HANDBOOK OF RENAL AND PANCREATIC TRANSPLANTATION

EDITED BY

IAIN A. M. MACPHEE | JIŘÍ FRONĚK

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Handbook of Renal and Pancreatic Transplantation

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- 60 full-colour figures to accompany Chapters 7 and 10
- Video clips of live donor nephrectomy to accompany Chapter 7

Handbook of Renal and Pancreatic Transplantation

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Preface

When we set out on planning this book there was no contemporary handbook for the practice of renal and pancreatic transplantation that was focussed on a European rather than North American approach. There are significant differences in transplant practice internationally and there is a need for a practical guide to application of the current evidence base.

This book aims to cover all aspects of transplantation from organ donation through long-term follow-up. We have aimed to provide information useful to all members of the multidisciplinary transplant team. This is not intended as a comprehensive textbook and readers are referred to the number of excellent existing works that serve this role.

We are delighted with the panel of experts from across Europe who agreed to contribute chapters and are extremely grateful for the time that they have contributed in putting the book together. We have learned a lot about transplantation in the editing process and hope that the reader will find the information equally useful. The videos demonstrating surgical technique for laparoscopic donor nephrectomy were developed from a successful course based on live surgical demonstrations. The drug treatment regimens described represent the authors' assessment of the available evidence and actual use in practice rather than adhering strictly to licensed indications and doses.

We are deeply grateful for the support of our families in tolerating the time required to put the book together.

Iain MacPhee
Jiří Froněk
February 2012

Abbreviations List

ACE	angiotensin-converting enzyme
ACMR	acute cell-mediated rejection
ADPKD	autosomal dominant polycystic kidney disease
ALG	anti-lymphocyte globulin
AMR	antibody-mediated rejection
ANCA	antineutrophil cytoplasmic antibody
APC	activated protein C
APTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
ATIII	antithrombin III
aTCMR	acute T-cell-mediated rejection
ATG	antithymocyte globulin
AVF	arteriovenous fistula
BMI	body mass index
BP	blood pressure
BSA	body surface area
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCMR	chronic active cell-mediated rejection
CDC	complement-dependent cytotoxicity
CDC-XM	complement-dependent lymphocytotoxic crossmatch
CDU	colour Doppler ultrasound
CITR	Collaborative Islet Transplant Registry
CKD	chronic kidney disease
CMV	cytomegalovirus
CMVIg	cytomegalovirus hyperimmunoglobulin
CNI	calcineurin inhibitor
CREG	cross-reactive group
cRF	calculated reaction frequency
CSE	combined spinal–epidural anaesthesia
CT	computerised tomography
CVD	cardiovascular disease
CVP	central venous pressure
DBTL	double-balloon triple-lumen
DCD	donor after circulatory death
DD	deceased donor
DES	drug eluting stent
DFPE	double filtration plasma exchange

DSA	digital subtraction angiography; donor-specific antibody
DTT	dithiothreitol
EBV	Epstein–Barr virus
ECD	expanded criteria donor
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay
ESRD	end-stage renal disease
FBC	full blood count
FC-XM	flow cytometric crossmatch
FMD	fibromuscular dysplasia
FSGS	focal and segmental glomerulosclerosis
G6PD	glucose-6-phosphate dehydrogenase
GFR	glomerular filtration rate
HAART	highly active antiretroviral therapy
HACA	human anti-chimeric antibody
HBD	heartbeating donor
HBV	hepatitis B virus
HCV	hepatitis C virus
HDU	high-dependency unit
HHV-8	human herpesvirus 8
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HR	hyperacute rejection
HSV	herpes simplex virus
HTK	histidine-tryptophan-ketoglutarate
HTLV1	human T-lymphotropic virus
HUS	haemolytic uraemic syndrome
IA	immunoadsorption
IBMIR	instant blood-mediated inflammatory reaction
ICP	intracranial pressure
IDDM	insulin-dependent diabetes mellitus
IFG	impaired fasting glucose
IgAN	immunoglobulin A nephropathy
IGT	impaired glucose tolerance
IHD	ischaemic heart disease
IL-2	interleukin 2
INF-γ	interferon-γ
IVIg	intravenous immunoglobulin
IVU	intravenous urogram
KT	kidney transplantation
LDK	living donor kidney
LVH	left ventricular hypertrophy
LVSD	left ventricular systolic dysfunction
MCGN	mesangiocapillary glomerulonephritis
MCP	membrane co-factor protein
MFI	median fluorescence intensity
MN	membranous nephropathy

