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Acute antibody-mediated rejection

Acute antibody-mediated rejection

Acute antibody-mediated rejection (AMR) occurs in <5% of renal transplants but is more serious and more di ffi cult to treat than cell-mediated rejection. It is caused by HLA DSA, which are produced by a sensitising episode from a previous transplant, a blood transfusion or pregnancy . Binding of DSA to mismatched HLA antigens on the surface of allograft endothelial cells leads to activation of the complement system and tissue injury . In the kidney , transplant biopsy will show inflammation of the vessels (vasculitis) and deposition of the complement component C4d in the peritubular capillaries (Figure 88.9). Treatment is by plasma exchange to remove circulating antibodies. Rituximab, an anti-CD20 monoclonal antibody , can also be used to destroy B cells and prevent further production of DSA. The pathophysiology is not well understood but the long-lived indirect antigen presentation pathway is likely to be important. CD4 T-cell activation also promotes donor-specific alloanti - body production, and this causes ongoing allograft damage.

Figure 88.9 Acute antibody-mediated renal allograft rejection. There is widespread staining for the complement component C4d within the peritubular capillaries (arrows), which indicates alloantibody binding to the graft vasculature. Depleting antibodies Calcineurin blockers ATG Ciclosporin Tacrolimus Alemtuzumab Resting Early T cell activation Costimulatory blockade CTLA-4Ig Figure 88.10 Site of action of immunosuppressive agents on T cell. ATG, antithymocyte globulin; CTLA-4Ig, cytotoxic T-lymphocyte-associated protein 4 immunoglobulin; MPA, mycophenolic acid derivatives; mTOR, mammalian target of rapamycin.

Acute cell-mediated rejection

Acute cell-mediated rejection

In the era of modern immunosuppressive drugs, the incidence of acute cell-mediated rejection (CMR) is only 10–20%. Acute CMR is largely mediated by direct antigen presentation. As donor APCs in the allograft have a lifespan of only a few weeks, the peak incidence of acute CMR is in the first 3 /uni00A0 months post transplantation. The characteristic biopsy finding of acute CMR is a marked interstitial lymphocytic infiltrate (Figure 88.8). In the kidney , the presence of lymphocytes inside the basement membrane of the renal tubular epithe - lium is referred to as tubulitis and is diagnostic of acute CMR. Initial treatment is by high-dose pulsed intravenous steroids (methylprednisolone 0.5 /uni00A0 g intravenously for 3 days), which is

Figure 88.8 Severe acute renal allograft rejection with a heavy mono

nuclear cell in /f_i ltrate and intimal arteritis.

rejection is treated with lymphocyte-depleting intravenous antithymocyte globulin (ATG).

Antigen presentation in transplantation

Antigen presentation in transplantation

There are two main types of antigen presentation to T lympho cytes (Figure 88.7). Direct antigen presentation involves donor APCs showing intact and unprocessed donor HLA (class I or class II) molecules on their cell surface to recipient T cells. In contrast, indirect presentation is performed by recipient APCs. These internalise foreign donor HLA molecules from the g raft, process them into short peptide fragments and then load them into the peptide groove of recipient (self) HLA class II molecules. The donor peptide–recipient HLA class II complex is then expressed on the cell surface and presented to recipient 6–12 weeks after transplantation because this is the lifespan of the donor passenger APCs that are present in the allograft. As indirect presentation involves recipient APCs it is a long-liv ed - response.

(a) Direct antigen presentation A TCR MHC II Donor T cell APC CD4 (b) Indirect antigen presentation A TCR MHC II Recipient T cell APC CD4 Figure 88.7 Direct (a) and indirect (b) antigen presentation. A, antigen; APC, antigen-presenting cell; CD, cluster of differentiation; MHC II, major histocompatibility complex class II; TCR, T-cell receptor. (Adapted with permission from Clatworthy M, Watson C, Allison M, Dark J. Transplantation at a glance . John Wiley and Sons Ltd, 2012.)

Antiproliferative agents (azathioprine and mycophe

Antiproliferative agents (azathioprine and mycophenolic acid)

These drugs are antiproliferative agents. Their mechanism of action is to block purine nucleotide synthesis. This prevents replication of DNA and thus interferes with lymphocyte prolif eration. The main side e ff ects of both drugs are bone marrow suppression (anaemia, leukopenia, thrombocytopenia) and gastrointestinal symptoms (nausea, vomiting and diarrhoea).

