organ preservation fluid in pancreas donation for islet isolation; current NORS standards must be followed in the UK. (C1)
- Careful assessment of the procured pancreas must occur at the islet isolation centre to identify factors that are associated with reduced islet isolation outcomes. (C1)

We suggest that

- Donor peak blood glucose level, serum amylase, and hypotension influence human islet isolation and can be used to determine whether to accept or reject an organ offer. (C2)
- There is no clear evidence to favour using UW solution alone or the two-layer method for pancreas preservation prior to islet isolation. (C2)

6.1 Deceased Donor Risk Characteristics and Risk Indices

Among the numerous donor variables that had been analysed in several retrospective studies, including more than 2500 donors (1-6) and in one meta-study (7), four could be clearly identified as being most important for the success of human islet isolation: donor high blood glucose levels; high amylase levels; administration of vasopressors; and a medical history that includes hypertension and/or cardiac arrest. Due to the variability in categorisation or stratification of data found in the different studies, it is

difficult to give clear recommendations in terms of acceptable parameters with respect to these risk factors. As critical thresholds we suggest a peak blood glucose level of ≤11.1 mmol/L and a serum amylase level of ≤140 U/L. Although the negative effect of vasopressors on human islet isolation outcome is significant, it is impossible to provide a strict dose range with respect to the multiplicity of vasopressors that may be required to keep the donor stable. A more practical variable appears to be hemodynamic instability, expressed as the lowest systolic blood pressure.

Pancreases from both DBD and DCD donors are suitable for islet isolation and early data from UK series demonstrate equivalent clinical outcome after transplantation of DCD and DBD islet preparations (8,9). For DCD donors, the functional warm ischaemia time should ideally be less than 30 minutes and no longer than one hour.

6.2 Deceased Donor Management

Pancreas donors for islet isolation will normally be multi-organ donors and should be managed as per BTS and NHSBT guidelines (10-12).

6.3 Deceased Donor Organ Retrieval

Meticulous donor surgical technique is required to optimise the likelihood of successful islet isolation. Pancreas retrieval should be carried out by an experienced retrieval team as per NHSBT guidelines (10). Pancreas retrieval for subsequent islet transplantation must be performed to the same high standard as for whole pancreas transplantation, with effective cooling of the pancreas during the retrieval process to minimise warm ischemia damage by autolytic processes. Indeed, it may not be known whether the organ will be used for solid organ transplantation or islet isolation at the time of retrieval.

Care must be taken to minimise direct handling of the pancreas in the warm phase in order to avoid haematomas and capsular breaches. In the cold phase, over-perfusion of the pancreas should be avoided and simultaneous portal and arterial perfusion may impair effective arterial perfusion of the organ if venting of the portal vein is not carried out. The pancreas should be rapidly cooled by arterial cold perfusion and topical ice (13) and retrieved in a timely manner with the spleen and duodenal loop in exactly the same way as for solid organ transplantation. The pancreas may be removed en bloc

with the liver or separately. Ideally the pancreas should reach the islet isolation facility no more than eight hours after cross clamping (six hours for DCD organs) (5-7), therefore it is important to place the pancreas on ice as quickly as possible and arrange rapid transport to the on-call isolation facility.

6.4 Preservation for Islet Transplantation

The average human pancreas contains approximately 1 million islets, diffusely scattered throughout the acinar tissue. Although these cell clusters represent only 1-2% of the entire pancreas mass, they receive 15-20% of the total pancreatic blood flow (14), reflecting the high metabolic demand of this tissue. Interruption of the blood flow has immediate effects on the oxidative glucose breakdown and energy generation of islets. Organ retrieval techniques and pancreas preservation solutions therefore play a crucial role in successful islet isolation.

The gold standard for pancreas preservation, University of Wisconsin (UW) solution, is increasingly being replaced by alternative media such as HTK solution, Celsior®, or IGL-1. This has primarily been driven by cost considerations, rather than clear evidence of superior efficacy. A prospective study comparing the efficacy of UW solution and Celsior® was halted due to concerns about poor islet recovery and isolation yield in the Celsior® group (15), though a retrospective study comparing islet isolations between pancreases flushed and transported with IGL-1, UW, and Celsior® found no differences in efficacy between the three groups (16). Significantly more data are available for pancreas preservation utilising HTK-solution, with several reports of equivalence with UW solution to preserve human pancreases for subsequent islet isolation (17,18). In the UK, NORS standards for organ preservation fluids must be followed (10).

6.5 Novel Preservation Technologies in Islet Transplantation

Since approximately 10% of normal metabolic activity is still operative in ischaemic tissue stored at 4°C, hypothermic organ perfusion and subsequent immersion in various preservation solutions (termed as static cold storage (SCS)), do not completely prevent irreversible pancreas injury once a critical period of cold ischaemia is exceeded (19). This can be explained by the specific preference of islets for the respiratory pathway of glucose breakdown, producing more than 95% of the total islet ATP content (20) if an

adequate supply oxygen for cellular energy generation is provided (21,22). As a consequence, any ischaemic situation has dramatic effects on the energy generation of islets, which affects energy-sensitive mechanisms such as the sodium-potassium ATPase. Several approaches have been described for the preservation of retrieved pancreases prior to islet isolation.

Machine perfusion is most commonly performed at hypothermia (4°C), or normothermia (36-37°C). Although studies from animal models have been published, there have not yet been any reports of human islet transplantation after hypothermic machine perfusion, though the technique appears feasible (23,24). Normothermic machine perfusion has not yet been assessed as a tool in human islet isolation, though pre-clinical studies have been reported (24,25).

Another approach to improve oxidative energy metabolism during ischaemia is to provide a continuous gaseous supply of humidified oxygen via the vessel(s) of an explanted organ (persufflation). Again, although pre-clinical studies have been performed (26), there are as yet no published reports of human islet transplantation after pancreas persufflation.

The novel organ preservation technology that has been assessed in greatest detail is the use of oxygen-charged perfluorocarbons (the two-layer method). This involves placing the pancreas in a container with a liquid non-toxic oxygen carrier (e.g. perfluorodecalin – PFD) along with UW. The PFD is denser than UW, and the pancreas floats between the two layers. The majority of studies have been performed using PFD, with conflicting results. Four retrospective large-scale studies (5,27-29) and four meta-analyses did not reveal a consistent significant advantage of using the two-layer method when compared to UW alone (7,30-32). Careful trimming of the pancreas before incubation in PFD/perfluorocarbon in order to remove non-parenchymal tissue interfering with oxygen penetration into the pancreatic core may be critical for the outcome of pancreas oxygenation. However, only a few studies have reported this important detail (27,33-35). At present, there is insufficient evidence to recommend one technique over the other. Either UW solution alone or the two-layer method can be used for pancreas preservation prior to islet isolation.

Novel oxygen carriers such as perfluorohexyloctane (F6H8) have recently been introduced. This molecule is characterised by increased lipophilia and improved oxygen

delivery into deeper tissue layers (36). Early studies suggest significantly increased islet isolation outcomes and a higher proportion of preparations fulfilling the criteria for islet transplantation, particularly after prolonged cold storage. Experience of the use of this agent is limited.

6.6 Organ Quality Assessment at the Implanting Centre before Islet Isolation

Organ quality assessment is based on visual inspection prior to and during pancreas trimming.

Retrospective large-scale studies (5,29) have shown that an intact pancreas capsule is associated with a higher islet yield. A moderate to extensive amount of surface fat or moderate fat infiltration of the pancreas increases the likelihood for good islet isolation outcome. Of similar importance for the successful release of viable islets from the ischaemic human pancreas is a homogeneous and effective flush of the pancreas with organ preservation solution. This is not only important to prevent ischaemia-induced tissue damage but also to remove any residual blood that can inhibit the activity of subsequently infused enzymes. Oedematous swelling can prevent effective distribution of the enzymes within the parenchyma (5). Tissue fibrosis also reduces the likelihood of an acceptable yield of human islets. Careful assessment of the procured pancreas prior to islet isolation is essential.

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Chapter 7 RECIPIENT SELECTION: PANCREAS

Recommendations

We recommend that:

- Insulin-treated patients with diabetes and chronic kidney disease must be considered for simultaneous pancreas and kidney (SPK) transplantation where their predicted survival, or survival free from progression of serious diabetic complications, would be improved by SPK relative to available alternative therapies. (A1)

- Insulin-treated patients with diabetes with a functioning kidney transplant must be considered for pancreas-after-kidney (PAK) transplantation where the predicted patient or kidney-graft survival, or survival free from progression of serious diabetic complications, would be improved by PAK relative to other treatment options. (B1)

- Patients with insulin-treated diabetes and recurrent severe hypoglycaemia must be considered for solitary pancreas or islet transplantation if they have stable, preserved kidney function (eGFR >40 mL/min/1.73m^2) and failure of other approaches to control their diabetes. (B1)

- Potential pancreas transplant recipients must undergo screening for cardiovascular disease, particularly asymptomatic atheromatous coronary artery disease. (C1)

- Potential pancreas transplant recipients must be carefully counselled about the available treatment options to allow them to make an informed decision. (Not graded)

- Insulin-treated patients with diabetes and chronic kidney disease in whom SPK transplantation is considered too high-risk can now be considered for simultaneous islet and kidney (SIK) transplantation. (Not graded)

7.1 Introduction

Both type 1 and type 2 diabetes mellitus impose a terrible burden on patients in terms of interference with daily life, the life-long fear of, and the long-term consequences of, small and large vessel end-organ damage, and significantly reduced life expectancy. Patients with renal failure are especially at risk of the life-threatening (and life-ruining) cardiovascular, neurological and retinal complications of diabetes. Whole organ pancreas transplantation with kidney transplantation, or (in specific circumstances where the control of diabetes is so problematic as to justify the risks of surgery and long-term immunosuppression) pancreas transplantation alone, offer significant benefits, but at the cost of a complex and high-risk procedure with significant possible complications. Islet transplantation provides a much lower risk option for beta-cell replacement, but frequently with a lower level of functionality (characterised by a less stringent definition of success). The challenge of patient selection for pancreas transplantation lies in achieving an appropriate balance between the degree of risk with the anticipated or potential benefit.

The safety of whole organ pancreas transplantation has significantly improved since the early days (1). Improved surgical techniques, better medical management, refined immunosuppressive protocols, and better selection of donor organs have all contributed to this improvement, but one of the important factors has been the recognition of the relevance of co-morbidity in the diabetic patient population. In parallel, over the last 50 years, there have been wide-ranging developments in insulin, insulin-delivery systems, and non-insulin drugs used to treat diabetes with clear data suggesting improving life-expectancy both before (2) and after (3) the turn of the millennium. Decisions in relation to pancreas transplantation are further complicated by significant advances in islet transplantation, which retains a substantial advantage in terms of peri-transplant risk, but which remains a significantly less effective technique for achieving medium or long-term insulin independence (4).

7.2 Survival Benefits of Pancreas Transplantation

For patients with type 1 diabetes and renal failure, simultaneous pancreas and kidney (SPK) transplantation has shown consistent survival benefit over deceased donor kidney transplantation alone in a number of registry analyses (reviewed in (5)). Some of this effect may be due to confounding due to the use of younger donors in SPK than

kidney-alone transplantation, as is suggested by the equivalent patient survival seen in SPK versus living donor kidney transplantation (6,7).

A contested analysis from the US registry has suggested inferior patient survival in patients undergoing pancreas-after-kidney (PAK) transplantation (8) compared to pancreas transplant wait-listed kidney transplant recipients, and these data may have contributed to a decline in PAK transplant activity in the US (9). Subsequent US data (possibly reflecting improved outcomes over the last two decades) suggest a trend for improved patient survival associated with PAK transplantation undertaken within a year of living donor kidney transplantation (10). A recent large US registry analysis (with attempted co-morbidity matching by propensity scoring) suggests a significant survival benefit from pancreas transplantation alone, and confirms the survival benefit of SPK transplantation over remaining on the transplant waiting list (11). Similar analyses from the UK registry have not yet been performed.

Relatively small numbers of patients with type 2 diabetes mellitus have undergone whole-organ pancreas transplantation compared to those with type 1, and there are no formal analyses of survival when compared to equivalent wait-listed patients. Published case series repeatedly show inferior outcomes in patients with high BMI (>30 kg/m^2), but provided the target population is confined to “thin type 2’s”, outcomes after SPK or PAK transplantation appear to be equivalent to those for patients with type 1 diabetics both in terms of survival and insulin independence (12,13). Equivalent survival benefit is therefore a reasonable assumption, bearing in mind the complexity of the ‘metabolic syndrome’ that frequently accompanies type 2 diabetes.

7.3 Quality of Life and Co-morbidity Benefits of Pancreas Transplantation

Data on patient reported quality of life (QoL) effects of pancreas transplantation have been surprisingly mixed (14), particularly in view of the enthusiastic reports from patients of the transformative positive effect of successful transplantation, as well as the desire of some patients to pursue re-transplantation after graft failure. With improving outcomes over recent years, more recent reports suggest clearer demonstration of improved QoL following successful transplantation (15).

Stabilisation or improvement in diabetic end-organ complications following successful pancreas transplantation has been similarly difficult to demonstrate (reviewed in (16))

despite the striking and much-cited demonstration of reversal of histological changes of diabetic nephropathy with prolonged euglycaemia after PTA (17).

Given the above evidence, insulin-treated patients with diabetes and chronic kidney disease must be considered for SPK transplantation where their predicted survival, or survival free from progression of serious diabetic complications, would be improved by SPK relative to available alternative therapies. Insulin-treated patients with diabetes with a functioning kidney transplant must be considered for pancreas-after-kidney (PAK) transplantation where the predicted patient or kidney-graft survival, or survival free from progression of serious diabetic complications, would be improved by PAK relative to other treatment options. Patients with diabetes and recurrent severe hypoglycaemia must be considered for solitary pancreas or islet transplantation if they have stable, preserved kidney function (eGFR >40 mL/min/1.73m^2) and failure of other approaches to control their diabetes (18).

See also sections 12.2.3 and 12.2.4 for a more detailed discussion of these issues.

7.4 Patient Assessment Prior to Pancreas Transplantation

There are few absolute contra-indications to pancreas transplantation. As pancreas transplantation has evolved, factors that were once considered absolute contra-indications have become relative contra-indications. However, active infection, untreated malignancy, major psychiatric history likely to result in non-concordance, and inability to withstand the necessary immunosuppression are generally considered absolute contra-indications (18). Consideration of relative contra-indications is based on a complex, individualised risk-benefit analysis that is not amenable to a simple objective protocol.

7.4.1 Cardiovascular Disease

This is common in this group of patients and is a significant cause of peri-operative morbidity and mortality. All pancreas transplant units carry out some form of cardiovascular assessment with the intention of: (i) identifying patients who can be transplanted but at higher risk; (ii) identifying patients who require cardiovascular intervention (typically coronary artery stenting or bypass); or (iii) identifying those patients with uncorrectable cardiac disease in whom the risk of pancreas

transplantation is excessive and therefore contra-indicated. Most units employ some means of measuring myocardial function (see below) to screen patients. Coronary angiography is used selectively by most transplant units, and in all patients by others.

Cardiovascular disease is the most common cause of death following pancreas transplantation (1). Most pancreas transplant candidates have other risk factors for cardiovascular co-morbidity including renal failure, hypercholesterolaemia, hypertension, smoking, and/or a positive family history. A unique complicating factor in the diabetic population can be the presence of significant ischaemic heart disease in the absence of angina, as a result of diabetic autonomic neuropathy.

Pancreas transplantation, particularly when combined with kidney transplantation, is a more invasive procedure than kidney transplantation alone. The cardiovascular stress caused by the much longer operative procedure and by postoperative complications (e.g. pancreatitis, abdominal sepsis) is often greater than that of other solid organ transplants. Cardiovascular evaluation is therefore especially critical and a higher level of cardiovascular fitness is required in candidates for pancreas transplantation compared with those for kidney transplantation.

Whilst the majority of clinicians agree about the importance of a detailed cardiovascular assessment prior to pancreas transplantation, there is some variation and little evidence about the best way in which to achieve this.

A detailed history and full clinical examination are essential. In non-smokers who have no symptoms or evidence of ischaemic heart disease, peripheral vascular disease or cerebrovascular disease, and who have no additional risk factors (such as family history, hypercholesterolaemia, hypertension), it can be argued that the only additional assessment required is a 12 lead ECG. Such patients are, however, a small minority and, in most units, all patients routinely undergo additional cardiovascular assessment.

The options for further cardiac assessment are echocardiography, myocardial perfusion scintigraphy, and coronary angiography. There are no evidence-based guidelines regarding the indications for each of these tests or their interpretation in this context. Echocardiography provides information about right and left ventricular function, a sensitive means to detect valvular disease, and quantification of pulmonary hypertension and ejection fraction. Non-invasive tests of myocardial function, such as

dobutamine stress echocardiography or myocardial perfusion scintigraphy, provide valuable information about areas of ischaemic myocardium and a valid trigger for further investigation. Although the correlation between the results of such tests and the results of coronary angiography is imperfect, these tests do provide an effective means of screening this group of high-risk patients and selecting those that require more invasive assessment.

Although there is no direct evidence of the benefit of treating detected coronary artery lesions before transplantation in pancreas transplant candidates, indirect evidence supports the policy of treating significant, correctable coronary artery lesions before listing (19). Equally, it is important to optimise the recipient risk factors for vascular disease through optimal medical management. A cardiologist with experience in assessing and managing patients prior to kidney and pancreas transplantation is an essential part of the multi-disciplinary team.

7.4.2 Iliac and Peripheral Vascular Disease

All patients need clinical assessment of their aorto-iliac and peripheral vasculature. If a patient has no symptoms of peripheral vascular disease and strong and symmetrically palpable femoral pulses, it is reasonable to proceed without further investigation. Although most units in practice use routine Doppler imaging of iliac vessels to aid operative planning, it is unlikely that intervention would be recommended in such patients even if correctable lesions were identified.

Weak or asymmetrical femoral pulses require further investigation. Similarly, a history of arterial leg ulceration, lower limb amputation, or symptoms consistent with peripheral vascular disease suggests that further radiological assessment is required. Absence of one or more peripheral pulses without any other concerning features is common in this patient population, and does not generally require further assessment.