MPGN	mesangioproliferative glomerulonephritis
MR	magnetic resonance
mTOR	mammalian target of rapamycin
NHBD	non-heartbeating donor
NODAT	new-onset diabetes after transplantation
NS	normal saline
OGTT	oral glucose tolerance test
PAK	pancreas after kidney
PALK	pancreas after living donor kidney
PAT	pancreas alone transplantation
PCA	patient-controlled analgesia
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PEEP	positve end-expiratory pressure
P-gp	P-glycoprotein
PJ	*Pneumocystis jiroveci*
PONV	post-operative nausea and vomiting
PP	plasmapheresis
PSV	peak systolic velocity
PT	prothrombin time
PTC	peritubular capillaries
PTH	parathyroid hormone
PTLD	post-transplant lymphoproliferative disorder
PVN	polyomavirus nephropathy
RAS	renal artery stenosis
RRT	renal replacement therapy
RSI	rapid sequence intubation
RTR	renal transplant recipient
SAB	single antigen bead
SCD	sudden cardiac death
SPK	simultaneous pancreas kidney
TEA	thoracic epidural analgesia
TEE	transoesphageal echocardiography probe
TMA	thrombotic microangiopathy
TNF	tumour necrosis factor
TPMT	thiopurine-S-methyltransferase
TTP	thrombotic thrombocytopaenic purpura
UTI	urinary tract infection
VZV	varicella zoster virus

1 History of transplantation

Jiří Froněk and Iain MacPhee

In setting the scene for this handbook, we would like to acknowledge the contribution of the masters on whose backs we all climb. This book is written as a practical guide to the contemporary practice of transplantation. This is a brief account of how we got to where we are now. Early (but unsuccessful) attempts at transplantation have been documented for centuries. Advances in basic science allowed transplantation to become reality within the 20th century. Nowadays organ transplantation is accepted as a standard treatment for end-stage failure of a number of organs. The pioneers of transplantation medicine in the 20th century had to overcome substantial obstacles, including developing new surgical techniques, understanding transplant immunology and defining areas in which transplantation is of benefit. Nor was this era easy for public understanding of the fundamental issues involved. It was not simple to explain and achieve widespread acceptance of the concept of 'brainstem death' as distinct from 'cardiovascular death'. Transplantation has raised a vast number of ethical, philosophical and legal issues. Achievement of societal 'buy in' to difficult issues such as removal of organs after one's death or donation of an organ by a living donor were essential barriers to be overcome. Transplantation development is a result of the effort of many people from all over the world, who worked together and cooperated with the same aim and who participated in generating and applying new knowledge. Here we summarise the key events that led to the widespread adoption of kidney and other organ transplantation in the form we know it today.

1901 – Karl Landsteiner described the existence of **blood groups**. In 1930 he became a Nobel Prize Laureate.

1902 – Alexis Carrel published an end-to-end **vascular anastomosis** technique, which became a fundamental technique for vascular surgery and at the same time enabled the development of organ transplantation. Carrel received the Nobel Prize in Physiology or Medicine in 1912.

1902 – Emerich Ullmann carried out the **first experimental kidney transplantation**. He sewed the kidney onto a dog's neck. The kidney functioned for 5 days.

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1906 – Mathieu Jaboulay made a **first xenotransplantation attempt in human medicine**. Pig or goat kidneys grafted onto the forearm of patients worked for around 1 hour.

1908 – Alexis Carrel and Charles Claude Guthrie pointed out the possibility of **use of organ hypothermia** for its long-term storage.

1912 – Görge Schöne was the first to state the suspicion that **graft rejection** has an immunological basis.

1913 – Abel, Rowntree and Turner created the **first 'artificial kidney'** and became the fathers of dialysis. Their machine was never used in human medicine.

1923 – The **first human peritoneal dialysis**.

1933 – Ukrainian surgeon Yu Yu Voronoy carried out the **first human cadaveric kidney transplant** on 3 April 1933. The donor was an elderly man, who died after a head injury, and the recipient was a 26-year-old woman with quicksilver poisoning. He carried out the operation under local anaesthesia and sutured the kidney onto the thigh blood vessels of the recipient, leading the ureter out through the skin. The kidney graft did not produce urine and the patient died 2 days after the operation.