Calcineurin inhibitors (ciclosporin and tacrolimus

Calcineurin inhibitors (ciclosporin and tacrolimus)

The calcineurin inhibitors (CNIs) are the mainstay of modern immunosuppressive regimens. CNIs prevent transcription of the IL-2 gene in T cells. As IL-2 is the main T-cell growth factor, inhibition of its production prevents T-cell proliferation.

Antiproliferatives Anti-CD25 MPA Azathioprine CD25 Late Proliferation activation mTOR inhibitors Sirolimus Everolimus

nephrotoxicity . CNIs have a narrow therapeutic index (a small di ff erence between the minimum e ff ective concentration and the minimum toxic concentration). CNI dosage must therefore be guided by monitoring drug blood levels.

Corticosteroids

Corticosteroids

These are potent anti-inflammatory agents that have wide-ranging e ff ects on the immune system. Prolonged exposure to steroids causes numerous potential side e ff ects, including: a Cushingoid appearance with a moon face, central obesity , abdominal striae and proximal myopathy; thin skin that bruises easily; hypertension; glucose intolerance that may lead to new-onset diabetes mellitus; osteoporosis; and peptic ulcer disease. These may be minimised by rapid reduction or withdrawal of steroids.

Delayed renal allograft function

Delayed renal allograft function

DGF is defined as the need for dialysis in the first 7 days post transplant. The patient will be oliguric or anuric and the serum creatinine will fail to fall in the early postoperative period. DGF is usually the clinical consequence of acute tubular necrosis related to ischaemia–reperfusion injury . It occurs in around 30% of DBD kidneys and 60% of DCD kidneys because of the significantly longer warm ischaemic period prior to organ cooling. In contrast, DGF occurs in <5% of live donor kidneys because of the short cold ischaemic time. An early Doppler ultrasound study should be performed in all patients with DGF to check that the graft is well vascularised. The management of DGF is supportive with haemodialysis, careful fluid balance and avoidance of CNI toxicity . Graft function usually recovers within a few days, but it may take several weeks. Primary non-function is the term used for grafts that never work. This occurs in <5% of renal transplants as a result of either vascular thrombosis or irreversible ischaemic injury leading to cortical necrosis.

Donation after circulatory death

Donation after circulatory death

Donation after circulatory death describes the recovery of organs for transplantation after death confirmed by circula tory criteria. These donors were formerly called asystolic or non-heart-beating donors. There have been very significant increases in DCD programmes in many countries over the last decade. The modified Maastricht classification is widely used to ca tegorise DCD (Table 88.2). Organ donation after unexpected and irreversible cardiac arrest is referred to as uncontrolled DCD. Donation after death resulting from the planned withdrawal of life-sustaining cardiorespiratory support is called controlled DCD. In DCD donors cardiorespiratory arrest occurs prior to starting organ retrieval. The organs are therefore warm but not being perfused with oxygenated blood for a period of time before they are flushed with cold preservation solution. This warm ischaemia period should be limited as much as possible. Controlled DCD donors are ICU-based and have su ff ered massive and irreversible cerebral damage but have an intact brainstem so that they are self-ventilating. In a situation wher further attempts at treatment would be futile, the withdrawal of supportive treatment inevitably leads to cardiorespiratory arrest, and this usually occurs within a short time. In the UK, after cardiac arrest there is a mandatory ‘no-touch’ period of 5 minutes. This is deemed to be the time beyond which there is irreversible loss of cardiac and cerebral function. The donor is transferred from ICU to the operating department and a rapid median sternotomy and midline laparotomy are performed. The ascending aorta and abdominal aorta are cannulated and the organs are perfused with ice-cold preservation fluid without any initial dissection. The warm ischaemic period is usually less than 10 minutes. Organ procurement is then car ried out in standard fashion. Uncontrolled DCD donors have usually su ff ered an unexpected and irrecoverable cardiac event either outside or inside hospital. After a period of attempted, but failed, cardiopulmonary resuscitation (CPR) and observation of the 5-minute rule, CPR with administration of high-concentration oxygen is recommenced, often using a mechanical resuscita tion device. In situ renal cooling is performed by placing a double-balloon, triple-lumen perfusion catheter into the aorta via a femoral artery cut-down (Figure 88.1). The donor can then be transferred to the operating theatre and the kidneys are Frederic Eugene Basil Foley , 1891–1966, urologist, Ancker Hospital, St P - tion is usually reserved for the kidneys only as they are able to recover from warm ischaemic periods of up to 45 minutes. - - - -