The optimal means of investigating peripheral vascular disease in this population is unclear. Duplex scanning is less useful in patients with diabetes and calcified, non-compliant arteries. In pre-dialysis patients, CT angiography may lead to impairment of already severely compromised renal function. Non-contrast CT scanning identifies vascular calcification but cannot accurately quantify the degree of stenosis or detect non-calcified lesions. Magnetic resonance angiography carries a small risk of nephrogenic fibrosing dermopathy (nephrogenic systemic fibrosis) due to gadolinium-

containing contrast medium. Non-contrast magnetic resonance angiography is technically feasible, but has its own limitations. The preferred method of investigation may in practice be determined by local resources and expertise.

Conventional angiography is reserved for the minority of patients in whom therapeutic vascular intervention is being considered.

7.4.3 Infection

In common with recipients of all types of organ transplant, potential pancreas transplant candidates undergo virological screening during pre-transplant assessment. The hepatitis B, hepatitis C, HIV, EBV, HSV and CMV status of all candidates must be checked and documented before registration for transplantation (18). Additional tests may be required dependent upon the patient's travel history, personal history and ethnicity, e.g. screening for HTLV1 and 2. Seropositivity is not necessarily a contra-indication to transplantation but may have implications both for donor organ selection and also post-transplant management (20-22). Whilst not routine in all centres, knowledge of varicella zoster antibody status may be useful for those recipients who come into contact with chicken pox after transplantation, and VZV-negative patients should be offered immunisation before transplantation.

Specific precautions are required for all transplant recipients (including pancreas) who have a previous history suggestive of tuberculosis, and advice from the infectious diseases or respiratory team must be sought.

7.4.4 Malignancy

The presence of an untreated malignancy is, at present, a contra-indication to any form of pancreas transplantation.

The response to a previous history of treated malignancy is much more difficult; the key question is how long to wait following treatment of a malignancy before undertaking transplantation. The most commonly used immunosuppressive agents are permissive of tumour growth and best avoided until there is reasonable evidence that cancer treatment has eradicated the tumour.

Malignancies can be separated into low, intermediate and high risk with respect to their potential for recurrence with immunosuppression. Successfully treated non-melanoma skin cancers, in situ carcinomas of the cervix and incidentally discovered small papillary cancers in nephrectomy specimens constitute a low risk group where there need be no delay after the treatment of malignancy before registration for transplantation.

The majority of cancers fall into an intermediate risk group. If there is histological evidence of complete removal of the malignancy and no evidence of recurrent or metastatic disease following appropriate investigation, it is reasonable to consider transplantation two years after treatment.

In a small number of cancers, recurrence can still occur unpredictably even many years after removal of the primary tumour. Malignant melanoma and invasive breast cancer are the most important examples of such cancers and a waiting period of as long as five years may be recommended before such patients can proceed to transplantation. Again, this is not an absolute stipulation.

Advice must be sought from relevant surgical and oncological teams and decisions made on a case-by-case basis after consideration of both the patient's tumour biology, and other factors. These should include the likely prognosis without a transplant, planned immunosuppressive regimen, estimated waiting time, and local and national policies.

7.4.5 Psychosocial Issues

The key issue relates to the risk of non-concordance with medication and medical advice after transplantation. Non-concordant behaviour is an important risk factor for adverse outcomes; this may have been identified earlier as a complicating factor in the management of diabetes or dialysis. The suitability of non-concordant patients for transplantation requires effective multi-disciplinary co-operation.

Psychosocial assessment is an important part of pre-transplant evaluation; pancreas transplant centres must have access to psychiatrists and/or psychologists experienced in transplantation as part of the multi-disciplinary team.

7.4.6 Anaesthetic Considerations

Candidates for pancreas transplantation present challenges for the anaesthetist. These relate to: cardiovascular risk; the fluid balance challenges of a long operation in a patient without renal function; the presence of diabetic autonomic and peripheral neuropathy; reperfusion effects; and difficulties in vascular access.

Reperfusion of the allograft usually has greater haemodynamic consequences during pancreas transplantation compared with a kidney transplant. Hypotension may occur secondary to significant blood loss when the pancreas is reperfused, but may also be caused by the release of vasoactive compounds. This is a complex problem that requires skilful management with fluid and inotropes.

The specialist transplant anaesthetist is an important member of the assessment team, enabling the anticipation of problems that would otherwise only be identified when the patient is admitted for surgery.

7.4.7 Other Pre-operative Assessment Issues

Candidates who have had a stroke or a carotid distribution transient ischaemic event within the last six months must undergo carotid Duplex ultrasonography. Those with internal carotid artery stenoses >70% may be suitable for carotid revascularisation. However, the evidence base supporting carotid intervention in symptomatic patients with chronic kidney disease is sparse. Screening carotid ultrasonography in asymptomatic candidates with chronic kidney disease is not currently thought to be indicated as the benefit to those with stenoses >70% is unclear and carotid intervention is likely to delay listing for transplantation (23).

Osteopenia is common. A DEXA scan for documentation of a patient's baseline status and treatment with bisphosphonates or other appropriate agents should be considered.

Gastrointestinal autonomic neuropathy often presents with a history of vomiting, constipation, or diarrhoea. This is not a contra-indication to transplantation but may inform the clinician of the need to consider pre- and/or post-operative nutritional management. Exacerbation of symptoms of gastrointestinal autonomic neuropathy in the early postoperative period is very common. Many units consider the intra-operative placement of a naso-jejunal or percutaneous jejunostomy tube in such patients.

Autonomic neuropathy causes significant bladder dysfunction in a small number of patients with diabetes. A directed history must be undertaken to assess for this possibility and specialist urological expertise must be sought as required. The presence of autonomic bladder dysfunction is a relative contra-indication to the urinary drainage of exocrine pancreatic secretions.

Coagulation disorders are frequent in this group of patients – a significant proportion of patients with diabetes and renal failure are hypercoagulable (24). Any history of prior thrombosis should be investigated by means of a directed thrombophilia screen, as a positive history represents the greatest risk factor for post-transplantation thrombosis. Thromboelastography may be undertaken during assessment, but is more commonly used at the time of surgery and post-operatively in order to inform anticoagulant management. There is no consensus on the need for testing for pro-thrombotic disorders in pancreas transplant candidates without a history of thrombotic events.

In patients being assessed for pancreas transplantation alone or for islet transplantation, a careful assessment of baseline renal function is required because of the risk of iatrogenic renal injury through calcineurin inhibitor exposure, or intercurrent haemodynamic stress (25). There is also a risk of triggering HLA sensitisation, especially after multiple-donor exposure during islet transplantation. Such patients are at risk of progressing to end-stage renal failure and requiring future renal transplantation.

SPK transplantation in patients under the age of 18 years is rare, as diabetic nephropathy usually takes a decade or more to manifest. Children with hypoglycaemic unawareness who may be candidates for pancreas transplantation alone often have significant psychosocial issues that underlie their poor glycaemic control. Candidates for pancreas transplantation who are aged less than 18 years require the involvement of clinicians with expertise in paediatric organ transplantation and other paediatric specialties.

Pancreas re-transplantation can be considered in selected patients with primary pancreas graft failure. Operative times are likely to be longer, and a US registry analysis showed that allograft outcomes are significantly worse than primary transplants (26). Careful consideration must be given to the risks and benefits for each potential candidate.

Extremes of BMI are significant risk factors for adverse outcomes post-transplantation. Recipients who are underweight (BMI <18.5 kg/m^2) have a higher rate of death after the early post-transplant period than patients with a normal BMI (18.5-25 kg/m^2), while those with a BMI >25 kg/m^2 have higher rates of pancreas graft loss and a higher rate of early post-transplant death (27). Underweight and overweight patients must be offered support with the aim of attaining a normal BMI before listing for transplantation. However, there are no available data on the survival benefit of pancreas transplantation in these patient groups, and it is therefore not possible to be certain at what BMI threshold a pancreas transplant becomes contra-indicated. In patients with type 1 diabetes mellitus, BMI must be taken into account, but each candidate should be considered on a case-by-case basis.

In patients with insulin-treated type 2 diabetes, access to pancreas transplantation in the UK is currently restricted to those with a BMI of <30 kg/m^2 (18). This is primarily due to concerns regarding increased insulin resistance in obese patients in the context of a limited supply of deceased donor organs and increasing rates of type 2 diabetes in the general population; transplant surgical factors may also be more challenging in the obese. Pre-transplant C-peptide level is not a criterion for pancreas transplantation for type 2 diabetes in the UK (18).

Some units routinely measure C-peptide (with concomitant glucose levels) and diabetes autoantibodies during patient assessment for transplantation. These values can be useful as a baseline to compare post-transplantation, and also to confirm the diagnosis of type 1 or type 2 diabetes, as these are often misdiagnosed. Given current UK eligibility criteria, C-peptide measurement is especially important in potential candidates for pancreas transplantation with a BMI of 30 kg/m^2 or more. Interpretation of C-peptide values (and the diagnosis of type 1 or type 2 diabetes) can be complex in patients with renal failure, and may need discussion with a transplant diabetologist.

7.5 Discussing Transplant Options

Patients with insulin-treated diabetes who are considered suitable for transplantation following initial evaluation should be counselled carefully about their treatment options, of which there are many. This process requires good communication skills by the assessing clinician, the provision of detailed, high quality written information, and the support of a knowledgeable and experienced transplant co-ordinator. Patients must be

given information on the risks and benefits of each option, the estimated survival benefits, and the likely impact on quality of life and existing complications of diabetes. Ethical and medico-legal principles must be adhered to (see Chapter 3 – Ethics). Patients must be given time for reflection and discussion with families and friends. These discussions are complex, and multiple meetings with transplant clinicians may be needed.

Patients with type 1 diabetes and chronic kidney disease have multiple options, including SPK transplantation and deceased donor kidney transplantation alone (with or without a subsequent PAK transplant); those with a potential living kidney donor also have the alternative of living donor kidney transplantation alone (with or without PAK transplantation).

Potential recipients who meet the criteria for a SPK transplant and do not have a living donor face a relatively clear decision, as SPK transplantation is associated with better long-term patient survival than deceased donor kidney transplantation alone (5). In the UK, the waiting time for SPK transplantation is far shorter than for deceased donor kidney transplantation.

Patients with a potential living kidney donor face a more complex decision, as patient survivals after SPK transplantation and living donor kidney transplantation alone are approximately equivalent (6,7). Other factors should be considered such as the patient's dialysis status, local waiting times for SPK transplantation, co-morbidities and risk of disease progression, severity of diabetic complications (and the patient's desire to become normoglycaemic), and the window of opportunity for the living donor to donate (28,29).

In those patients with type 2 diabetes who meet the criteria for SPK transplantation without a living donor, there is little choose between SPK transplantation and deceased donor kidney transplantation alone in terms of patient survival (30). Factors such as the patient's wish to be insulin-free and their willingness to accept early peri-operative morbidity should be taken into account. A large US registry analysis has shown that living donor kidney transplantation appears to bring patient and graft survival benefits over SPK transplantation in selected patients with type 2 diabetes (30), and patients must be informed of this evidence.

Other details on outcomes after pancreas transplantation are described in Chapter 12.

Insulin-treated patients with diabetes and chronic kidney disease, in whom SPK transplantation is considered too high-risk, can now be considered for simultaneous islet and kidney (SIK) transplantation. This is most relevant for those with significant cardiovascular disease who are expected to be unable to tolerate the prolonged anaesthesia required for SPK transplantation and the high rate of operative re-intervention. It is important that patients are informed of the relatively high risk that the donor pancreas may not provide the necessary transplantable yield of islets.

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Chapter 8 RECIPIENT SELECTION: ISLETS

Recommendations

We recommend that:

- Potential islet transplant recipients must first be seen in a specialist hypoglycaemia clinic to optimise their medical management. (Not graded)

- Potential islet transplant recipients with problematic hypoglycaemia must follow an evidence-based approach to optimise medical management as part of their assessment process. This must include structured education (e.g. DAFNE) and sensor augmented insulin pump therapy before islet transplantation is considered. (B1)

- Islet transplantation must be considered for patients with type 1 diabetes that have on-going problematic hypoglycaemia (defined as more than two episodes of severe hypoglycaemia in the last two years and impaired awareness of hypoglycaemia) despite optimal medical management. (B1)

- Islet transplantation must be considered for patients with type 1 diabetes that have a functioning renal transplant but are unable to achieve optimal glycaemic control despite optimised conventional therapy. (B1)

8.1 Introduction

Hypoglycaemia is one of the most feared complications of diabetes treatment. Impaired awareness of hypoglycaemia affects around 17-40% of patients with Type 1 diabetes mellitus (T1DM) and increases the risk of severe hypoglycaemia (SH) three- to six-fold (1-3). SH is defined as “an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions”, occurs in around 25% of patients with T1DM, and contributes to substantial morbidity (2,4). It can be assessed using one of several assessment tools. The most common are the Gold score (5), the Clarke score (6), and the Pedersen-Bjergaard score (7). Geddes et al reviewed these three assessment methods and concluded that the Gold and Clarke scores were more specific and should preferentially be used (8).

Attempts to restore awareness of hypoglycaemia using medical interventions, under the guidance of a specialist diabetologist, must be the initial step in management for these patients. A meta-analysis by Yeoh et al on the outcomes of these interventions concluded that structured diabetes education and frequent contact (which may include behavioural therapies), with the use of flexible insulin therapy, is the best initial step (9-15). If further intervention is required, the use of advanced diabetes technology, such as continuous subcutaneous insulin infusion and continuous glucose monitoring, can improve impaired awareness of hypoglycaemia and reduce the frequency of severe events (10).

8.2 Benefits of Islet Transplantation

Successful islet transplantation is a relatively recent development, ushered in by the Edmonton group in 2000 (16). Since then, islet transplantation has expanded but still accounts for just 10% of all beta-cell transplants. Twenty to thirty islet transplants are performed each year in the UK.

The aims and outcomes of islet transplantation currently differ from pancreas transplantation. Rather than insulin independence, the goal of islet transplantation is substantial, or complete, remission from episodes of SH along with improved glycaemic control. Graft survival is defined as C-peptide positivity, rather than insulin independence. Details on outcomes after islet transplantation are described in Chapter 13.

Given the relatively small number of islet transplants performed and the short follow-up period, it is still too early to demonstrate a beneficial effect on patient survival. With increasing graft survival beyond five years after islet transplantation (17), this is expected to change, especially given the mortality burden associated with hypoglycaemic unawareness.

A systematic review has demonstrated reduced fear of hypoglycaemia and improved diabetes-specific quality of life measures after islet transplantation (18), but detailed analyses of broader measures of quality of life (including the effect of immunosuppression-related complications) have not yet been done. The impact of islet transplantation on micro- and macro-vascular complications of diabetes is discussed in Chapter 13.

8.3 Patient Assessment Prior to Islet Transplantation

Potential islet transplant recipients with problematic hypoglycaemia must follow an evidence-based approach to optimised medical management as part of their assessment process. An international group has performed a systematic review for all interventions to restore hypoglycaemia unawareness and have published their findings as a pathway for patients with problematic hypoglycaemia (Figure 1) (19). In particular, recent studies have demonstrated the benefits achieved with new technology in this group of patients, achieving between 60-87% reduction in severe hypoglycaemia (20,21). Patients should be seen in a centre with experience both in using these technologies and in dealing with patients with type 1 diabetes and recurrent hypoglycaemia.

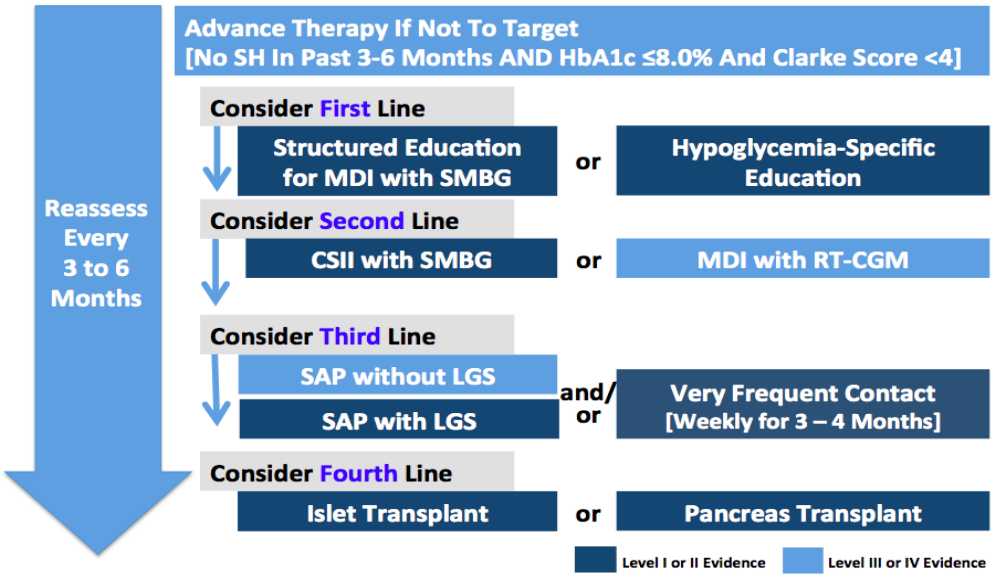
If optimal medical management is unsuccessful, then patients must be considered for islet transplantation. The clinical assessment and work-up tests are the same as for pancreas transplantation, though imaging of the aorto-iliac arteries and peripheral arteries is only required where clinically indicated. Liver ultrasonography must be performed to identify pathologies that may increase the risk of islet administration via the portal vein. In addition, C-peptide levels, liver function tests, and diabetes autoantibodies are required, along with LDL levels. Estimated and measured GFR is required, due to concerns about the effect of calcineurin inhibitor immunosuppression on renal function after islet transplantation (22,23).

8.3.1 Indications for Islet Transplantation

NICE guidelines recommend that islet transplantation must be considered in patients with T1DM who are ≥18 years old and who continue to have problematic SH despite optimised medical therapy (24). This includes structured education such as DAFNE, insulin pump therapy and a trial of continuous glucose monitoring, ideally with a sensor augmented pump. In the UK, patients must have had more than two episodes of SH in the last two years, have impaired awareness of hypoglycaemia, and have been confirmed by a diabetologist to have disabling hypoglycaemia (25).

Figure 1 Management pathway for patients with type 1 diabetes and problematic hypoglycaemia, prior to consideration of islet transplantation (19).