1943 – Willem Kolff created the **first functioning dialysis machine**, thanks to the discovery that heparin is able to prevent blood coagulation.

1943 – Thomas Gibbon and Peter Medawar published their **first experience with skin allografts**, used in the treatment of burned World War II pilots. Peter Medawar was awarded the Nobel Prize in 1960.

1948 – Gorer, Lyman and Snell described a **dominant histocompatible locus** on a mouse. In 1980 Snell, together with Dausset and Benacerraf, became Nobel Prize Laureates.

1951 – René Küss described a kidney transplantation technique that is still used today.

1952 – Michon and Hamburger were the first to use a **kidney from a living related donor** in Paris. The kidney, transplanted from mother to son, functioned for 22 days.

1954 – On 23rd December, Joseph Murray, John Merrill and Hartwell Harrison carried out the first successful kidney transplantation between identical twins in Boston. The recipient, Richard Herrick, lived with a functioning kidney from his brother for 8 years, he died of a heart

attack in 1962 with recurrence of his original illness (chronic glomerulonephritis) in the graft. Joseph Murray became a Nobel Prize Laureate in Medicine in 1990.

1955 – **First heart valve transplants**: Gordon Murray of Toronto, Ontario, used the main aortic valve of a male automobile accident victim to perform the world's first heart valve transplant on a patient with a severely leaking aortic valve. The transplanted valve functioned well for over 8 years.

1958 – Jean Dausset described the first **HLA antigen**.

1959 – Murray and Merrill carried out the **first kidney transplantation between non-identical twins**.

1962 – The **first dialysis centre** was established in Seattle.

1963 – **First liver transplant**: Thomas E. Starzl of the University of Colorado in Denver attempted the first liver transplant, but the patient died within a few days.

1963 – **First lung transplant:** James D. Hardy of the University of Mississippi in Jackson performed the first single human lung transplant, but the patient died within days.

1964 – Starzl described **ABO-incompatible kidney hyperacute rejection** caused by antibodies against the graft.

1965 – Paul Terasaki, T. L. Marchioro and Thomas Starzl described a **hyperacute kidney rejection**.

1966 – Paul Terasaki and Thomas Starzl reported the results of **prospective donor selection according to HLA standardisation level.**

1966 – **First pancreas transplant:** Richard C. Lillehei and William D. Kelly of the University of Minnesota, Minneapolis, transplanted a pancreas into a 28-year-old woman; the graft did work, but she died 3 months later from pulmonary embolism.

1967 – **First successful liver transplant:** Thomas E. Starzl of the University of Colorado in Denver performed the first successful liver transplant. The liver functioned for 13 months.

1967 – **First successful heart transplant:** Christiaan Barnard, at Groote Schur Hospital in Cape Town. The recipient died 18 days later of pneumonia.

1967 – Starzl and Iwasaki published Immunosuppression induction of **antilymphocyte globulin** and subsequently azathioprine and prednisone as maintenance treatment.

1969 – Discovery of mould *Beauveria nivea* (Tolypocladium infantum Gams), which produces **ciclosporin**.

1972 – Stähelin and Borel described **immunosuppressive qualities of ciclosporin.**

1974 – **First islet cell transplant:** David Sutherland of the University of Minnesota in Minneapolis performed the world's first islet cell transplant. The procedure worked for only a short time.

1978 – Roy Calne was the first to use **ciclosporin in human medicine**.

1979 – David Sutherland of the University of Minnesota in Minneapolis performed the **first living-related pancreas transplant**.

1981 – Benedict Cosimi described for the first time the **use of monoclonal antibody** in human medicine.

1983 – **First successful single lung transplant:** Joel Cooper of the Toronto Lung Transplant Group, Toronto General Hospital (now part of the University Health Network), performed a single lung transplant. Patient lived for more than 6 years before dying of kidney failure.

1983 – **First multi-visceral transplant:** The first multi-visceral transplant was performed at the University of Pittsburgh Medical Center in Pennsylvania.

1984 – **First heart–liver transplant:** The first heart–liver transplant was performed at the University of Pittsburgh Medical Center in Pennsylvania.