TABLE 88.2 Modi /f_i ed Maastricht classi /f_i cation of donation after circulatory death (DCD). Category Description Type of DCD Location I Dead on arrival at Uncontrolled ED hospital Uncontrolled ED II Unsuccessful resuscitation after cardiac arrest Controlled ICU III Anticipated cardiac arrest after withdrawal of support IV Cardiac arrest in brain- Controlled ICU dead donor V Unexpected cardiac Uncontrolled ICU arrest in ICU ED, emergency department; ICU, intensive care unit.

Dual kidney transplantation

Dual kidney transplantation

This involves the transplantation of a pair of marginal quality kidneys from the same donor into one recipient in order to provide adequate nephron mass. Both kidneys can be placed in the same iliac fossa. This approach is used for kidneys from elderly DCD donors and so-called expanded criteria donors, which are defined by age >60 years or age >50 years with at least two of the following: hypertension; terminal creatinine >133 /uni00A0 µmol/L; death from stroke.

Early postoperative course

Early postoperative course

Accurate fluid and electrolyte balance are maintained with the help of central venous pressure monitoring. Hyperkalaemia is common in the early post-transplant period, especially in patients with DGF . This should be managed initially with intra venous glucose and insulin but early dialysis is often required. Recovery is straightforward in the majority of renal transplant patients. The bladder catheter is remo ved on postoperative day 5 and most patients can be discharged on day 6.

Evaluation of the deceased donor

Evaluation of the deceased donor

The absolute contraindications to organ donation include active systemic sepsis and transmissible infection. Malignancy within the last 5 years is also an absolute contraindication with the exception of tumours that do not metastasise (primary brain tumours, non-melanotic skin cancer and in situ carci - noma of the cervix). However, there is now evidence that organs from high-risk donors can be transplanted safely and e in situ - - aul, MN, USA.

Distal balloon Left kidney Right kidney Aorta Inferior vena cava Proximal balloon Foley catheter Double-balloon triple-lumen catheter Figure 88.1 In situ perfusion of kidneys in a non-heart-beating donor (donation after circulatory death [DCD]). A double-balloon aortic cath

eter is introduced through a groin incision and 10–15 litres of chilled preservation solution is administered. The perfusate is vented through a Foley catheter introduced into the femoral vein.

conventional donors. Thus, as a further response to the organ donor shortage, organs are now being transplanted from donors with meningitis/encephalitis, human immunodeficiency virus (HIV), hepatitis B and C and high-risk behaviour with the potential for blood-borne infection.

FURTHER READING

FURTHER READING

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HLA matching

HLA matching

Allograft rejection is directed against human leukocyte anti gens (HLAs). These are a group of cell surface glycoprotein molecules. HLA molecules are divided into class I (A, B and C) and class II (DR, DP and DQ). Class I molecules are expressed e xpressed by antigen-presenting cells (APCs) such as dendritic cells and B lymphocytes. HLA molecules are encoded for in the major histocompatibility complex (MHC) on chromosome 6. They are highly polymorphic, i.e. their amino acid sequences di ff er widely between individuals . To give an example, there are >1000 variants of the HLA-B gene. This genetic vari - ability means that most transplant donors and recipients have di ff erent HLA profiles. Donors and transplant recipients are HLA-typed using DNA sequencing. The antigens at HLA-A, -B and -DR are together described as the tissue type. The lev el of mismatch between the HLA molecules deter - mines the strength of the immune response. Every individual has two copies of each HLA gene and so for each locus (A, B or DR) it is possible to have 0, 1 or 2 mismatched genes. As the number of mismatches increases so does the chance of immune recognition and r ejection. The best matched grafts are described as having a mismatch of 0–0–0, i.e. no mis - matches at A, B or DR, respectively . A completely mismatched graft would be annotated as a 2–2–2 mismatch. The e ff ects of the di ff erent HLA antigens are not uniform. DR mismatches have a more powerful e ff ect than B mismatches , and A mis - matches are the least important. The tissue types of potential renal transplant recipients are held by national organisations, - such as NHS Blood and Transplant in the UK, and used to allocate donor organs to patients with the lowest level of HLA mismatch.