CSII – continuous subcutaneous insulin infusion. LGS – low glucose suspend. MDI – multiple daily injections. RT-CGM – real-time continuous glucose monitoring. SAP – sensor augmented pump. SMBG – self-monitoring of blood glucose.



Islet transplantation must also be considered in patients with T1DM who have had a renal transplant and who have a history of SH within the last two years, or suboptimal glycaemic control (defined as HbA1c >7% (53 mmol/mol)) (24,25). Adequate stable renal allograft function is required for transplantation, with GFR >40 mL/min/1.73m^2.

Eligibility criteria widely used internationally (25,26) include:

- 18 to 65 years of age
- Undetectable C-peptide levels
- More than five years since diagnosis of T1DM
- Recurrent neuroglycopaenia, including impaired awareness of hypoglycaemia or severe glycaemic lability which is resistant to intensive insulin therapy

The age criteria above are guidelines only and patients must be considered on a case-by-case basis.

In the UK, undetectable C-peptide levels are not required for patients otherwise eligible for simultaneous islet kidney (SIK) transplantation, given the challenges in measuring C-peptide in those with renal failure. In this patient group, C-peptide must be <200 pmol/L with concomitant glucose >5 mmol/L. In addition, patients for SIK transplantation do not require a history of SH. Patients must have insulin-treated diabetes and a calculated or measured GFR of <20 mL/min/1.73m^2 at the time of listing (25).

8.3.2 Contraindications for Islet Transplantation

Absolute contraindications include (25-27):

- Insulin requirements >1 U/kg/day
- Weight > 85 kg
- Nuclear medicine GFR <60 mL/min/1.73m^2 (except in those for SIK or IAK transplantation)
- Detectable fasting or postprandial blood C-peptide (>0.3 ng/mL)
- Incurable malignancy
- Active sepsis
- Active peptic ulceration
- Major psychiatric history likely to result in non-concordance
- Inability to withstand immunosuppression
- Excessive cardiovascular risk

Relative contraindications include (25-27):

- Substance abuse (including tobacco)
- HbA1c >12% (107.7 mmol/mol)
- Body mass index (BMI) >28 kg/m^2
- Progressive, severe complications of diabetes
- Untreated coronary artery disease
- Unstable retinopathy
- Proteinuria >300 mg/day
- Nuclear medicine GFR 60-80 mL/min/1.73m^2
- Untreated hyperlipidaemia (LDL cholesterol >130 mg/dL)
- BP >160/100 mmHg despite maximal antihypertensive therapy
- Chronic infection (e.g. HCV/HBV/EBV)

- Liver changes (threefold increases in liver enzymes, cholestasis, haemangioma)
- Calculated reaction frequency (anti-HLA antibodies) >20%
- The need for long-term oral steroid therapy

The assessment of infection, malignancy, and psychosocial issues is in line with those for pancreas transplantation (see Chapter 7). As portal vein cannulation for islet infusion can be achieved under local anaesthesia and conscious sedation, the degree of cardiovascular fitness required for an islet transplant is less than that for a pancreas transplant. As with assessment of potential candidates for pancreas transplantation, decisions on the suitability of patients for islet transplantation must be made on a case-by-case basis.

In the UK, there is provision for considering patients who fall outside the standard criteria through a request for an 'exception', to be made by individual application to the NHSBT Pancreas Advisory Group.

8.4 Discussing Transplant Options

The principles already outlined for discussion of pancreas transplant options also hold true for discussing treatment options for patients considering islet transplantation (see Chapter 7). Patients who are suitable for both pancreas transplantation and islet transplantation should have the expected risks, benefits, waiting times, and relative graft survivals (and how these definitions differ) of both treatments explained in detail. Many factors need to be taken into account when counselling patients about their beta-cell replacement options, including local post-transplant outcomes, waiting times, listing criteria, the patient's wishes for insulin-independence, and their cardiovascular fitness. Details on outcomes after islet transplantation are described in Chapter 13.

At present, SIK transplantation is primarily reserved for those patients who are deemed not fit enough for SPK transplantation. Outcome data on SIK transplantation are limited to a small number of reports, but suggest similar kidney graft outcomes and HbA1c between the two different treatments but a higher rate of insulin independence in the SPK group at the cost of higher early post-operative morbidities (28,29). Similarly, PAK transplantation is more likely to deliver insulin-independence than islet after kidney transplantation, but with increased early risks (30).

In some centres, the rates of insulin independence after islet transplantation are approaching those of PTA (31). With advances in the field, these findings are likely to become more widespread.

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Chapter 9 PANCREAS TRANSPLANTATION AND PERI-OPERATIVE CARE

Recommendations

We recommend that

- Cold ischaemic time independently impacts on pancreas graft outcome, and must be minimised. (B1)
- Bench preparation of the pancreas must be performed by an appropriately trained surgeon in the correct environment and with adequate organ cold preservation. (D1)
- There are a variety of surgical techniques for pancreas bench preparation and implantation, but within units we recommend that a standardised approach is used for the majority of patients. There is not enough evidence to suggest that a specific surgical approach is clearly superior. (Not graded)
- Every pancreas transplant must have a thromboprophylaxis protocol. There is not enough evidence to suggest that a specific approach is clearly superior. (Not graded)
- Early hyperglycaemia must be investigated with either cross-sectional imaging or exploration of the graft. (D1)
- Pancreas re-transplantation must be considered in all patients with original graft failure, independent of the original graft type or when the graft fails. (B1)

We suggest that

- Managing the exocrine secretions of the graft by either bladder drainage or enteric drainage must be tailored to the individual patient and be within the experience of the surgeon and transplant centre. (D2)

9.1 Introduction

The inspection, preparation, and implantation of the pancreas are key steps that directly affect both short- and long-term pancreas graft survival, and which may be influenced by the transplant team. Similarly, the cold ischaemic time (CIT) of the pancreas is another factor that falls directly within the remit of the implanting team, and must be kept as short as possible. Efficient patient preparation, organ retrieval (Chapter 5) and transport, immunological assessments (Chapter 11), and surgical and anaesthetic techniques all contribute to minimise organ CIT.

All UK centres have made progressive reductions in pancreas cold ischaemic times within recent years. For DBD donors, the median CIT in the UK in 2006 was 13 hours, and by 2016 had fallen to 11 hours; while the corresponding figures for DCD donors were 14 and 10 hours respectively. The ‘safe’ CIT for pancreas transplantation has not yet been identified and the CIT must be minimised for all transplants (1).

Bench work and implantation techniques are described below, along with key issues in the peri-operative management of the pancreas transplant recipient.

9.2 Workbench Preparation of the Pancreas

The workbench preparation of the pancreas allograft is arguably one of the most important aspects of pancreas transplantation (2). It offers the best and final opportunity to visualise the quality of the allograft, as well as ensuring there is no retrieval-related damage or anatomical abnormality that would render the organ unsuitable. Workbench preparation of the pancreas should start as soon as possible after the organ has arrived at the recipient hospital. It must be done in a calm, patient and meticulous manner to minimise postoperative complications that can arise from benching mistakes.

It is recognised that there will be variation between pancreas transplant centres in workbench preparation, particularly in relation to who does the bench work, how many surgeons are involved, and the set-up and instruments used. This chapter does not aim to standardise these operational aspects but, instead, offers one approach to the crucial steps of organ preparation. However, in order to minimise pancreas CIT, it is recommended that two surgical teams are present; one to perform the pancreas (and kidney) bench work, and the other to start the recipient laparotomy once the organs have been judged suitable for implantation.

9.2.1 Preparing the Workbench

Given that workbench preparation can take between 1-2 hours, it is important that the bench is set up in an orderly fashion so as to minimise the risk of lost swabs and needles or misplaced instruments. A number of centres have moved to having a designated scrub nurse involved with the workbench process. It is essential that the pancreas is appropriately cooled throughout the benching process. The pancreas should be bathed in cold preservation solution appropriate for the organ (e.g. University of Wisconsin (UW) solution). No ice should come into direct contact with the pancreas because of the risk of freezing. There is wide variation regarding instruments used for the preparation process. There is no evidence to suggest that any instrument confers specific benefit and the approach used will be at the discretion of the surgeon.

When ready, the pancreas is taken out of its transportation box. Apart from the standard checks of the organ paperwork, the surgeon must also check that vessels are present along with the pancreas. In the case of SPK transplantation, it is suggested that the kidney is also removed from its transportation box at this stage for brief inspection, thus ensuring that the organ is suitable for transplantation.

9.2.2 Inspection of the Pancreas

Once in the UW-filled dish, the pancreas should be carefully inspected to ensure that it is suitable for transplantation. This must be meticulous and systematic. Bench work preparation of a pancreas must be performed by an appropriately trained surgeon in the correct environment with adequate organ cold preservation.

The graft should be inspected for its fat content and perfusion, and palpated to detect fibrosis and tumours. Observations should be made regarding any swelling and oedema of the pancreas and for the presence of haematomas, as well as evidence of pre-mortem pancreatitis. The following must also be carefully inspected: pancreatic capsule (tears); parenchyma (perfusion and damage); portal vein (length and quality); superior mesenteric artery (SMA – quality and damage); splenic artery (quality and damage); mesenteric root (length and presence of staple line); proximal and distal gut staple lines (leakage); and duodenum (perfusion, damage, haematomas).

The final aspect of the inspection phase is the examination of the donor vessels (common iliac artery (CIA) with internal and external iliac arteries). Occasionally,

additional vessels will be supplied if the iliacs are diseased or damaged, e.g. arch of the aorta with brachiocephalic, left common carotid, and left subclavian arteries. The resultant 'Y' arterial conduit must be carefully viewed for evidence of atheromatous disease and damage. A key area to inspect for traction injury or a dissection-related injury is at the point that the CIA divides into the internal and external arteries. If there is a sizable hole, care has to be taken with the repair, as suturing can lead to a stenosis that will impact on flow. Although the donor iliac vein is rarely used, it should also be inspected for quality and damage.

9.2.3 Workbench Preparation

When the benching surgeon is satisfied that the allograft is of appropriate quality and can be transplanted, the key steps of the benching process can start. These steps include:

- Removal of the spleen from the tail of the pancreas
- Shortening of the duodenum and further ligation of the common bile duct (CBD)
- Removal of excess fat along the inferior pancreatic border with ligation of the inferior mesenteric vein (IMV)
- Shortening and over-sewing of the mesenteric root
- Removal of excess fat along the superior border of the pancreas
- Elongation of the portal vein
- Creation of the 'Y'-graft anastomosis
- Flushing and ligation of the gastroduodenal artery (GDA)

The spleen should be left in place during the retrieval operation to provide a handle during the removal process and to minimise the handling of the parenchyma. However, previous donor splenectomy is not a contraindication to successful pancreas transplantation (3). Current practice is to remove the spleen from the tail of the pancreas during benching. This process should involve careful dissection of the splenic vessels within the hilum of the spleen as far away as possible from the tail of the pancreas. Once identified, each vessel should then be double ligated with 2/0 or 3/0 polyglactin 910 ties and divided. Mass ligation should be avoided as post-reperfusion bleeding may be increased and there is also a risk of subsequent arteriovenous fistula formation (3). The peri-hilar fatty tissue is then either ligated with ties and divided, or separated with a harmonic scalpel or Ligasure™ until the spleen is completely removed.

The pancreas is routinely retrieved en-bloc with the duodenum from the level of the pylorus to the duodenal-jejunal junction near the ligament of Treitz. Gut leaks risk contamination by gut flora and infectious complications in the recipient such as fungal arteritis and the development of mycotic aneurysms (4). Opening of the CBD should be avoided to reduce the risk of contamination of the pancreas with gut flora. Many surgeons place an additional 2/0 polyglactin ligature to the CBD.

At benching, the duodenum will most probably need shortening in order to remove acid-secreting cells, especially if the pylorus remains. The duodenum should be carefully dissected away from the pancreas down to the proximal point of D1 and from the duodenal-jejunal junction to the distal part of D3. At these landmarks the duodenum is resected with a stapler, and both staple lines are then inverted with either a running or interrupted seromuscular 3/0 polydioxanone or polpropylene suture (Figures 9.1 and 9.2). As a general rule, it is better to leave the duodenum slightly longer as it will end up shorter than expected after inversion of the staple line. If too much of the duodenum is dissected away from the pancreas then there can be a compromise to the collateral flow to the head of the pancreas as well as the likelihood of a pancreatic leak (3). Preparation of the duodenum for a bladder-drained implantation is done in exactly the same way.

There are different views and approaches to the handling of the contents of the duodenum. During the bench process, some centres evacuate the contents of the duodenum and then flush it with antibiotics. There is no evidence to support this approach and there is a significant risk of contamination of the workbench solution, so this approach is not recommended. It is safer to keep the duodenum closed until after reperfusion, when the duodenum is formally opened to construct the anastomosis with either the recipient’s bowel or bladder. Once the duodenum has been prepared it is suggested that the UW solution in the dish is changed so as to minimise contamination.

The transverse mesocolon can be carefully removed from the inferior border of the pancreas. During dissection of this tissue the IMV is identified and double ligated, as it is often not ligated during the retrieval operation.

During the retrieval operation, the root of the small bowel mesentery should have been stapled at least 2 cm away from the uncinate process and head of the pancreas in order to avoid injury to the inferior pancreaticoduodenal artery. Occasionally the root can be

very short, which should raise concerns regarding whether the blood supply to the inferior portion of the head of the pancreas is intact. In this situation, the SMA can be gently flushed with preservation solution to determine if back flushing occurs through the open GDA, which would indicate an intact pancreatico-duodenal arch. The mesenteric root should be shortened if it has been left long and this can be done using a vascular stapler. Even with the use of a vascular stapler there is not always adequate haemostasis and therefore when the root is the desired length it should be oversewn using a 3/0 or 4/0 polypropylene suture. It is important to note that mesenteric root closure can result in the development of an arteriovenous fistula between the SMA and superior mesenteric vein (SMV), though this is rare.

The superior border of the pancreas generally requires less preparation that its inferior counterpart. This is in part due to the fact that some dissection will have occurred during the retrieval operation in order to identify the splenic artery, SMA, GDA and portal vein. Also, the splenic artery often has a tortuous course and may well be found in the extrapancreatic tissues well away from the pancreas proper. The splenic artery and SMA should be gently dissected away from surrounding fibro-fatty tissue in order to be ready for the 'Y'-graft anastomosis.

To ensure that the portal vein is long enough for transplantation, it should firstly be inspected to ensure that the venous confluence of the splenic vein and SMV are intact with a rim of at least 1 cm of portal vein proximal to the confluence. This is usually enough for transplantation to proceed. Two 6/0 polypropylene sutures can be placed in the 3 o'clock and 9 o'clock positions on the portal vein and the vein pulled out from within the pancreas under gentle traction. This enables the surgeon to carefully ligate and divide the superior pancreatico-duodenal and coronary veins (if present) and provide extra venous length for implantation (Figure 9.3). Rarely, donor iliac vein can be used to create an extension vein graft on a portal vein that is <1 cm in length. If the vein is too short, careful consideration should be given to abandoning transplantation. Most UK surgeons prefer to avoid a venous extension graft; although a large US registry analysis did not find an association between venous extension grafts and graft loss (5), an analysis by UKT showed worse outcomes.

Perhaps the most critical part of benching is that of creating the 'Y'-graft anastomosis. The arterial supply to the pancreas is from the splenic artery, GDA and SMA. During the retrieval process these vessels should have been preserved, with the SMA and

splenic artery having been divided near their origin. The GDA should have been divided, but not ligated, a few millimetres from its origin with the common hepatic artery. It is preferable to achieve arterial perfusion of the pancreas with a single arterial anastomosis and therefore the splenic artery and SMA need to be bought together on a common stem to achieve this. A number of techniques have been used (6-9), but the most common technique for arterial reconstruction is to utilise a naturally bifurcating artery, such as the donor common iliac artery, as a 'Y'-graft. Creation of a 'Y'-graft involves anastomosing the donor internal iliac onto the splenic artery and the external iliac onto the SMA (Figure 9.4). The internal and external iliac vessels should not be left long, so that the risk of twisting or kinking is reduced. The internal iliac to splenic artery anastomosis should be done first as this is more technically challenging. 6/0 polypropylene should be used for the anastomosis, and this can be done in either an interrupted or continuous fashion. Once the splenic artery anastomosis has been performed, attention moves to the SMA. There is generally a good size match between the external iliac and the SMA and again this can be done as an end-to-end anastomosis. In practice, the relative position of the splenic artery in relation to the SMA means that the external iliac sometimes has to be cut at an angle to get the best possible inline flow effect from the common iliac into the SMA. 6/0 polypropylene sutures should again be used in either an interrupted or continuous fashion. When performing both anastomoses, care must be taken to keep the orientation of the arteries in a plane that avoids any twisting or rotation that could subsequently affect perfusion. The completed 'Y'-graft should then be flushed with cold preservation fluid to check for any leaks or technical errors. The pancreas should not be flushed with UW from the bowl, as this may contain particulate matter (e.g. fat). It is important to note that the venous effluent of the pancreas is almost always sanguinous because of the capacity of the spleen; attempts to flush the pancreas to render the venous effluent clear are discouraged (2,3).

Bench preparation is now almost complete. For many surgeons, the last phase involves gently flushing and ligating the GDA. The GDA should be inspected to ensure that perfusate is flowing out of it when the 'Y'-graft is flushed, suggesting that the pancreatico-duodenal arch is intact. If the GDA has not been needed for vascular reconstruction it now can be doubly ligated. Very occasionally, the GDA will have been ligated during the retrieval operation. In this situation it is advisable to remove the ligature and gently open the artery to assess perfusion qualities as already outlined. This also provides the option of using the GDA for duodenal revascularisation if needed. With the 'Y'-graft complete and flushed, the pancreas is now ready for implantation.

9.3 Pancreas Implantation

The implantation techniques discussed in this section apply to both SPK and pancreas-only transplants (PAK and PTA transplantation). There are a variety of surgical techniques for pancreas implantation and not enough evidence to suggest that a specific surgical approach is clearly superior; however, we recommend that each transplant unit adopts a standardised approach for the majority of patients.

9.3.1 Incision

Although a supra-inguinal extraperitoneal approach has been used successfully by some (10), most centres in the UK perform the procedure intra-peritoneally through a midline incision. Intra-peritoneal placement of the pancreas graft may facilitate absorption of the fluid that is often produced in the vicinity of the gland; however, it can also be associated with an increased incidence of post-transplant peritonitis and intra-abdominal fungal infection (11).