1986 – **First successful double lung transplant:** Joel Cooper of the Toronto Lung Transplant Group, Toronto General Hospital performed a double lung transplant, patient lived until 2001, died of a brain aneurysm.

1988 – **First successful liver–bowel transplant:** David Grant of the University Hospital of London Health Sciences Centre in London, Ontario, transplanted a liver and small bowel into 41-year-old recipient, who had been unable to eat or drink after having her small bowel removed in 1987.

1988 – **First two-in-one liver transplant:** Two patients at Paul Brousse Hospital in Villejuif, France, received a liver transplant, when one donated organ was cut in half.

1989 – First successful living-related liver transplant: Christopher Broelsch of the University of Chicago Medical Center transplanted a portion of a mother's liver into her 21-month-old daughter. Both mother and daughter are still healthy today.

1989 – First combination heart, liver, and kidney transplant: Surgeons at Presbyterian Hospital in Pittsburgh, Pennsylvania, transplanted a heart, liver and kidney into a 26-year-old woman. She survived for 4 months.

1990 – First successful living-related lung transplant: Vaughn A. Starnes, at Stanford University Medical Center in Palo Alto, California, transplanted the lobe of one lung into a 12-year-old girl (the lobe was donated by her mother).

1992 – Thomas Starzl described chimerism by transplanted patients, a possible manifestation of allograft tolerance.

1995 – First **laparoscopic live donor nephrectomy:** In 1995 Lloyd Ratner and Louis Kavoussi descried the laparoscopic live donor nephrectomy technique, first performed at Johns Hopkins.

1998 – Hand-assisted laparoscopic live donor nephrectomy technique described by Wolf *et al.*

1998 – First combined liver and bone marrow transplant: Surgeons at King's College Hospital in London, performed the first combined liver and bone marrow transplant procedure on 18-year-old recipient, suffering from CD40-ligand deficiency.

2000 – Edmonton protocol: The technique of islet isolation from a deceased donor pancreas followed by portal vein administration was first adopted in 1999 and published on 2000 by Shapiro. Islet transplantation can be used as alternative technique to pancreas transplantaion.

2002 – Hand-assisted retroperitoneoscopic live donor nephrectomy technique described by Wadström and Lindström.

2005 – First living donor islet transplant: On 19 January, a team of surgeons at the Kyoto University Hospital in Japan, under the supervision of Dr James Shapiro, took islet cells from the pancreas of a 56-year-old woman and transplanted them into the liver of her 27-year-old diabetic daughter.

At the beginning of 20th century, the modern transplantation era started with an experiment on an animal model. Despite failures and pessimism in experimental transplantation, some surgeons persisted in trying to transplant kidneys into patients. Although these procedures

were unsuccessful, owing to absence of immunosuppression, development of the surgical techniques, including heterotopic transplantation, was a key step on the pathway. Dialysis allowed transplantation to become an elective rather than emergency life-saving procedure. Advances in graft conservation, immunology, immunosuppression and the field of extracorporeal perfusion methods led to a rapid development of deceased donor transplantation programmes. The development of living donor transplantation was a little overshadowed by other exciting new developments until 1990s, when we saw an international revival of interest in living donation owing to the inadequate supply of deceased donors to meet the demand for transplantation and also better long-term results with transplants from live donors.

In spite of medical advances that have reduced the incidence of end-stage organ failure for some diseases, the demand for deceased donor organs continues to out-strip supply. Some organs, or their function, can be temporarily replaced by artificial ones, for example left ventricular assist devices, but this replacement is generally only temporary, providing a bridge to transplantation. The use of organs of other animal species (xenotransplantation) is a matter for the distant future – if at all – owing to a number of immunological, physiological and infectious barriers. Maximising the supply of organs for transplantation is now a key priority for development. One possibility is better organisation of deceased donor programmes, including legislative modifications. There has been renewed enthusiasm for the retrieval of organs from individuals who have died suddenly and unexpectedly [donors after circulatory death (DCDs), previously known as non-heartbeating donors (NHBDs)]. The boundaries of living donation are also being probed, including extending criteria for suitability to donate a kidney and extension of living donation to other organs, including lung segment, liver, pancreas or intestinal transplantation.