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Hyperacute rejection

Hyperacute rejection

Hyperacute rejection is extremely rare. It can result from an inadvertent ABO blood group-incompatible transplantation after a clerical error in recording blood groups. It may also occur when there are preformed circulating donor-specific HLA antibodies (DSA) or ABO antibodies. In either case, - immediately after revascularisation of the transplant anti - bodies will bind to ABO or HLA antigens on the surface of the graft vascular endothelial cells. The antibodies are comple - ment fixing and this leads to activation of the complement cascade and phagocytes. This leads to endothelial damage with release of tissue factor and activ ation of the clotting cascade . - Widespread intravascular thrombosis causes infarction of the allograft within minutes or hours. This is untreatable and inevitably results in graft loss.

Hypothermic machine perfusion

Hypothermic machine perfusion

The transplant organ is placed in a sterile chamber and cold preservation fluid is continually recirculated through the vasculature at low temperature and pressure (30 /uni00A0 mmHg) (Figure 88.4). The perfusion fluid is based on UW solution and some systems include oxygenation. This technique flushes the microcirculation more e ff ectively . There are trial and meta-analysis data showing that hypothermic machine perfu - sion reduces the rate of delayed graft function (DGF) in renal transplantation, but the e ff ect size is small.

® ® Figure 88.4 The LifePort hypothermic perfusion machine (LifePort Kidney Transporter courtesy of Organ Recovery Systems).

IMMUNOLOGY OF TRANSPLANT REJECTION ABO blood group

IMMUNOLOGY OF TRANSPLANT REJECTION ABO blood groups

ABO blood group antigens are glycoproteins with di ff erent carbohydrate components. ABO antigens are expressed not only on the surface of red blood cells but also on endothelial cells. In all organ transplants there must therefore be ABO blood group compatibility between the recipient and the donor organ, using the same rules for blood transfusion (Table 88.3

TABLE 88.3 Blood group compatibility. Donor blood group Permissible recipients O (universal donor) O, A, B and AB A A and AB B B and AB AB (universal recipient) AB

IMMUNOSUPPRESSION

IMMUNOSUPPRESSION

Modern immunosuppression is so e ff ective that acute rejec - tion rates of 10–20% can be achieved in all types of solid organ transplantation. The challenge is to deliver su ffi cient immunosuppression to prevent rejection while minimising drug side e ff ects. Imm unosuppression also increases the risk of both infection and malignancy . This is a non-specific e ff ect related to the total burden of immunosuppression rather than agent-specific side e ff ects. The mechanisms of action of current immunosuppressive drugs depend on anti-inflammatory e ff ects and the prevention of lymphocyte activation and proliferation (Figure 88.10). Lymphocytes are some of the most rapidly dividing cells in y and their activation and clonal expansion forms the the bod immunological basis of acute allograft rejection. Immunosuppression for transplantation has two phases: induction and maintenance. Induction therapy commonly consists of a combination of high-dose intravenous steroids and the anti-CD25 monoclonal antibody basiliximab, which locks IL-2 receptors. Other induction agents for high-risk b cases are ATG and the monoclonal antibody alemtuzumab (Campath). The commonest maintenance immunosuppressive regi - men for solid organ transplants consists of triple therapy with a calcineurin inhibitor (ciclosporin or tacrolimus), an antiprolif - erative agent (azathioprine or mycophenolic acid) and steroids.

Immunosuppressive regimen for renal transplantatio

Immunosuppressive regimen for renal transplantation

Immunosuppression for renal transplantation generally comprises induction therapy with the anti-CD25 monoclonal - antibody basiliximab followed by a maintenance regimen of a calcineurin inhibitor (most usually tacrolimus), an antipro - liferative agent (usually mycophenolic acid) and corticosteroid (prednisolone). The anti-CD52 monoclonal antibody alemtu - zumab can be used for induction instead of basiliximab for -

Figure 88.15 Completed laparoscopic dissection of the left kidney, which is ready for stapling of the vessels and removal in an Endocatch bag.

avoidance strategy in patients at high risk of developing diabe tes post transplantation.