The pancreatic implant is preferentially performed in the right of the recipient, since the right CIA is more accessible and the inferior vena cava (IVC) lies on the right. For SPK transplantation, the kidney is usually placed in the left iliac fossa, and many units use a separate incision for this.

9.3.2 Exposure

After entering the peritoneal cavity, the right colon and small bowel are mobilised to expose the retroperitoneal structures. The mobilisation is continued until the third part of the duodenum is encountered. If systemic venous drainage is planned, the right common iliac vein or lower end of the IVC is most commonly used for graft venous outflow. In order to facilitate this, the right common iliac artery and target vein are circumferentially dissected. If portal venous drainage is to be undertaken, the SMV can be used and therefore the SMV and its tributaries should be exposed and isolated within the root of the mesentery. In patients undergoing bladder drainage of exocrine secretions, the right common and external iliac veins should be mobilised.

If the kidney is to be placed intra-peritoneally, some surgeons prefer to mobilise the sigmoid colon and left iliac vessels prior to kidney implantation, to reduce the risk of retractors damaging the pancreas if vessels on the left are mobilised after pancreas implantation. The impact of pancreas CIT on outcome must be kept in mind if this

strategy is adopted. Implanting the kidney before the pancreas is not recommended due to associated prolonged pancreatic CIT (12).

9.3.3 Implantation techniques

Implantation techniques for pancreas transplantation have evolved considerably over time. Most of the variation has been in relation to management of the exocrine secretions (13-15), and controversies related to venous drainage (portal or systemic route) (16). Currently, most transplanting centers in the UK use enteric exocrine drainage and systemic venous drainage. If bladder drainage is used, the pancreas must be implanted 'head down'.

The arterial 'Y'-graft of the pancreas is usually anastomosed to the recipient's right CIA and the donor's portal vein to the right common iliac vein or the IVC. Both are usually done as an end-to-side anastomosis using either 5/0 or 6/0 continuous polypropylene sutures. In the case of severe atherosclerosis of the recipient right CIA, the aorta, right internal iliac artery or external iliac artery may be used if free of significant atheroma. It is preferable to keep the arterial conduit as short and as straight as possible.

Venous extension grafts can be used to salvage a pancreas with a short portal vein or to facilitate an easier anastomosis. While a US study showed the use of venous jump grafts was not associated with increased graft loss or mortality (5), data from UKT is less supportive and many surgeons remain concerned that the use of such grafts increases the risk of graft thrombosis.

An alternative venous outflow technique is to anastomose the portal vein to the SMV. Portal drainage of the pancreas is more physiologic with respect to immediate delivery of insulin to the recipient liver. This results in reduced circulating insulin levels relative to those in systemic venous-drained pancreas grafts (16,17) and aims to avoid potential complications related to hyperinsulinaemia (i.e. accelerated arteriosclerosis and dyslipidemia). While some experimental models have suggested a benefit for portal drainage of insulin (18), convincing evidence is still lacking in the clinical setting (19).

Four studies have analysed the outcome of venous drainage technique (20-23). Although the one-year graft survival rates were comparable between both groups and the venous thrombosis rates were similar (4-7%), there was a trend towards lower surgical complication rates (early re-laparotomy, bleeding, or leakage) in the portal

drainage group. In the two prospective studies (20,21), one demonstrated a trend toward lower surgical complication rates in the portal drainage group (4/17 vs. 7/17) (21), and the other a trend toward lower intra-abdominal infections (11% vs. 26%) (20). Glycaemic control was excellent using both techniques, but a retrospective study observed less hyperinsulinaemia after portal drainage (23).

Based on the available data from these series, it can be concluded that portal venous drainage provides minimal (if any) advantage over systemic drainage. Potential disadvantages of portal venous drainage include poor access for percutaneous biopsy due to surrounding bowel loops, and the risks of venous torsion. Given these issues, and the absence of strong prospective evidence favouring one technique over the other, either method of venous drainage is acceptable.

9.3.4 Exocrine drainage

Historically, SPK transplantation was associated with a high morbidity due to intra-abdominal sepsis. This was ascribed to anastomotic leakage believed to be due to duodenal rejection (24). Bladder drainage was introduced in 1983 in order to reduce the incidence of postoperative technical complications, in particular a reduction in intra-abdominal sepsis (14). This technique allowed for the early detection of graft rejection by measuring serial urine amylase, especially for solitary pancreas transplants. However, chronic complications occurred in up to half of patients (e.g. urinary tract infection, cystitis, urethritis, reflux pancreatitis, haematuria, metabolic acidosis and dehydration), leading to conversion to enteric drainage in approximately a quarter of the recipients. By the late 1990's, most centers had converted to primary enteric drainage, not only for SPK transplants, but also for solitary pancreas transplants (25).

To date there have been no prospective trials comparing bladder-drained to enteric-drained grafts. There have been a number of single-center retrospective reviews, all of which showed little difference in patient and graft outcomes but all showing a significantly increased rate of urinary tract infection and urological complications in the bladder-drained patients (17,26-29).

One of the difficulties associated with enteric drainage is the management of an anastomotic leak, which often needs further surgery if the patient becomes septic. However, a leak after bladder drainage can usually be managed with long-term urinary catheterisation. To help the management of a leak in an enterically-drained graft, if it

occurs, some surgeons prefer to use a Roux-en-Y to isolate the pancreas (30).

The use of primary enteric drainage reduces the incidence of urological complications, with no significant differences in graft survival rate between the two techniques. This analysis favors enteric drainage, and the majority of centers currently perform this technique.

9.4 Re-transplantation

Re-transplantation in SPK recipients is becoming increasingly frequent and surgeons are often asked to evaluate recipients for re-transplantation. The technical demands of repeat SPK transplantation are significant. Re-operating on previously dissected iliac vessels as well as deciding on when to remove previously transplanted organs requires pre-operative planning and intra-operative flexibility.

There is little published evidence to help clinicians decide which patients are likely to derive the most benefit from pancreas re-transplantation. Unpublished UK data show that 62 patients underwent pancreas re-transplantation between 1998-2010 and that the one-year graft survival of the second pancreas was 85%, which compares favourably with the 87% one-year pancreas graft survival of all UK first SPKs between 2007-2010 (n=552). In contrast, a US study looking at repeat SPK transplantation in prior SPK recipients found that pancreatic allograft survival was 78% at one year and 67% at two years (31). A US registry analysis demonstrated worse graft survival outcomes in pancreas re-transplantation (32). This suggests significant variations between centres and possibly surgeons.

In most repeat transplants, the distal IVC can be used for pancreatic venous drainage. Where the distal IVC or right-sided iliac venous system is inaccessible, portal venous drainage can be employed, or the pancreas can be positioned in a head-down position and drained via the left iliac system. A long donor iliac ‘Y’-graft will provide flexibility for choosing an appropriate portion of recipient artery for implantation. Transplant pancreatectomy is generally required for adequate mobilisation of the bowel and for access to the iliac vessels, as well as for additional space in which to position the allograft, especially in instances of primary enteric drainage. A chronically rejected pancreatic allograft that is small and fibrotic may be left in place, as it does not impede mobilisation. A transplant nephrectomy may also be required, depending on space and

whether SPK or pancreas transplantation alone is indicated. As in pancreas re-transplantation, significant flexibility is required to determine the optimal site for implantation.

In addition to the increased technical complexities of re-transplantation, the immunologic barriers of re-transplantation offer additional challenges. All recipients should be regarded as higher immunologic risk recipients and receive appropriate immunosuppression (see Chapter 11).

Pancreas re-transplantation can be associated with acceptable one-year patient and graft survival. Therefore pancreas re-transplantation must be considered in all patients presenting with original graft failure independent of the original graft type and when the graft failed.

9.5 Peri-operative Care

The pancreas allograft is associated with the highest surgical complication rate of all solid organ transplants. During the early 1980s, 25% of all pancreas grafts worldwide were lost from surgical complications ('technical failures'). Since then, surgical and anaesthetic technique has significantly improved and the most recent data suggest technical failure rates to be between 7 and 9% (33). Despite these improvements, surgical complications after pancreas transplantation remain relevant, because even contemporaneous series report re-laparotomy rates as high as 35%.

A retrospective analysis by Troppmann et al highlighted the impact of surgical complications on morbidity, hospital costs, and allograft and patient survival rates (11). Pancreas complications were found to be associated with increased perioperative mortality and decreased patient survival rates. It is important to ensure that graft salvage should not compromise recipient mortality. Graft pancreatectomy should therefore be considered in order to avoid further morbidity, and possible mortality.

The transplant recipient is prone to a number of peri-operative problems, most of which result from ischaemia-reperfusion injury, and which include graft thrombosis, inflammation and infection, and glucose control. Recipients of pancreas transplants should be cared for in a level 2 or 3 facility (i.e. a high dependency unit or intensive care unit) immediately post-transplant, depending on the individual patient's needs.

9.5.1 Thromboprophylaxis

In most units, pancreas graft thrombosis remains the most frequent serious surgical complication, occurring in 3 to 12% of grafts (34). With rare exceptions, it results in the need for re-laparotomy and transplant pancreatectomy. The aetiology of pancreas graft thrombosis is multifactorial, including donor risk factors, back table preparation techniques, and suboptimal post-operative strategies to minimise the risk of thrombosis. CIT in excess of 12 hours has also been identified as a significant independent risk factor for pancreas graft thrombosis (35).

Clinical symptoms of pancreas graft thrombosis include the sudden onset of otherwise unexplained hyperglycemia (arterial or venous thrombosis); graft tenderness and enlargement (venous thrombosis); dark, massive haematuria (venous thrombosis of bladder-drained grafts); or markedly decreased or absent urinary amylase on a spot urinary amylase check (arterial or venous thrombosis of bladder-drained grafts). The diagnosis must be made quickly, utilising imaging studies or early re-laparotomy.

The pancreas is susceptible to venous thrombosis at a micro and macrovascular level due to the delicate organ structure, extensive microvascular bed, and low flow state after mesenteric and splenic ligation. Direct portal venous cannulation (rather than SMV or IMV cannulation) to perfuse the liver is essential, as well as venting of the portal vein to minimise back pressure within the pancreas venous system and capillary bed.

Ischaemia-reperfusion induces an element of graft pancreatitis, which for the majority of cases is self-limiting and resolves with conservative management. The pancreatitis reduces intra-parenchymal capillary flow and creates a procoagulant, thrombogenic local milieu within the (already) low flow graft. Hypercoagulable recipients are also at higher risk for losing their pancreas graft and patients with a strong history of thrombosis should therefore undergo a detailed thrombophilia screen pre-operatively and have a clear perioperative anticoagulation plan.

Because of the above factors, thromboprophylaxis is critical in the early post-operative period and pancreas transplant centres must have management protocols in place. As yet, there is no rigorous evidence base as to the best strategy. Antiplatelet agents such as aspirin are administered in most centres although a significant number of patients may already be on such treatment as part of their diabetic and renal medication strategy. Additional strategies reported by some institutions include low-dose

unfractionated heparin infusion, subcutaneous unfractionated or low molecular weight heparin, dextran, or prostacyclin infusion. Whatever the local strategy, it is accepted that thromboprophylaxis will be associated with an increased re-laparotomy rate for bleeding, as an unavoidable consequence of an aggressive anticoagulation protocol. However, this is felt to be preferable to a high graft loss rate due to thrombosis.

Perhaps more important than the specific thromboprophylaxis strategy is the approach to monitoring and measuring the degree of coagulation in a patient. In centres that use intravenous unfractionated heparin infusions, APTT will be routinely recorded in order to adjust dosing. An alternative method is the use of thromboelastography. A number of centres now use thromboelastograph monitoring to test the patient's ability to form a clot, the strength of the clot when it is fully formed, and how quickly it is broken down (36). The test generates a coagulation index score that clearly defines the hypo- and hyper-coagulable state and can also allow for any heparin effect.

If thrombosis occurs, the location and extent of the thrombus, the graft function and perfusion, and the recipient's clinical state will determine management (37). Small non-occlusive thrombus with evidence of good graft enhancement may initially be managed with aspirin alone, or treatment doses of unfractionated or low molecular weight heparin, albeit with a low threshold for exploratory laparotomy if there is clinical deterioration or major derangement of blood sugars. However, where there is poor enhancement of the graft on imaging and evidence of thrombus, re-laparotomy should be undertaken with a low threshold for transplant pancreatectomy.

Standard precautions should be taken at the time of surgery to protect a functioning arteriovenous fistula (AVF). Given that kidney graft survival at one year is >95%, in the event of AVF thromboses, this should be treated on symptomatic grounds.

9.5.2 Inflammation and Infection

Ischemia-reperfusion induces an inflammatory response within the pancreas allograft that is broadly labeled 'graft pancreatitis'. Other factors such as procurement factors, workbench preparation, and the handling process during implantation may also play a role.

The incidence and natural history of allograft pancreatitis is difficult to quantify, as there is no universally agreed diagnostic definition. In the majority of cases, the inflammatory

process settles after around 72 hours and patients begin to recover. However, more serious cases may be associated with both organ loss and death. Symptoms of ongoing inflammation include abdominal pain and distension, graft tenderness, nausea, vomiting, ileus and fever. In these circumstances there must be a low threshold for laparotomy, wash out, and drainage with an acceptance that graft pancreatectomy (especially after three or more laparotomies) may be required to control the inflammatory response and ensure that patient morbidity and mortality remains low.

Graft pancreatitis often results in the development of peri-pancreatic, pelvic and intra-abdominal collections. The donor duodenum of the pancreas allograft is colonised with a wide variety of gut commensals including Candida species. These commensals often contaminate the perfusion fluid used to transport the pancreas from the retrieval site to recipient hospital. It is good practice to routinely culture the perfusion fluid in the transport bag around the pancreas in order to identify any potential contaminants that will inform a subsequent anti-microbial strategy if there is post-transplant intra-abdominal infection. All patients undergoing pancreas transplantation must be given broad-spectrum antibiotic prophylaxis at the time of surgery, including an antifungal agent.

9.5.3 Glucose Control

Any spikes in blood sugar levels should trigger the consideration of imaging of the pancreas to look for venous and/or arterial thrombosis or re-laparotomy (see 9.5.1). In the early post-operative phase, steroids and other medication (e.g. tacrolimus, nutritional support) can cause hyperglycaemia, as can acute allograft rejection. When no evidence of thrombosis is found, other causes of hyperglycaemia need to be excluded before it can be attributed to delayed pancreatic graft function.

A glucose tolerance test before discharge enables a measurement of the early post-operative characteristics of the working pancreas, and an abnormal result appears to be a strong independent predictor of subsequent graft failure (38). Patients with abnormal glucose tolerance tests may benefit from more intensive monitoring and follow-up. Supplemental insulin or incretin therapy should be considered.

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Figure 9.1 – Duodenal Shortening

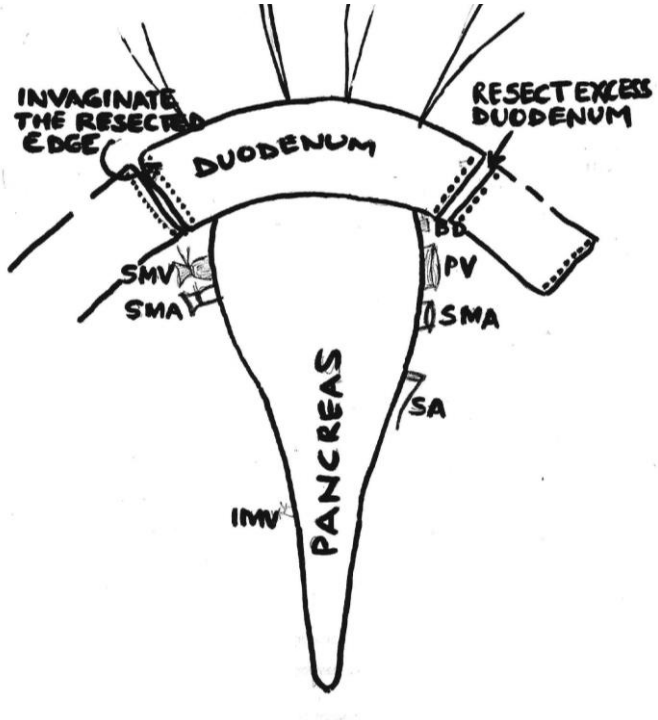


Figure 9.2 – Completed Duodenum

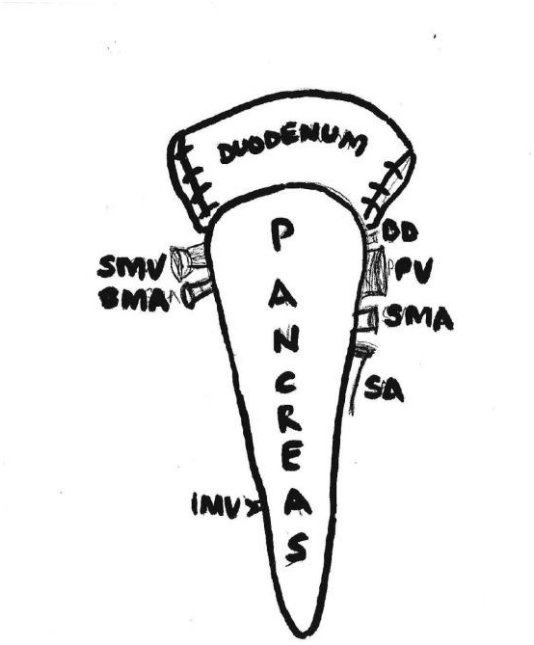


Figure 9.3 – Preparation of Portal Vein

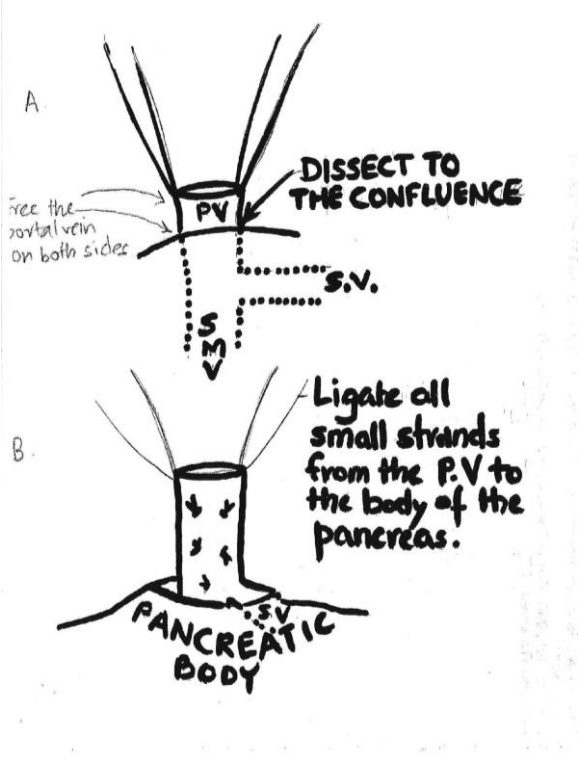
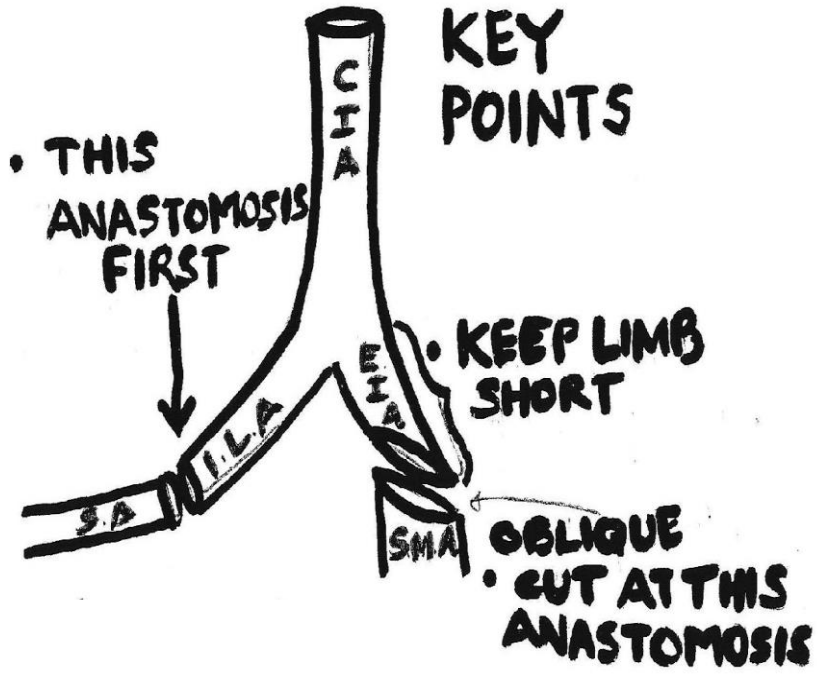