Advances in transplantation medicine have improved and lengthened the lives of many people. The number of deceased donors per year remains in many countries more or less stable, despite attempts to increase this number. By contrast, the number of patients on the waiting list is growing. The need for development of transplantation is no less now than it was several decades ago. This time we have to make sure that the public is presented with a realistic view of organ transplantation in support of appropriate policy decisions. Motivating society to support organ donation, altruism and understanding of the key challenges facing transplantation remain key activities for those of us involved in the field.

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2 Assessment of the potential renal transplant recipient

Patrick B. Mark and Alan G. Jardine

Background

For many patients with end-stage renal disease (ESRD), renal transplantation provides benefits in both survival and quality of life compared with maintenance dialysis therapy and is generally accepted to be the optimum treatment for ESRD. However, in assessing which patients are likely to benefit from renal transplantation, a number of issues arise.

First, it is imperative that the potential renal transplant recipient (RTR) does not exhibit such a burden of co-morbid disease (most often cardiovascular disease) that the transplant operation cannot be justified owing to risk of peri-operative mortality. Peri-operative mortality in most transplant centres is low, with 1-year patient survival following renal transplantation of the order of 97% in the UK. Therefore, in reality peri-operative mortality is a less common problem for the majority of patients where transplantation has been considered a viable option. Screening should aim to identify remediable disease before transplant listing. As in most countries, only a third of patients with ESRD in the UK are listed for renal transplantation; screening should improve outcomes for patients whether or not they go on to receive a transplant. The transplant operation itself should be technically feasible from a surgical point of view, without anatomical or vascular pathologies that make implanting the transplant impossible. The surgical aspects of renal transplantation are dealt with elsewhere. More detailed consideration will be given to the management of cardiovascular disease in potential RTRs as part of the assessment process as well as other specific conditions likely to be associated with increased peri-operative risk.

Second, following the transplant operation, both patient and graft survival should be such that the quality and/or duration of life should represent a significant improvement compared with that provided by dialysis therapy. Early graft loss where the graft fails because of predictable causes (e.g. some recurrent renal diseases or non-compliance with immunosuppressive therapy) is a potential waste of a resource in

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short supply, which in the case of deceased donor kidneys may have been better allocated to another potential RTR. Issues that might lead to early graft loss should be identified during the assessment process. Given the shortage of deceased donor kidneys, available kidneys should be considered a resource to maximise the benefits of transplantation to the wider community of patients with ESRD.

Finally, renal transplantation commits the RTR to lifelong immunosuppression, with inherent risks of infection and malignancy, as well as an increased risk of cardiovascular disease related to both pre-existing disease and that associated with hypertension, new onset diabetes after transplantation (NODAT), hyperlipidaemia and renal impairment. During the assessment of the RTR, attention should be paid to potential risks of committing the patient to long-term immunosuppression. Specific diseases, such as previous cancer, will be examined later in the chapter.

Many excellent guidelines examining optimal assessment of potential RTRs have been published, either under the auspices of national societies of transplantation or as review articles examining specific co-morbidities that impact on the transplant process [1,2]. In all cases, guidelines – including this chapter – can only serve to indicate possible strategies that might be beneficial for managing RTRs. By their nature, guidelines cannot be exhaustive and deal with every eventuality. Each potential RTR will present unique challenges. With that in mind, this chapter will examine conditions likely to present concerns during the process of renal transplantation, grouped by disease and organ system.

Preparation of the potential transplant recipient

Timing of assessment

Ideally, before a patient with progressive renal disease requires renal replacement therapy (RRT), it should be established whether the patient would be a suitable candidate for renal transplantation. Most centres would consider it appropriate to list the suitable candidate for a deceased donor kidney transplant when they are within approximately 6 months of requiring dialysis. Pre-emptive transplantation (whether with a deceased donor or live donor kidney), where the patient receives a transplant before initiation of dialysis, has been associated with better patient and graft survival. Similarly, increasing time on dialysis has been shown to have a detrimental effect on both these outcomes [3]. Thus, early assessment for transplantation should be part of standard preparation for RRT. Early assessment allows both optimisation of the potential RTR's health in preparation for transplantation, as well as facilitating identification and work-up of live donors. In many cases where the patient attends a renal clinic, this timing should be fairly predictable, based on the trend of decline in glomerular filtration rate, combined with knowledge of the rate of progression of the specific renal disease. Unfortunately, early referral for transplant listing may not be