Figure 9.4 – Preparation of the 'Y'-Graft



Chapter 10 ISLET ISOLATION, INFUSION, AND PERI-OPERATIVE CARE

Recommendations

We recommend that

- Cold ischaemia times from retrieval to starting isolation must not exceed national recommendations. (C1)
- Islet isolation must take place in a Human Tissue Authority licensed, Good Manufacturing Process approved laboratory. (Ungraded)
- Islets must meet the minimum release criteria for number, purity and viability. (C1)
- Maintenance of euglycaemia with the use of a variable rate insulin infusion is required for a minimum of 24 hours in the peri-operative period to prevent loss of islets through oxidative stress. (C1)
- Anti-coagulation must be used to help prevent the Instant Blood Mediated Inflammatory Reaction in the early post-transplant period. (C1)
- Use of a sealant along the percutaneous transhepatic needle track will minimise the risk of intra-operative bleeding. (C1)

10.1 Introduction

This chapter covers the areas of pancreas bench work and the techniques of islet isolation, along with the perioperative management of the patient undergoing islet transplantation.

10.2 Pancreas Retrieval

Successful islet isolation requires that the donor pancreas is optimally retrieved using the same procedure used for whole organ retrieval (see Chapter 5), with the exception that no vessels are required for the islet procedure. The critical requirement is that the pancreas is kept cool from the cross-clamp time to when the pancreas is packed with

organ preservation solution, most commonly University of Wisconsin (UW) solution. The pancreas is stored and transported to the islet isolation laboratory in wet ice.

Cold ischaemia time (CIT) is critical for all organ transplantation, and particularly so for islet transplantation (1). The CIT (time between cross-clamp in the donor to time of distension with collagenase and neutral protease) should not exceed that set out in national recommendations made by the Islet Sub-group of the NHS Blood and Transplant Pancreas Advisory Group which is currently 8 hours.

10.3 Islet Isolation Procedure

The islet isolation procedure requires digestion of the pancreas to isolate the endocrine (islet) cells from the exocrine (acinar) tissue. The procedure can be divided into three stages and takes approximately five hours to complete. In the UK, islet isolation must take place in a facility regulated by the Human Tissue Authority under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and must be compliant with Good Manufacturing Process rules. An islet isolation laboratory is a highly regulated environment with clean-room facilities, and, to maintain its Human Tissue Authority licence, must undergo regular inspection and audit. There should be a clear step-wise standard operating procedure for the islet isolation process and all individuals involved in the process must have adequate training. Islet isolation laboratories should be working towards accreditation from the Medicines and Healthcare Products Regulatory Agency, in line with the production of other human cells intended for human infusion.

10.3.1 Dissection

The pancreas is first dissected free of the duodenum, spleen, connective tissue and superficial fat. A cannula is inserted at the pancreatic ampulla into the pancreatic duct and clamped or tied in place. Alternatively, a midline incision can be made at the neck of the pancreas to expose and open the pancreatic duct, with cannulae inserted in both directions.

10.3.2 Distension

Freshly made cold collagenase solution is introduced into the pancreatic duct cannula(e) either by syringe loading or using a commercially available recirculating-

perfusion system. Clamping or suturing the parenchyma can stop any leakage. Collagenase infusion continues until the pancreas is firm and well-distended. Several commercial enzymes are available for this step; an important consideration is the ratio of collagenase class I and II isoforms within the mixture, as well as the amount of neutral protease or thermolysin activity added (2,3).

10.3.3 Digestion

The pancreas is cut into pieces to facilitate islet release and transferred to a Ricordi chamber (a small 500-600 mL bioreactor). Here it is heated to 35-37^{o}C for 10-30 minutes to dissociate the exocrine and endocrine components using a recirculating pump coupled to a heating unit. Samples of tissue released from the pancreas are collected from a biopsy port incorporated into the recirculating system at routine intervals, and islets within the sample are identified by the addition of a zinc-chelating dye (dithizone) under light microscopy. When a sufficient number of clean, well-cleaved islets are observed in the samples, the dissociated pancreatic tissue is collected from the chamber, cooled, and washed in a buffered physiological saline-based solution.

10.3.4 Purification

The dissociated tissue is finally collected into UW solution and incubated at 4-8^{o}C for up to 60 minutes to facilitate density gradient isolation of the islets from the exocrine tissue. Several different gradient media have been used for this procedure, although a commonly used system is based on a UW solution / Ficoll mixture that affords a high tissue capacity (4). Mixing higher and lower density Ficoll solutions produces a continuous density gradient. This is pumped into a spinning COBE 2991 cell processor that allows media to be pumped in and out whilst in operation. The pancreatic tissue is then slowly loaded onto the gradient and the islets and exocrine cells distribute according to their densities (i.e. the islets are less dense than acinar tissue). The gradient is then collected as 10-12 fractions and the purified islets are collected & pooled from the fractions to optimise yield and purity.

When isolation of the islets from the exocrine tissue is incomplete, the purification procedure can be repeated on the impure islet fraction or modified by varying the density gradient range.

10.3.5 Incubation and Culture

Immediately following purification, the islet preparation undergoes preliminary quality testing to determine if it meets yield, viability & purity criteria before being placed in tissue culture for a minimum of 24 hours. After this time, it is reassessed using the criteria prior to transplantation. In this way, only stable, viable grafts proceed to implantation.

10.3.6 Quality Assessment and Release Criteria

Islets must meet accepted release criteria before they can be released for clinical use. These will include:

1) Final count after culture to ensure the islets meet the required numbers for the individual patient.
2) Confirmation of the purity and viability (membrane integrity) of the cells, as determined by dithizone staining.

The minimum islet release criteria in the UK are a count of 250,000 islet equivalents (IEQ), purity >50%, and viability >70%. Safety criteria, such as endotoxin content and microbial contamination, must also be met. For recipients of first islet transplants, minimum counts are 5000 IEQ per kg recipient body weight, with minimum counts for a second transplant performed as a priority of >10,000 IEQ per kg (5). For recipients of simultaneous islet-kidney (SIK) transplants, acceptable islet counts are lower as the patient is more likely to benefit from a marginal islet preparation given that this will facilitate transplantation of a kidney. The issue of islet purity and its impact on islet transplant outcome is debated; it may be that less pure fractions containing non-islet cells may either promote engraftment or influence ductal-to-endocrine cell differentiation (6).

Some laboratories also perform further functional testing including glucose stimulated insulin secretion and / or oxygen consumption ratio testing to determine the health of the islets, although this is not routine clinical practice.

10.4 Islet Transplantation

Patients listed for pancreatic islet transplantation are predominantly those undergoing pancreatic islet allo-transplantation alone, but other patient groups can be transplanted (7). The indications and patient selection are discussed in chapter 8. Following confirmation of satisfactory islet preparations, as per the above criteria, the islet transplant procedure can be performed.

The islets are transplanted into the liver via the portal vein. In the UK, this is performed at most centres under radiological (computed tomography) guidance in a radiology suite. It can also be achieved via mini-laparotomy, or laparoscopically, to access the portal vein. If an SIK transplant is being performed, unpurified islets can be infused through the portal vein if there is access through the laparotomy. When performed under radiological guidance, this is usually performed under sedation, although it can be done with a general anaesthetic if required.

The hepatic portal vein is accessed with a needle, and the portal pressures noted. Multiple sequential transplants may be performed via the portal vein (8). The bag with the islets is infused via the portal vein under gravity and the portal pressures noted during the course of the infusion (usual range 5-10 mmHg). The total islet packed cell volume is noted (usually <10 mL). Following the islet transplant, a bag with wash media is also run through via the portal vein. Once the portal vein catheter is removed, the tract can be sealed with an appropriate sealant to reduce the risk of bleeding (9).

An ultrasound scan of the liver is performed 4-8 hours post-transplant to look for hepatic perfusion and peri-hepatic haematomas, or earlier if there is abdominal pain. Insulin infusions and anti-coagulation is given (see below). The patient should be monitored for 2-3 days post-transplant to ensure there are no early complications, e.g. intra-abdominal bleeding or infection.

10.5 Peri-operative Care

After the islet infusion has been given, recipients require adjunctive therapies in order to minimise complications and to ensure that graft function and survival is maximised. Immunosuppression regimens for islet transplantation are discussed in Chapter 11.

10.5.1 Glycaemic Control

Good glycaemic control using dietary modification and exogenous insulin is important in the early post-transplant period in order to minimise islet loss.

When islets first lodge in the hepatic sinusoids they are avascular and a large proportion of islets are lost within the first 24 hours immediately post-transplant (10,11), mainly through inflammatory-mediated mechanisms including an instant blood-mediated inflammatory reaction (IBMIR). IBMIR describes the activation of the complement and coagulation cascades and infiltration of leucocytes and is responsible for the loss of up to two-thirds of the islets within the first few days post-transplant. Islet viability is further compromised because of the time required to form a vascular supply to the islets, exposing them to relative hypoxia (12,13). Elevated glucose concentrations increase levels of reactive oxygen species in the beta cells (14,15). Islets have low intrinsic antioxidant capacity compared with other metabolic tissues and are vulnerable to apoptosis in this setting.

The process of islet engraftment starts approximately 7 to 10 days post-transplant and the process of angiogenesis is largely complete by six weeks post-transplant.

To minimise the loss of islets it is important to control blood glucose levels. In practice, keeping blood glucose concentrations between 4-7 mmol/l in the peri- and post-transplant periods avoids stimulation of the beta cells (16). A variable rate insulin infusion is required for a minimum of 24 hours to prevent loss of islets through oxidative stress. Once a usual oral intake has resumed, patients should be restarted on their usual insulin doses. They should be under close monitoring over the next few weeks, as insulin doses usually drop significantly as the islets engraft and become metabolically active.

As high carbohydrate meals induce hyperglycaemia, we recommend a carbohydrate-restricted diet (<40 g of carbohydrate at any one meal) to minimise stress to the islets and ensure tighter glycaemic control post-meal. We recommend meals have 30-35 g and snacks 0-15 g of carbohydrate, and that the insulin required is individualised to each patient, reflecting the amount of rapid-acting insulin needed to cover the amount of carbohydrate and the amount of insulin needed to correct the pre-meal glucose reading to their target glucose value. Post-transplant, we recommend this dietary regimen continue for 4-6 weeks whilst the islets are engrafting (17). After that, it is still

important that patients adhere to their individualised insulin to carbohydrate ratio (except in cases of insulin independence).

It is also important to attenuate IBMIR and inflammation as much as possible. The strategies employed include the use of a number of therapies as discussed in the section below, and in chapter 11.

10.5.2 Anticoagulation

Anticoagulation is given to attenuate IBMIR (18,19) and for more general thromboprophylactic purposes. In patients with a normal clotting screen immediately pre-transplant, we suggest that they receive between 35-70 units of heparin per kg recipient body weight in the bag containing islets (not in the rinse solutions) (19). Four hours post-transplant, a clotting screen should be rechecked and, if the APTT ratio is <1.5, the patient should receive subcutaneous heparin at a prophylactic dose whilst an inpatient (e.g. unfractionated heparin 5000 units twice a day). On discharge, the patient should be prescribed a low molecular weight heparin, e.g. dalteparin 2500 units subcutaneously once daily for a total of seven days (20).

In patients receiving an SIK transplant, the use of anticoagulation will have greater risks, and will need to be assessed on an individual basis.

10.5.3 Other Therapies Post-transplant

Post-transplant, many organisms can infect a graft. Prophylactic antibiotics are administered with the first dose 1-2 hours before islet transplantation, followed by two doses post-transplant at 8-hour intervals. In most patients, a combination of piperacillin/tazobactam is given; in penicillin-sensitive patients, intravenous vancomycin and ciprofloxacin may be administered instead.

Pneumocystis pneumonia (PCP) may be associated with significant morbidity and mortality. Co-trimoxazole for six months is effective for PCP prophylaxis (21). If the patient is allergic to co-trimoxazole, dapsone is effective as a second-line treatment and continued for six months (22).

Antihistamines, typically chlorpheniramine, are given immediately before islet transplantation. The rationale for their use is to inhibit inflammation in the immediate post-transplant period and therefore to protect islet viability. Paracetamol is also

prescribed pre-transplant and continued post-transplant on account of its potent antipyretic and analgesic actions.

CMV and other viral infections occur more frequently in the first months after transplantation, when the doses of immunosuppressants are highest. Valganciclovir prophylaxis may be given to all islet transplant recipients, although in some units it is prescribed only if the CMV status of the donor or recipient is positive (23). When used, valganciclovir should be continued for at least 3 to 6 months following transplantation.

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Chapter 11 HISTOCOMPATIBILITY AND IMMUNOSUPPRESSION

Recommendations

We recommend that

- Once a patient is listed for pancreas or islet transplantation, it is recommended that samples be obtained for HLA antibody analysis at least every three months. (B1)

- Potential sensitising events must be notified promptly to the histocompatibility and immunogenetics laboratory and samples sent for HLA antibody analysis approximately 2-4 weeks after the event. (Not graded)

- To reduce cold ischaemic times in pancreas and islet transplantation, virtual crossmatch and/or donor peripheral blood lymphocyte crossmatching techniques must be available. (C1)

We suggest that

- There is no strong evidence to support the use of depleting over non-depleting antibody induction immunosuppression in SPK transplantation. Pancreas units must assess the risks and benefits of each approach. (C2)

- The use of depleting antibody induction therapy is recommended in recipients of PTA and PAK transplants. (C2)

11.1 Introduction

Improvements in HLA matching, immunosuppression, and antibody screening have contributed to improved pancreas allograft survival over the last 20 years. Histocompatibility testing for kidney transplantation can be applied to SPK transplantation (1), and, by inference, the same histocompatibility criteria can also be applied to PTA and PAK transplantation. HLA typing and antibody detection and the characterisation criteria for islet transplantation are similar to pancreas transplantation, but there are some differences. Given the small numbers of patients on the islet waiting

list, opportunities for HLA matching are limited; and as patients often require more than one islet transplant from different donors a patient can be exposed to multiple HLA mismatches. The detection and characterisation of HLA-specific antibodies is therefore of prime importance for islet cell transplantation. Furthermore, islets themselves are small groups of cells that have been isolated by mechanical and digestive techniques from the intact pancreas and so may be thought of as particularly vulnerable to HLA-specific antibody.

It is recommended that this guidance be read in conjunction with the BTS Guidelines on the Detection and Characterisation of Clinically Relevant Antibodies in Allotransplantation (joint with The British Society of Histocompatibility & Immunogenetics), available at https://bts.org.uk/wp-content/uploads/2016/09/06_BTS_BSHI_Antibodies-1.pdf.

11.2 Donor HLA Typing

All histocompatibility and immunogenetics (H&I) laboratories in the UK now perform HLA typing using DNA-based methods. This usually enables an HLA typing result to be obtained within four hours of the receipt of the deceased donor's blood sample in the laboratory. This rapid HLA typing facilitates the communication of donor HLA details to allow the national allocation of deceased donor organs. The NHSBT Pancreas Advisory Group defines the minimum standard for HLA typing of deceased donors. The UK National Pancreas Allocation Scheme allocates donated pancreases and islets to patients listed nationally using an objective, open, evidence-based and clinically appropriate allocation scheme (2).

Although medium resolution or antigen-level typing for HLA-A, -B, and -DRB1 is required for matching purposes, it is important to have data on other HLA loci, as sensitised patients may develop antibodies specific for any of the classical HLA loci. There is evidence that antibodies to loci other than HLA-A, -B and -DRB1 may be detrimental to kidney and (by inference) pancreas transplantation (3-5). Currently, typing for the HLA-A*, -B*, -C*, -DRB1*,-DRB3*/4*/5* and DQB1* loci are required for deceased donor typing. HLA-DPB1* typing may also be necessary for allocation of pancreases to sensitised recipients, and H&I laboratories are requested to be able to provide these data.

11.3 Recipient HLA Typing and Matching

The HLA typing requirements for patients prior to listing on the national waiting list for pancreas and islet transplantation do not differ from those required for deceased donor kidney transplantation, as described above. It is recommended practice, in line with European Federation of Immunogenetics accreditation, to request a second sample for confirmatory HLA typing to ensure that no errors are made with sample labelling or processing. High resolution HLA typing may sometimes be useful for defining the precise allele specificity of alloantibody for some patients, particularly where the HLA type of the sensitising individual is available.

Early reviews of HLA matching in pancreas transplantation tended to indicate that HLA matching was of low importance (6). In 180 SPK transplants, there was no evidence that HLA matching was associated with improved kidney or pancreas survival at three years, although significantly more acute rejection was seen in the poorly matched group (6). A further review of 205 SPK recipients showed that HLA matching was significantly associated with rejection-free graft survival (7). A recent single centre study of 1219 pancreas transplants showed a linear correlation between the number of mismatches and frequency of rejection. Though HLA matching did not predict pancreas graft survival it did significantly reduce acute rejection, particularly for solitary pancreas transplantation (8). The impact of HLA matching on the future chances of re-transplantation should also be considered, with sensitisation of recipients increasing with increasing numbers of mismatched HLA antigens.

The small number of patients waiting for islet transplantation limit the opportunities for HLA matching, but, where possible, matching should be encouraged. This is particularly important in islet transplantation as most recipients will require a second islet infusion. To increase the chance of finding an appropriate donor HLA match for the second or subsequent islet transplant, an additional HLA points system is applied to patients receiving islet transplantation in the UK (2).

Particular care is required when a kidney or pancreas is transplanted into a sensitised patient. Special consideration must be given to the donor HLA mismatch grade and to avoid HLA mismatched specificities to which the patient is sensitised. The reduced access to suitably matched organs means that sensitised patients wait for longer than average for suitable transplantation.

11.4 Recipient Antibody Screening

All patients who may require a pancreas or islet cell transplant must be screened for the presence of antibodies specific to HLA. If sera are carefully screened, HLA-specific antibodies can be defined and a patient's crossmatch reactivity against a particular donor of known HLA type predicted. Pancreas transplant centres should ensure that laboratory processes are in place to minimise the chance of kidneys and/or pancreases being shipped and then being crossmatch positive.

Since their introduction, there have been a number of modifications to the commercially available bead array assays that have sought to facilitate analysis of the results and their interpretation in the clinical setting. It has been observed that high levels of HLA-specific antibodies may give a misleadingly low or negative assessment of alloantibody levels and that this blocking effect is most likely due to complement fixation by HLA-specific antibodies (9). The binding of complement reduces the ability of secondary IgG detection antibodies to bind to targets, and leads to misleadingly low values in the assay. A number of test modifications can be used to overcome this problem, including heat inactivation or dilution of sera, ethylenediaminetetraacetic acid treatment, and dithiothreitol treatment. When using single antigen beads for monitoring IgG HLA-specific antibodies in sensitised patients, it is important to consider pre-treatment of sera to reveal potentially clinically relevant HLA class I and class II antibody specificities that may otherwise be masked or only suspected to be present at low levels. Each method of pre-treatment has its merits; however, whichever is chosen should be locally validated prior to routine use.

Antibodies can vary in specificity and quantity over time so it is necessary for two clotted blood samples to be tested by the H&I laboratory before a patient is registered for transplantation. These blood samples should ideally be separated by a minimum of a few weeks. The British Society of Histocompatibility & Immunogenetics (BSHI) and British Transplantation Society (BTS) guidelines recommend that blood samples be sent for antibody screening every three months while a patient is waiting for a pancreas or islet transplant (10,11). It is also good practice for regular samples to be sent for antibody screening while a patient is being worked up for transplantation, and this will facilitate prompt registration on the waiting list for organ allocation.

Antibodies directed at HLA can arise from sensitisation events including blood transfusion, pregnancy, and previous transplantation. It is important for H&I laboratories

to be informed if the patient has received any of these sensitising events in the past as it helps interpretation of HLA antibody test results and risk stratification of the crossmatch result. Equally, it is important that the laboratory is told of any sensitisation events while the patient is registered for a transplant as these may rapidly alter the antibody status of the patient. It is recommended that a sample is sent for antibody testing between 2-4 weeks after any sensitisation event.

It is recommended that antibody testing should be performed by two different techniques, including a highly sensitive technique to determine the specificity of the antibodies. HLA-specific antibodies that are not apparently generated by exposure to alloantigens have been detected in unsensitised males with the latest sensitive screening techniques (12). It is believed that these antibodies are detected due to a proportion of denatured HLA antigen present on the assay beads (13), and they have been shown to be clinically irrelevant (14). It is important that laboratories consider this in the choice of methods employed and the final analysis of patient sera. Details are outside the scope of these guidelines.

11.5 Definition of Unacceptable Mismatches

If a patient is found to have antibodies to HLA antigens, these antibodies will be characterised to define their specificity. The results of these analyses should be used to define unacceptable mismatches. Unacceptable mismatches are HLA antigens registered with NHS Blood and Transplant as unacceptable for a given patient, ensuring that the recipient will not be offered a potential organ expressing these mismatches. These will include HLA antigens for which the patient has been shown to develop specific antibodies. Further unacceptable mismatches may be identified, which can include mismatched antigens on previous failed transplants to which specific antibody has not been demonstrated. This is because there may be immunological memory of exposure even if there is no antibody currently detectable. Mismatches that do not elicit an antibody response are repeated with no apparent detriment but it is important that there are sufficient screening data to determine that there has been no antibody response. This can only be the case where regular post-transplant serum samples have been collected and analysed – in particular, samples taken at the time of and subsequent to graft loss. Where it is judged that the screening history is incomplete, such as when mismatches from a past pregnancy are unknown, all mismatched antigens should be regarded as representing a potentially increased immunological risk.

For patients with a functioning transplant requiring transplantation of an additional organ (e.g. PAK transplantation), previous mismatched antigens should not be listed as unacceptable unless antibody specific for the mismatched antigens has been demonstrated. This recommendation is based mostly on case reports. However, a UK analysis of recipients of cardiothoracic organs who subsequently received a sequential kidney transplant did not show an adverse effect of a repeated mismatch on kidney transplant outcome (15).

11.6 The Donor / Recipient Crossmatch Test

A number of factors determine the clinical significance of a crossmatch. These include the specificity and immunoglobulin class of the antibodies, the timing of the patient samples in relation to the sensitisation event(s), the strength of the reaction, and the sensitisation history. Both complement-dependent cytotoxicity (CDC) and flow cytometry crossmatches may be performed for pancreas and islet transplantation. It may be preferable to use the more sensitive flow cytometry crossmatch for sensitised or highly sensitised patients and those undergoing repeat islet transplantation. It should be noted, however, that special consideration will be required for patients receiving repeat islet transplantation. For the first islet transplant, patients usually receive alemtuzumab as induction therapy. The presence of alemtuzumab in the patient sera can render the ‘wet’ (CDC or flow) crossmatch invalid, requiring a virtual crossmatch only prior to the second islet infusion.

For a detailed discussion of the clinical relevance of the crossmatch please refer to the BSHI / BTS guidelines (10,11). Much of the evidence is based on renal transplantation. What follows is a distillation of that guidance, with relevance to islet and pancreas transplantation.

11.6.1 The Cytotoxic Crossmatch

It is generally accepted for kidney and pancreas transplantation that cytotoxic IgG antibodies directed against donor HLA-A, -B, -Cw, -DR and -DQ specificities present at the time of transplant risk hyperacute rejection in the majority of cases (16-18). IgM autoreactive antibodies react with autologous as well as allogeneic lymphocytes in the CDC crossmatch test and have been shown to be irrelevant to transplant outcome (19). They therefore give rise to false positive results. The clinical relevance of IgM HLA-

specific antibodies is not entirely clear, although in many cases they appear not to be detrimental (20).

Decisions regarding the transplantation of patients with cytotoxic antibodies in non-current sera should take into account the proposed immunosuppression, patient sensitisation history, and the requirement for effective post-transplant management. The clinical urgency of the transplant, and the likelihood that the patient will receive another adequate organ offer within a reasonable time frame also need to be considered.

11.6.2 Flow Cytometric Crossmatching (FCXM)

FCXM has been shown to be more sensitive than conventional CDC crossmatch for the detection of anti-HLA antibodies (21), and positive results have been shown to be associated with graft rejection (22). Although many centres use the FCXM as a threshold test for the detection of donor-specific antibodies (DSA), it is more useful if the FCXM cut-off is based on a retrospective analysis of transplant outcomes. The FCXM is a useful test to gauge the amount of IgG DSA present binding to donor cells, and thereby allow stratification of risk.

Stratification of outcome according to the FCXM results has been shown, with the highest survival in patients with T- and B-cell negative FCXM, intermediate survival with a B-cell positive FCXM and poorest survival with T- and B-cell positive FCXM (23,24). This stratification has also been shown in relation to the development of chronic rejection, with the incidence highest in T- and B-cell positive, intermediate in B-cell positive and lowest in T- and B-cell negative FCXM groups (25). As with the CDC crossmatch, the specificity of the antibody causing the positive crossmatch is a critical factor.

Although some published studies have found no significant association between a low threshold positive FCXM and graft outcome, the majority indicate that a positive FCXM is predictive of early graft rejection and failure. In particular, large multicentre studies do indicate a significant association between FCXM and graft outcome (25, 26).

FCXM against donor peripheral blood lymphocytes (PBLs) is a useful technique, where locally validated. This can be performed before donor lymph nodes or splenic samples

are available, i.e. prior to organ retrieval. This approach can facilitate the minimisation of pancreas cold ischaemic time.

The reporting of crossmatch results must clearly distinguish between positive reactions thought to be clinically relevant and those thought not to be.

11.6.3 Retrospective or Virtual Crossmatching

The purpose of the pre-transplant crossmatch is to detect (and allow avoidance of) pre-formed donor HLA-specific antibodies that may impact on successful transplant outcomes. In certain circumstances, however, it may be possible to proceed to transplant without the need for a prior 'wet' (CDC or flow) crossmatch. This is known as a virtual crossmatch. Each unit must define a clear policy for the use of virtual crossmatching, with well-defined criteria and close liaison between the transplant team and the laboratory.

If the recipient has never experienced potential sensitising events and/or has never produced HLA-specific antibodies, a pre-transplant crossmatch is probably unnecessary. It has been demonstrated that this works in practice (27). In this study, crossmatches that were performed retrospectively (post-transplant) were all negative, indicating that prediction of a negative crossmatch was reliable in this carefully selected sub-set of patients. This approach has been shown to significantly lower organ cold ischaemic times (27-29).

The sensitivity of the antibody screening methods now available means that it is possible in the majority of cases to predict a negative crossmatch, even in highly sensitised patients. Therefore, many laboratories now also perform virtual crossmatching for antibody-positive patients with a well-defined antibody profile. If a retrospective (virtual) crossmatch strategy is to be implemented for such patients, close liaison between the transplant team and the histocompatibility laboratory is essential, and excellent communication of potential sensitising events is vital.

Clinical teams should be made aware of the limitations of the antibody screening methods available and the potential for errors in donor HLA typing that could lead to an unexpectedly positive retrospective crossmatch post-transplant.

11.7 Immunosuppression for Pancreas Transplantation

Defining the optimal immunosuppressive strategy for pancreas transplantation is challenging, primarily due the absence of adequate randomised controlled trials. In addition, rates of pancreas rejection and subsequent graft loss appear 2-4 times higher for PTA rather than SPK transplants (30-32). Furthermore, experience with percutaneous pancreas allograft biopsy is limited in the UK, and therefore some units diagnose pancreas rejection on the basis of changes to serum or urinary amylase or lipase alone. Amylase and lipase are regarded as sensitive for pancreas rejection, but with specificities of 50% or less (33-35). Relying on renal or duodenal allograft histology to diagnose pancreatic parenchymal rejection in SPK transplant recipients can be misleading due to the 20-40% rates of discordant rejection (36,37).

Given the above concerns, the use of depleting antibody induction regimens (e.g. anti-thymocyte globulin (ATG) or alemtuzumab) is common in pancreas transplantation (30), though the evidence-base supporting this approach is not clear. Niederhaus et al have recently reviewed studies of induction immunosuppression (31). Study sizes were small, sometimes non-randomised, and often included different types of transplants. There was no clear benefit to the use of depleting antibodies at induction when compared to non-depleting antibodies (e.g. daclizumab, basiliximab). A small randomised controlled trial showed no differences in graft or patient survival between alemtuzumab (n=28) and ATG induction (n=18) in SPK transplant recipients, though this study was likely to be underpowered to detect clinically relevant differences (38). A large US registry analysis showed no differences in pancreas or renal allograft survival on multivariable analysis when comparing alemtuzumab, ATG, non-depleting induction, and no induction in SPK transplant recipients (39). Similar analyses have not been performed on UK registry data for SPK transplantation, though non-depleting induction was shown to be an independent risk factor for pancreas graft loss in PTA (40).

Depleting antibody induction regimens have the advantage of enabling more confidence with early steroid withdrawal or avoidance, which is attractive due to the risks of steroid-induced hyperglycaemia. However, the higher rates of opportunistic infection or viral re-activation (e.g. cytomegalovirus) must be taken into account if these agents are used.

In current practice, the majority of pancreas transplant units the UK give alemtuzumab at induction. This is given subcutaneously, after pre-medication of methylprednisolone and chlorpheniramine.

The optimal maintenance immunosuppressive regimens in pancreas transplantation are poorly defined. In general, target trough tacrolimus levels are higher than for most kidney-only recipients due to the relative difficulties in monitoring pancreas allograft function and diagnosing and treating pancreas rejection. Likewise, the optimal anti-proliferative immunosuppressant dosages are unknown in pancreas transplant recipients. The use of depleting agents at induction requires reduced dosages of mycophenolate mofetil in the early post-transplant phase to avoid unacceptable levels of lymphopenia and the associated risks of reactivation of quiescent viruses (e.g. cytomegalovirus) and serious opportunistic infections.

11.8 Immunosuppression for Islet Transplantation

As above, the evidence-base for identifying the optimal immunosuppression regimen for islet transplantation is limited. In the early Edmonton series, interleukin-2R blockade (daclizumab) was combined with sirolimus and low dose tacrolimus in an attempt to achieve a steroid-avoiding protocol, which also reduced exposure to diabetogenic calcineurin inhibitors (41). Subsequent studies have suggested a role for anti-inflammatory monoclonal antibody therapy, e.g. infliximab (42). Data from the Collaborative Islet Transplant Registry have shown, however, that T-cell depletion using either alemtuzumab or ATG, combined with etanercept (a tumour necrosis factor inhibitor), mycophenolate mofetil, and standard dose tacrolimus, results in a significantly higher incidence of insulin independence and better long-term graft outcomes (43). In the UK, most units now use alemtuzumab and etanercept induction, with mycophenolate mofetil and tacrolimus maintenance therapy.

Etanercept and alemtuzumab are given approximately one hour prior to the first islet transplant, following confirmation from the islet isolation laboratory that the islet preparation has met the relevant criteria and that the patient is fit to receive the islet transplant. These are given after premedication with intravenous corticosteroid, paracetamol, and anti-histamine (e.g. chlorpheniramine 10 mg). Typical target tacrolimus trough levels are 6-10 ng/mL for the first 6-8 weeks, with maintenance levels of 6-8 ng/mL.

If insulin-dependent after one month, the patient is prioritised for a second islet transplant with an aim of transplanting within a three-month period from their first graft. T-cell depleting induction agents are not usually given with the second transplant as

these agents typically have immunoregulatory effects for a year. For second or subsequent transplants, basiliximab can be given at the time of transplantation, and then repeated on the fourth post-transplant day. The use of depleting antibody agents at induction for the first islet transplant may interfere with 'wet' crossmatching techniques for a second islet transplant, as these compounds may still be active in recipient serum. This must be taken into account when considering crossmatching policies for second islet transplants.

11.9 Development of HLA-specific Antibodies after Pancreas or Islet Transplantation

11.9.1 Pancreas

As with kidney transplantation, antibody-mediated rejection in pancreas transplantation is diagnosed with C4d staining of capillaries in the graft biopsy accompanied by a donor-specific antibody, microvascular injury, and graft dysfunction (44,45).

A strong correlation was shown between C4d positive interacinar capillary staining and donor-specific HLA antibodies in 27 biopsies from 18 patients with a pancreas transplant (46). Although these DSAs were not definitively described as de novo, de novo HLA Class I and II antibodies have been associated with acute rejection of the pancreas alone in a pancreas after kidney transplant (47). A further report details the results of 27 pancreas patients who had biopsies to diagnose rejection (48). All the patients that lost their graft to rejection had C4d deposition, and those with C4d and HLA-specific DSAs had a worse prognosis. A single centre study of 433 pancreas transplants, including 317 SPK and 116 pancreas alone transplants, concluded that de novo DSA formation was a strong independent predictor of pancreas graft failure (hazard ratio 4.66, $p<0.001$) (49).

In order to identify the production of de novo antibodies post-transplant, it is important to specify the reactivity against mismatched donor antigens. Accordingly, samples should be taken from transplant recipients at regular intervals, on an agreed basis (this may be determined on an individual patient basis according to perceived immunological risk), and at the time of biopsy, suspected rejection, and in cases of declining graft function where there is no other clinical cause.

Since the production of donor HLA-specific antibodies following pancreas transplantation is associated with poor outcome, there is a potential benefit in monitoring patients for the production of post-transplant antibody, although it is unclear that this translates into improved outcomes. A conservative approach would be to review and optimise a patient's immunosuppression if de novo DSAs are detected post-transplantation. This might include increased doses of tacrolimus and mycophenolate mofetil (50-52), though the optimal approach to de novo DSAs in the absence of overt pancreas graft dysfunction is unknown.

11.9.2 Islet

In islet-only transplant recipients, 23% patients developed DSAs whilst on immunosuppression (53), and the incidence of sensitisation in combined kidney and islet transplants has been reported to be similar to that of kidney-only transplants (54). The incidence of HLA-specific antibodies has been reported to rise significantly after the failure of islet transplants and withdrawal of immunosuppression (55). A recent study has emphasised the importance of de novo DSA formation in islet cell transplantation, where their development was associated with rapid loss of graft function (56).

In order to monitor a patient's antibody status after their first islet transplant, it is recommended that samples are obtained regularly until the next transplant. Current BSHI guidelines recommend samples should be received post-transplant at days 7, 14, 21, 28 post-transplantation, and at monthly intervals thereafter if the profile appears stable. All DSAs should be reported to the clinical team and should be used to inform decisions about the selection of subsequent islet transplants. Not all HLA-specific antibodies detected in the screening programme must necessarily be listed as unacceptable specificities. If the crossmatch is negative and there is appropriate discussion with the clinician responsible for the transplant programme, it is possible that a transplant may proceed in the presence of DSAs detected only by Luminex technology.

Whilst mismatched classical HLA antigens present targets for antibody responses, other antigens may also be important in this context and be associated with pancreas and islet graft failure. MHC class I chain-related antigen A and MHC class I chain-related antigen B expression have been described on pancreatic islet and acinar tissue in normal and rejecting allografts (57). As MHC class I chain-related antigen is not

normally expressed on lymphocytes, pre-existing MHC class I chain-related antigen A antibodies would not be detected by current crossmatching tests.

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Chapter 12 RECIPIENT OUTCOMES: PANCREAS TRANSPLANTATION

Recommendations

We recommend that

- Centres performing pancreas transplantation must submit data to the UK Transplant Registry according to NHSBT requirements. (Not graded)
- In addition to the minimum data set, additional data must be collected to allow pancreas graft function to be categorised according to the Igls criteria. (C1)
- An HbA1c of >6.5% or a rise of HbA1c by >0.5% should prompt consideration of investigations to identify an underlying cause of potential graft dysfunction. (Not graded)

12.1 Introduction

The success or failure of a procedure must be considered in the context of the indications for it, as well as its potential risks and side effects. Historically, the key outcomes after pancreas transplantation were considered to be graft survival and patient survival. However, there are other important outcomes such as re-operation rates (and other early surgical complications), patient quality of life, and the impact of the procedure upon other complications of diabetes. This chapter will provide data on the above, and also consider the challenges in reporting graft function in pancreas transplantation. Recent changes to the definition of graft function after pancreas transplantation are also discussed.

It is expected that improved analyses of outcomes after pancreas transplantation will enable clinicians and patients to make better decisions on beta-cell replacement therapy options and assist in driving quality improvements.

12.2 Standard Outcomes Measures after Pancreas Transplantation

12.2.1 Patient and Graft Survival

Patient survival is straightforward to define as it relates to death post-transplantation, irrespective of graft function or cause of death. Examination of pancreas graft survival is more difficult, as different definitions of graft survival have been employed. In this context, it is important to understand whether patient death with a functioning pancreas graft has been coded as pancreas graft failure.

A functioning transplanted pancreas should be able to normalise blood glucose levels to non-diabetic levels without hypoglycaemia or the need for additional anti-hyperglycaemic medication. In most publications, the standard definition of graft failure in pancreas transplantation has been a return to exogenous insulin treatment (at any dose) or graft pancreatectomy, whichever occurs first. However, this assumes that clinicians have the same threshold for starting exogenous insulin treatment, which is unlikely to be the case. Indications for starting oral anti-hyperglycaemic agents are also likely to vary. Use of any anti-hyperglycaemic agents to support pancreas graft function indicates a degree of graft dysfunction. More specific definitions of partial graft function are therefore required in order to facilitate improved management of these patients and research into pancreatic allograft dysfunction. These issues are discussed more fully in section 12.3. Because the likelihood of graft survival varies depending on the type of pancreas transplant (SPK, PTA, etc.), it is important that the recipient population is also carefully defined.

Risk-adjusted patient and graft survivals are reported annually in the UK (1). The current NHSBT definition of pancreas graft failure is a return to exogenous insulin treatment (at any dose) or graft pancreatectomy, whichever occurs first. In the most recent analysis, one- and five-year patient survival rates were 95-98% and 70-90%, depending on the centre. Death-censored one-year pancreas survival after first SPK transplantation varied from approximately 80-95%, with five-year graft survival between 60-90%.

Other transplant registries use different definitions of graft survival after pancreas transplantation. The International Pancreas Transplant Registry defines grafts as functioning if recipients are insulin-independent, though death with a functioning graft is considered as graft failure, unless stated otherwise. The most recent data, analysing over 21,000 pancreas transplants between 1984 to 2009 with a minimum of five years

of follow-up showed that five- and 10-year graft function rates were 73% and 56% for SPK, 64% and 38% for PAK, and 53% and 36% for PTA, respectively (2).

12.2.2 Peri-operative Surgical Complications

Consideration must also be given to the early post-operative surgical risks of a pancreas transplant, as peri-operative complications are common and can be life-threatening. The need for further open abdominal surgery is an easily definable outcome measure after pancreas transplantation.

Up to 40% of recipients require re-laparotomy within the index admission to deal with early complications such as haemorrhage, graft thrombosis, and enzyme or enteric leaks (3,4). Unsurprisingly, patients requiring re-laparotomy have higher rates of graft failure (4), in part because major complications requiring re-laparotomy often necessitate graft pancreatectomy for patient survival. Candidates for pancreas transplantation must be consented for these risks and selected for transplantation on the basis that they are reasonably expected to be able to withstand such complications, both physiologically and psychologically. Complications that require major open surgery can still occur many years post-transplantation (e.g. pseudoaneurysm and associated major haemorrhage), though these are relatively uncommon (5). Use of a standardised system for reporting other post-transplant surgical complications would facilitate reporting and subsequent comparisons between centres and implantation techniques (6,7).

12.2.3 Quality of Life Measures (see also section 7.3)

By rendering an individual free of the need for exogenous insulin, successful pancreas transplantation might reasonably be expected to have a significant beneficial impact on quality of life (QoL) due to avoidance of the need for regular blood sugar monitoring, injections, and removal of the fear of episodes of severe hypoglycaemia. However, complications associated with major surgery and the need for immunosuppression (and its attendant risks) may impose a significant physical and psychological burden on pancreas transplant recipients. In general, the literature on QoL after pancreas transplantation is limited due to the relative rarity of the intervention and the complexity of separating the impact of euglycaemia from dialysis freedom in SPK recipients. Furthermore, there are a variety of tools used to measure physical, mental, and

diabetes-related QoL, which makes comparisons between studies that use different metrics highly challenging (8,9).

A small prospective study of 37 patients has shown that half of SPK recipients experience a sustained QoL improvement post-transplant compared to their pre-transplant state (10). Comparing transplant options in US patients with insulin-dependent diabetes and end-stage renal disease, SPK recipients reported greater improvements in physical health and diabetes-specific areas than those who opted for kidney-transplantation alone, although mental health status was higher in the kidney-only group (11). A further study that examined QoL in four groups of patients with type 1 diabetes and ESRD (SPK recipients, deceased donor kidney recipients, living donor kidney recipients, and wait-listed patients) showed that QoL in the three transplant groups improved compared with waiting list patients, and that an SPK transplant had a positive effect on diabetes-related QoL. General QoL scores were similar between the three transplant groups (12). These findings were similar to those from an earlier, smaller study from the same research group (13), though a Japanese study has suggested that SPK transplantation improves QoL compared to kidney-only transplantation (14). A large Portuguese study has demonstrated improved QoL after SPK transplantation when recipients were asked to recall their level of functioning pre-transplant, and that failure of one graft was associated with worse QoL scores (15). Results from a UK study of QoL in SPK recipients are awaited (16).

There is a paucity of QoL studies in PTA recipients. Patients with a functional graft after PTA have been shown to have improved QoL when compared to those with failed grafts, though validated measures were not used (17).

12.2.4 Diabetic Complications (see also section 7.3)

Those who opt for pancreas transplantation often do so in the expectation that their long-term complications of diabetes mellitus will be stabilised if euglycaemia is achieved. This is at least partially supported by the results of large studies showing that tight glycaemic control in patients with type 1 diabetes appears to slow progression of both microvascular and macrovascular diabetic complications (18). However, this is a complex area to study due to the need to distinguish between different pancreas transplant options, the relative impact of differing baseline disease burden and immunosuppression on diabetes complications, and the effects of chronic uraemia and

fluid overload in those with end-stage renal disease (ESRD). This field has been reviewed elsewhere (18,19).

In patients with ESRD due to diabetic nephropathy, a functioning pancreas transplant appears to aid the preservation of renal allograft function. A recent UK registry analysis has demonstrated that SPK recipients with a functioning pancreas graft had better kidney graft survival than patients with type 1 diabetes who received a living donor kidney, and those who had a failed pancreas transplant (20). At the cellular level, biopsies of kidney grafts in patients with type 1 diabetes with kidney-only transplants show increased basement membrane thickness at 9-12 years post-transplantation when compared to kidneys in SPK recipients (21). Histological changes consistent with diabetic nephropathy may appear within 1-2 years of kidney-only transplantation, although a functional impact may take as long as 10-20 years. (18). However, the ability of pancreas transplantation alone to prevent the progression diabetic nephropathy (22) is complicated by possible nephrotoxicity due to calcineurin inhibitors and insults associated with major surgery. ESRD has been shown to occur in approximately 10% of PTA recipients at 5 years post-transplant (23). Avoidance of high tacrolimus levels is likely to help prevent deteriorating renal function (24,25).

The effect of pancreas transplantation on diabetic retinopathy appears variable, but generally positive. Improvement in non-proliferative retinopathy has been reported in approximately 30-40% of patients, with a further 30% showing no change and 30% having disease progression (26). In patients with laser-treated and/or proliferative retinopathy, stabilisation is far more common (approximately 90%), with just 10% having progression. When compared to non-transplant diabetic control groups, transplant recipients have higher chances of disease improvement or stabilisation (27). It has been reported that rapid worsening of diabetic retinopathy can occur in the early post-transplant period (28); one study has reported that pan-retinal photocoagulation within a year prior to pancreas transplantation may be a risk factor for early progression of retinopathy (29).

Peripheral neuropathy has been shown to improve after SPK transplantation when compared to recipients with functioning kidney transplants and diabetes (29). Prognostic factors for recovery include less severe initial neuropathy, smaller recipient body weight and longer duration of diabetes. Nerve regeneration has been demonstrated by sensitive techniques within 6-12 months of successful SPK

transplantation, even if clinical improvements in neuropathy could not at the time be detected (30). However, it appears that severe neuropathy is not reversible, even after many years of euglycaemia (31).

Gastrointestinal autonomic neuropathy is manifested by gastroparesis, with intermittent early satiety, vomiting, diarrhoea, or constipation. Limited evidence suggests that gastroparesis improves in the long-term post-transplantation (32), though gastrointestinal symptoms are often refractory to treatment and may also worsen in the early post-operative period. The impact of novel agents such as neurokinin-receptor antagonists on gastroparesis is awaited (33).

The effect of pancreas transplantation on the macrovascular complications of diabetes is complex, and relatively poorly described. A small study has shown that angiographic evidence of CAD progression occurred at similar rates between SPK patients (n=25) and LD kidney recipients (n=17) with functioning grafts at a median of 10 years post-transplantation (34). Most data come from transplant registries; a recent UK registry analysis suggests that the presence of a functioning pancreas transplant reduces the overall risk of death when compared to living donor kidney-only recipients (20). Similarly, a Norwegian registry study examined the risk of long-term cardiovascular mortality after transplantation and found that SPK transplantation was associated with reduced rates, after risk adjustment, when compared to patients with type 1 diabetes and ESRD who had received living donor kidney transplantation only (35).

12.3 Challenges in Reporting Outcomes for Pancreas Transplantation

Historically, success in pancreas transplantation has been defined by independence from exogenous insulin, without any clear guidance on the expected glycaemic control. This means that reporting cannot be confidently compared between units that may have different thresholds for initiating insulin. This may limit the ability to compare outcomes between centres. As insulin use is a criterion for pancreatic graft failure, there may also be conscious or subconscious reluctance to start insulin from either the healthcare team or the patient (or both), even if early insulin usage may protect ‘partial’ graft function or keep glucose levels in target.

The use of capillary or continuous glucose monitoring to examine fasting or post-prandial glucose levels, or glucose variability (an early marker of graft dysfunction),

does not appear to be uniform. Perhaps surprisingly, measurement and reporting of HbA1c post-transplant is also highly variable, despite this being a requirement for data collection for the UK registry.

Better definitions of pancreas graft function and clearer reporting requirements are therefore needed. UK centres performing pancreas transplantation must submit data to the UK Transplant Registry according to NHS Blood and Transplant requirements.

12.3.1 Defining Pancreas Graft Function

Defining optimal graft function in pancreas transplantation is the least contentious issue to consider, as most groups and international registries define this as the ability to maintain normoglycaemia without the need for any anti-hyperglycaemic agent. Therefore, it is important to define normoglycaemia. The World Health Organization definition for diabetes is HbA1c >6.5% (36), and so optimal pancreatic graft function should be able to maintain HbA1c $\leq$6.5% without pharmacological support.

Following on from the above, it is possible to have 'partial' pancreas graft function, i.e. a pancreas transplant recipient with excellent blood glucose control who is receiving a much smaller dose of insulin than pre-transplant and with no severe hypoglycaemic events. This should not necessarily be regarded as 'treatment failure'. Even small amounts of C-peptide can have a protective effect on glucose variability and hypoglycaemia (37). Defining 'partial' graft function requires a consideration of both functional and clinical criteria. Better recognition of partial graft function may also allow interventions to reverse graft dysfunction or protect residual function.

C-peptide can be used as a measure of pancreas function. However, it can be difficult to interpret as the transplanted pancreas is usually systemically drained, leading to high C-peptide levels in circulating blood (38). Also, with increasing numbers of transplants performed in patients with type 2 diabetes (39), or where the diabetes may have been incorrectly classified pre-transplantation, it is not possible to distinguish C-peptide production from the native pancreas and the transplanted pancreas. Furthermore, given that the majority of pancreases are transplanted together with a renal graft, renal graft function will also have an impact on the measurement of C-peptide due to renal excretion.

A consensus conference was convened in Igls in 2017 to examine these issues. This proposed that outcomes for all types of beta-cell replacement should be defined through a composite of glycaemic control (HbA1c), severe hypoglycaemia events, insulin requirements, and C-peptide levels (Table 1) (40).

Table 1 Igls definitions for classification of beta-cell replacement therapy function (adapted from (40))

Beta-cell graft functional status	**HbA1c, % (mmol/mol)**	**Severe hypoglycaemia, events per year**	**Insulin requirements, U/kg/day**	**C-peptide**
Optimal	≤6.5 (48)	None	None	>Baseline
Good	<7.0 (53)	None	<50% baseline	>Baseline
Marginal	Baseline	<Baseline	≥50% baseline	>Baseline
Failure	Baseline	Baseline	Baseline	Baseline

C-peptide should also be >0.5 ng/mL (>170 pmol/L) fasting or stimulated. Insulin dose <0.5U/kg/day may include the use of non-insulin glucose-lowering agents.

In order to utilise this framework, additional data must be collected to allow pancreas graft function to be categorised according to the Igls criteria. More standardised measurement of C-peptide production is required. The gold standard measurement should be a dynamic test such as an oral glucose tolerance test (75 g glucose load) with measurements at baseline and 120 minutes. A more widely used test is the mixed meal test, which is similar in principle but involves a 50 g carbohydrate load along with protein and fat (e.g. 220 mL of Fortisips) with measurements of both glucose and C-peptide at baseline and 90 minutes. It should be noted that pre-transplant measurements are also necessary to enable the use of this approach.

Some patients who require SPK transplantation may have had their diabetes type misdiagnosed (e.g. type 2 diabetes diagnosed as type 1 diabetes). It is therefore necessary to measure stimulated C-peptide levels before transplantation. Where the C-peptide is clearly <500 pmol/L, it is likely that the patient is insulin-deficient and has type 1 diabetes. If the C-peptide is >500 pmol/L, discussion should be undertaken with the linked diabetologist who should review the case. C-peptide can be over-estimated in renal failure, but in cases with very high C-peptide values pre-transplant,

(i.e. >2500 pmol/L), it may be of value to reconsider the need for the pancreas transplant. This will depend on a number of factors such as current diabetes control, patient factors (e.g. donor BMI and national criteria for transplantation in patients with type 2 diabetes), complications of diabetes, total insulin requirement, and the possibility of managing diabetes with alternative agents (e.g. GLP-1 agonists) once renal failure is treated with the renal transplant.

Frequent monitoring of HbA1c is also necessary to use the Igls framework. Three-monthly monitoring is recommended in the first year post-transplant; however, the optimal frequency of HbA1c monitoring is not known. Likewise, the need for (and frequency of) patient self-monitoring of capillary blood glucose is not known.

At present, there is no evidence base to define the optimal approach to post-transplant monitoring in pancreas recipients, or the investigation and management of patients with apparently deteriorating graft function. We suggest that HbA1c >6.5% (48 mmol/mol), and rises of HbA1c of more than 0.5% (5 mmol/mol) over a year should prompt review by a transplant surgeon and diabetologist and consideration of further investigation. Such investigation may include graft imaging (e.g. ultrasound scan or CT), more detailed functional assessments (e.g. intensive capillary blood glucose monitoring, stimulated C-peptide measurement), measurement of donor-specific HLA antibodies and diabetes autoantibodies, and pancreatic graft biopsy.

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Chapter 13 RECIPIENT OUTCOMES: ISLET TRANSPLANTATION

Recommendations

We recommend that

- Centres performing islet transplantation must submit data to the UK Transplant Registry according to NHSBT requirements. (Not graded)

- The above should include assessment at 1, 3 and 12 months after transplantation, and yearly thereafter. The data should include:
    - Metabolic monitoring (monitoring of graft function using mixed meal tolerance tests with paired glucose and C-peptide). (B1)
    - Monitoring of clinical outcomes, including documentation of mild and severe hypoglycaemia, glycaemic control, and any anti-hyperglycaemic medication used. (B1)
    - Immunological monitoring, including measures of alloantibodies and autoantibodies. (Not graded)
    - Quality of life monitoring. (Not graded)
    - Monitoring and management of on-going complications of diabetes. (B1)
    - Monitoring and management of on-going complications of immunosuppression. (B1)

- In addition to the minimum data set required by NHSBT, additional data must be collected to allow islet graft function to be categorised according to Igls criteria and BETA-2 score calculation. (C1)

- Patients are encouraged to perform structured self-monitoring of blood glucose (i.e. fasting and post-meal glucose values) and to contact the transplant team if there are any significant changes in values. (Not graded)

13.1 Introduction

Successful deceased donor pancreatic islet allotransplantation was first achieved through the development of the Edmonton protocol, which demonstrated that insulin independence could be achieved in individuals with type 1 diabetes complicated by recurrent severe hypoglycaemia or metabolic instability (1). Since then, islet transplantation has expanded significantly and is now an accepted treatment for selected patients with poorly controlled type 1 diabetes. As islet isolation techniques and immunosuppressive regimens have improved, so have the expectations of post-transplant outcomes.

Outcome measures after islet transplantation are evolving rapidly, and include graft function, patient and graft survival, complications of islet transplantation, quality of life (QoL) measures, and diabetic complications. This chapter examines these measures, as well as considering the related field of immunological monitoring post-transplantation. In order to facilitate the collection of essential outcome measures, centres performing islet transplantation must submit data to the UK Transplant Registry according to NHS Blood and Transplant requirements.

13.2 Standard Outcomes Measures after Islet Transplantation

13.2.1 Patient and Graft Survival

The most reliable data on post-transplant patient survival come from large registry analyses such as the Collaborative Islet Transplant Registry (CITR). These reports indicate 3% crude mortality over a mean of 4.4 years follow-up (2). No study-related deaths were reported in a US trial of islet transplantation (3). An early publication of the UK islet transplant experience did not report patient survival rates post-transplant (4).

In the UK, islet graft survival is defined as stimulated C-peptide of >50 pmol/L (4). Using this definition, five-year graft survival following routine islet transplantation in the UK is 48% (5). The mixed meal tolerance test (MMTT) provides a standardised, reproducible assessment of the C-peptide response to an oral mixed constituent meal (6), and is the recommended stimulus to enable C-peptide measurement. Patients must attend fasted and take any long-acting insulin they may be using the night before. Paired glucose and C-peptide concentrations are then measured before and 90 minutes after 240 mL of Fortisip liquid, drunk over 2-4 minutes.

13.2.2 Graft Function

Islet graft function is a more challenging outcome to define and measure. Graft function can be considered in one or more of three domains: 1) biochemical or hormonal measures of graft function (e.g. blood glucose / HbA1c, C-peptide); 2) treatment required to maintain acceptable glycaemic control (e.g. exogenous insulin therapy); or 3) clinical events associated with poor glycaemic control (e.g. severe hypoglycaemia). These measures are interdependent, though patients may place more emphasis on achieving one rather than the other (in particular, the avoidance of hypoglycaemic unawareness may be more desirable than insulin independence).

Forty-two out of 48 recipients who underwent islet transplantation in the Clinical Islet Transplant Consortium-07 (CIT-07) trial achieved the primary endpoint of HbA1c <53 mmol/mol and freedom from severe hypoglycaemic events at one year post-transplantation, and 71% of patients maintained this at two years. Fifty-two percent of patients were insulin independent at 365 days post-transplantation, with median insulin independence duration of 684 days at 730 days follow-up (3). Refinements in the Edmonton protocol over time, including adaptation of the immunosuppression regimen and islet isolation techniques, have led to incremental improvements in sustained insulin independence. Review of CITR outcomes after 677 islet alone, islet after kidney, or simultaneous islet kidney transplants between 1999 and 2010 demonstrated successive improvements in three-year insulin independence from 27% (1999-2002) to 44% (2007-2010) (7).

The UK islet transplant programme has achieved a target HbA1c of <53 mmol/mol in 70% of recipients (median pre-transplant 64 mmol/mol, median 12 months post-transplant 44.5 mmol/mol) in early analyses (4). The most recent NHSBT data show median insulin doses of 0.45 units/kg pre-transplant and one-year post-transplant doses of 0.31 units/kg (5).

Previously, different groups have used varying thresholds for each of the three domains above, making it difficult to compare outcomes. Composite scores have therefore been developed which take into account more than one of these metrics.

The composite Igls criteria have recently been published, and can be used for both pancreas and islet transplantation (Table 1). Consistent use of these criteria is expected to enable better benchmarking of graft outcomes between international groups, and

should drive quality improvement measures. Large-scale analyses of islet transplant outcomes have not yet been performed using the Igls definitions.

Table 1 Igls definitions for classification of beta-cell replacement therapy function (adapted from (8)).

Beta-cell graft functional status	**HbA1c, % (mmol/mol)**	**Severe hypoglycaemia, events per year**	**Insulin requirements U/kg/day**	**C-peptide**
Optimal	≤6.5 (48)	None	None	>Baseline
Good	<7.0 (53)	None	<50% baseline	>Baseline
Marginal	Baseline	<Baseline	≥50% baseline	>Baseline
Failure	Baseline	Baseline	Baseline	Baseline

C-peptide should also be >0.5 ng/mL (>170 pmol/L) fasting or stimulated. Insulin dose <0.5 U/kg/day may include the use of non-insulin glucose-lowering agents.

A disadvantage of the Igls definitions is that individual patients may not fit exactly within the four discrete functional status outcome categories. Other metrics of islet graft outcomes have been published that enable finer gradations of graft function to be expressed. The SUITO (Secretory Unit of Islet Transplant Objects) index expresses functional islet mass on a scale of 100 (normal healthy person) to 0 (patient with type 1 diabetes with no insulin secretory capacity) using fasting C-peptide and blood glucose levels only (9). Although lower SUITO scores are associated with higher rates of hypoglycaemic events (10), the index does not take hypoglycaemic therapy or events into account, unlike the Igls criteria. The beta score developed by the Edmonton group does include daily insulin (or oral hypoglycaemic agent) treatment, but does not consider hypoglycaemic events (Table 2) (11). A beta score of ≥7 is considered to be optimal graft function.

Because the beta score requires a MMTT, a refined score (BETA-2) has been developed that uses as a single fasting blood sample and generates a continuous outcome measure (12).

Table 2 Scoring scheme for the beta score (adapted from (11))

Component	Score 2	Score 1	Score 0
Fasting plasma glucose (mmol/L)	≤5.5	5.6-6.9	≥7.0
HbA1c (%)	≤6.1	6.2-6.9	≥7.0
Daily insulin (units/kg) or OHA use	None	0.01-0.24 and/or OHA use	≥0.25
Stimulated C-peptide (nmol/L)	≥0.3 [a]	0.1-0.29	<0.1 [b]

OHA – oral hypoglycaemic agent.

[a] If fasting C-peptide ≥0.3 nmol/L, then the stimulated C-peptide level is assumed to be ≥0.3 nmol/l.

[b] If stimulated C-peptide is <0.1 nmol/L then the total score is 0.

The optimal frequency of monitoring graft function post-transplant is not known. Self-monitoring of blood glucose levels 3-4 times daily is recommended, and the specialist team should be contacted if there are significant changes in values or patterns to allow fuller evaluation of graft function. Continuous glucose monitoring profiles may be undertaken at post-transplant assessment visits to enable assessment of glycaemic variability and exposure to clinically significant glucose levels <3 mmol/L. Self-monitoring device downloads may also provide information on episodes of glucose <3 mmol/L and calculation of other indices of glycaemic control. It is recommended that glycaemic outcomes should be assessment by three-monthly measurement of HbA1c. The measurement and monitoring of hypoglycaemia is discussed in more detail below.

13.2.3 Hypoglycaemic Events

As one of the primary outcome measures in islet transplantation, it is critical that hypoglycaemia exposure is appropriately measured and documented. It is recognised that glycaemic thresholds at which symptoms of hypoglycaemia occur vary between patients, and also within the same individual, due to changes in glycaemic control over time. However, definitions of degrees of hypoglycaemia that use serum glucose values as cut-offs enable the diabetes community to provide consistent comparisons of interventions to reduce hypoglycaemia.

The International Hypoglycaemia Study Group has proposed three levels of hypoglycaemia (Table 3) (13). It is recommended that information is collected at each clinic visit post-transplant to enable categorisation of hypoglycaemic events. A full assessment of the impact of each event of severe hypoglycaemia should be recorded, including preceding symptom awareness, administration of glucose gel or glucagon injection, and any requirement for paramedic or secondary care involvement. It is desirable to obtain downloads of any blood glucose monitoring that is performed. Continuous glucose monitoring can be used to assess overnight glucose control and glycaemic variability.

Table 3 International Hypoglycaemia Study Group proposed grades of hypoglycaemia (adapted from (13))

Level 1 A glucose alert value of 3.9 mmol/L (70 mg/dL) or less.
Level 2 A glucose level of less than 3.0 mmol/L (<54 mg/dL) is sufficiently low to indicate serious, clinically important hypoglycaemia.
Level 3 Severe hypoglycaemia, as defined by the American Diabetes Association, denotes severe cognitive impairment requiring external assistance for recovery

The NHS islet transplant programme has achieved prevention of recurrent severe hypoglycaemia without compromising glycaemic control at a median of 24 months post-transplant (4). Severe hypoglycaemic events were reduced from 20 episodes per patient per year pre-transplant to 0.3 episodes per patient per year, with resolution of impaired awareness.

Impaired awareness of hypoglycaemia should be assessed at each post-transplant outcome assessment visit by the validated Gold questionnaire (with impaired awareness defined as a Gold score of ≥4) (14). It remains difficult to adequately assess impaired awareness in the setting of no recent hypoglycaemic events, and definitive assessment of counter-regulatory responses would require complex interventional metabolic clamp studies beyond the potential of routine clinical monitoring. A more discriminative questionnaire measure to capture hypoglycaemia experience and

awareness is currently being validated by the UK Islet Transplant Consortium (15). Alternative measures include the Lability Index and HYPO score, but these have not been adopted in the UK due to the complexity of prospective data collection (16).

13.2.4 Peri-operative Surgical Complications

Islet transplantation is most commonly performed by percutaneous transhepatic catheterisation of the portal vein under direct fluoroscopic or ultrasound guidance. Less commonly, some units perform cannulation of small veins within the small bowel mesentery via mini-laparotomy, especially if simultaneous islet-kidney transplantation is performed. Both of these approaches are associated with complications.

Transhepatic portal vein puncture carries the main procedural risks of haemorrhage, portal vein thrombosis, and biliary tract damage. In the CIT-07 trial, portal vein and peri-hepatic haemorrhage requiring surgical intervention or transfusion occurred in 5 of 56 percutaneous portal vein cannulations (3). Pre-transplant screening for coagulopathy, ultrasound assessment for hepatic pathology (e.g. cirrhosis, haemangioma, and vascular malformations), the suspension of anti-coagulants pre-procedure, and routine ablation of the catheter tract appear to reduce bleeding risk. Partial portal venous thrombosis has been observed in up to 4% of procedures, although the incidence has reduced following the monitoring of portal pressure during islet infusion, infusion of <5 mL islet packed cell volume, and the concomitant use of therapeutic heparin (17).

A short-lived derangement in liver function tests is a common observation post-transplant, with one series showing transaminase elevation more than twice the upper limit of normal in over half of recipients (18). Liver function derangement is usually short-lived, with spontaneous resolution in 90% of cases within one month, and no association with graft outcome.

13.2.5 Quality of Life Measures

Islet transplantation reduces recurrent severe hypoglycaemia and improves overall glycaemic control. It is important, however, to balance these potential positive benefits against the requirement for long-term immunosuppression (with the associated side effect burden) and drug and graft monitoring.

Psychosocial outcomes are critical in the evaluation of islet transplantation. A systematic review of patient reported outcome measures analysed 10 studies on patients undergoing islet transplantation (19). The tools used to assess QoL varied between studies, and study sizes were generally small (fewer than 30 patients). In general, the review found that islet transplantation had a positive effect on fear of hypoglycaemia and improvement in diabetes-specific quality of life measures, including impact and worry. The largest study of 99 islet transplant recipients from Edmonton, Canada, showed a reduction in hypoglycaemic fear scores post-transplant. Insulin-independent recipients had less fear of hypoglycaemia than those who remained on insulin post-transplant. General health status, measured by the Health Utilities Index Mark 2, was unchanged post-transplant (20).

Few studies report transplant-specific quality of life measures such as the impact of long-term immunosuppression. New measures are therefore required, as current validated questionnaires fail to consider the outcomes of adherence to (and side-effect burden of) maintenance immunosuppression and the fear of graft rejection. Further assessment of the impact of islet transplantation on QoL and validation of most useful patient reported outcome measures is on-going within the UK Islet Transplant Consortium. It remains a priority to develop appropriate tools to fully assess QoL after islet transplantation.

13.2.6 Diabetic Complications

The Diabetes Control and Complications Trial (DCCT) demonstrated reduced risk of microvascular disease complications with intensive glucose control versus conventional medical therapy soon after diagnosis of type 1 diabetes (21). The observed reduction in risk was highly correlated with HbA1c with no significant difference observed in glycaemic variability of glucose profiles when adjusted for mean glucose (22). Reduced progression of retinopathy and nephropathy was associated with residual beta-cell function, as assessed by C-peptide at trial commencement (23). Over 30 years of follow-up following the DCCT as part of the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a strong association between elevated HbA1c and later atherosclerosis and cardiovascular disease has been confirmed (24). Given these data, it seems reasonable to assume that patients with improved glycaemic control after islet transplantation will have a reduction in the micro- and macro-vascular complications of diabetes. However, the potential adverse effect of immunosuppression must also be considered. The number of studies in this field is small.

The net impact of islet transplantation and immunosuppression on renal function remains unclear. Sirolimus- and tacrolimus-based nephrotoxicity has been demonstrated, with regression of microalbuminuria in four out of five patients undergoing immunosuppression withdrawal after graft failure (25). A cross-over study comparing the impact of islet transplantation and optimised medical therapy on microvascular disease progression reported reduced rate of renal function decline post-transplantation in patients with baseline microalbuminuria and proteinuria (26,27).

Islet transplantation has demonstrated superiority to on-going medical therapy in stabilising advanced diabetic retinopathy, with no disease progression at a median of 67 months post-islet transplant in comparison to 47 months medical follow-up in one study (27). Stabilisation of neuropathy has also been observed post-islet transplantation, with improvement in nerve conduction velocities (28-30).

The effect of islet transplantation on macrovascular diabetic complications has been less well studied. An analysis of 34 islet-kidney recipients (8 simultaneous islet-kidney transplant and 26 islet after kidney transplant) observed improved endothelial function, lower carotid artery intimal-medial thickness and better cardiovascular outcomes in those patients with maintained islet graft function at one-year post-transplant versus participants with maintained renal graft function but loss of the islet graft (31).

13.3 Immunological Monitoring in Islet Transplantation

Associations between the formation of de novo donor-specific anti-HLA antibodies (DSAs) and graft dysfunction have been reported in many forms of solid organ transplantation. However, studies assessing the impact of de novo DSAs and graft survival have been conflicting in islet transplantation (32-34). Brooks et al demonstrated an early temporal association between the development of DSAs within a month of transplantation with a rapid decline in graft function observed, and absolute graft failure at 12 months, in the absence of a second non-sensitising transplant (33).

The presence of pre-existing anti-HLA antibodies at the time of islet transplantation is associated with increased rates of graft failure (35). Also, the appearance of diabetes autoantibodies (GAD65, IA2, Zn8) after islet transplantation, or a rise in titre, is also a poor prognostic factor (36).

Given the above, it is suggested that antibody status be determined regularly post-transplant. The optimal duration between testing, and the ideal management of the recipient if DSAs or diabetes autoantibodies appear, are both currently unknown. It is suggested that serum samples for HLA antibody status should be assayed at 2 weeks following each islet transplant and then at least six-monthly in parallel with diabetes autoantibodies to allow early identification of allo- or auto-immune reactivity, and the consideration of augmented immunosuppression (37).

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Appendix:

Summary Table of Outcome Measures in SPK Transplantation

Measure	Data	Data source	Further information and considerations
Median waiting time, days (95% confidence interval)	342 (325-359)	NHSBT Annual Report on Pancreas and Islet Transplantation 2017/18 https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12251/nhsbt-pancreas-and-islet-transplantation-annual-report-2017-2018.pdf	Waiting time will vary according to the potential recipient's blood group, HLA sensitisation status, and the implanting centre. Data includes those waiting for pancreas-only transplant also.
Patient survival at 1 and 5 years post-transplant (95% confidence interval)	98 (96-99) 88 (85-90)	NHSBT Annual Report on Pancreas and Islet Transplantation 2017/18 https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12251/nhsbt-pancreas-and-islet-transplantation-annual-report-2017-2018.pdf	Risk-adjusted.
Death-censored pancreas graft survival at 1 and 5 years post-transplant (95% confidence interval)	89 (86-91) 79 (75-82)	NHSBT Annual Report on Pancreas and Islet Transplantation 2017/18 https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12251/nhsbt-pancreas-and-islet-transplantation-annual-report-2017-2018.pdf	Risk-adjusted. Pancreas graft failure defined as graft pancreatectomy or return to exogenous insulin therapy, whichever occurred first.
Re-laparotomy rate within 3 months of transplantation	23%	Banga N, Hadjianastassiou VG, Mamode N, et al. Nephrol Dial Transplant 2012; 27: 1658-63.	
Kidney delayed graft function	15.5%	Barlow AD, Saeb-Parsy K, Watson CJE. Transpl Int 2017; 30: 884-92.	Delayed graft function defined as the need for dialysis within 7 days of transplantation.
Kidney primary non-function	1.4%	Barlow AD, Saeb-Parsy K, Watson CJE. Transpl Int 2017; 30: 884-92.	Primary non-function defined as the kidney never functioning (i.e. dialysis dependence), regardless of cause
Pancreas primary non-function	1.5%	Barlow AD, Saeb-Parsy K, Watson CJE. Transpl Int 2017; 30: 884-92.	Primary non-function defined as the pancreas never functioning (i.e. insulin dependence), regardless of cause
All-cause kidney graft survival at 1, 5, and 10 years post-transplant	96% 89% 80%	Barlow AD, Saeb-Parsy K, Watson CJE. Transpl Int 2017; 30: 884-92.	Defined as death, re-transplantation, or return to dialysis, whichever occurred first. The most common cause of kidney graft loss was death with a functioning graft (37%).
All-cause pancreas graft survival at 1, 5, and 10 years post-transplant	86% 76% 68%	Barlow AD, Saeb-Parsy K, Watson CJE. Transpl Int 2017; 30: 884-92.	Defined as death, re-transplantation, or return to insulin treatment, whichever occurred first.