Introduction

INTRODUCTION

Successful solid organ transplantation represents one of the great medical advances of the twentieth century . The field continues to be an exciting and fast-moving one. Unfor tunately , there continues to be a shortage of suitable donor organs for transplantation. In the UK there are approximately 4000 patients waiting for a kidney but only 3750 transplants are performed annually . This has led to a median waiting time for transplantation of around 3 years. Similar shortages exist for heart, lung, liver and pancreas transplantation across the world. Most transplant organs are from deceased donors, of which there are two types: donation after brainstem death (DBD) and donation after circulatory death (DCD). Living donation is limited to kidney , liver and lung transplantation.

KIDNEY TRANSPLANTATION End-stage renal disease

KIDNEY TRANSPLANTATION End-stage renal disease

The incidence of end-stage renal disease (ESRD) in the UK is approximately 120 per million population and around 8000 people require renal replacement therapy annually . The lead ing causes of ESRD are diabetes, hypertension and chronic glomerulonephritis (Summary box 88.1). ESRD is largely a disease of older adults with the mean age at commencement of renal replacement therapy being 64 years. Harvey Williams Cushing , 1869–1939, Professor of Surgery , Harvard University Medical School, Boston, MA, USA. Christian Johann Doppler , 1803–1853, Professor of Experimental Physics, Vienna, Austria, enunciated the Doppler principle in 1842. Common causes of ESRD /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

Chronic glomerulonephritis Polycystic kidney disease Diabetic nephropathy Chronic pyelonephritis Hypertension Obstructive uropathy Renal vascular disease

Learning objectives

Learning objectives

To recognise and understand: The immunological basis of allograft rejection • The principles of immunosuppressive therapy • The side effects of immunosuppressive therapy • The major issues concerning organ donation •

Living donation

Living donation

Living kidney donation is possible because most individuals have two healthy kidneys and it is possible to live a normal life with a single kidney . Parts of non-paired organs can also be removed from live donors; these include liver and lung lobes, the tail of the pancreas and segments of small intestine. The majority of liver transplants performed in India are from live donors and the number of programmes has expanded rapidly in recent years. The liver has the capacity to regenerate follo wing resection of a segment or lobe. The growth of new liver tissue happens quickly and the liver returns to its pre resectional mass. Liver resection is di ffi cult because of the complex segmental anatomy (Figure 88.2). In children, the left lateral segment (segments II and III) of an adult provides enough liver function and this is a relatively straightforwar procedure. In adult-to-adult live donor liver transplantation the whole right lobe of the liver is removed from the donor (segments V–VIII). This is a more complex operation and the risk of donor mortality is 0.5–1%. Transplants from live donors have a number of advan tages over deceased donor organs. Live donor organs are Claude Couinaud , 1922–2008, French surgeon and anatomist, described the segmental anatomy of the liver in his seminal book chirurgicales . seen in deceased donors. In the agonal period before death deceased donors exhibit marked changes in physiology related to a catecholamine storm and this can cause org an dysfunc - tion. Clearly , live donor organs are not subjected to this insult. Potential live donors undergo a rigorous assessment process that includes imaging of the relevant vasculature by CT or magnetic resonance angiograph y (MRA) and tests of organ functional capacity . The operations are planned elective pro - cedures undertaken in daylight hours and often adjacent the - atres so that the cold ischaemia time is very short. It is usual for live donor organs to function immediately after transplantation and this is essential for liver and lung transplants. As a result of these advantages the long-term outcomes of live donor trans - plantation are superior to deceased donor outcomes. Set against these advantages for the recipient is the fact that the live donor is subjected to a major operation that they do not need. All live donor operations have uncommon but - potentially life-threatening morbidity rates and there is a small risk of death. The ethical issues raised b y live donation are understandably complex. d

Right hepatic vein VII VIII VI V Cystic duct Gallbladder Figure 88.2 Segmental anatomy of the liver (Couinaud segments).

Living donor kidney transplantation

Living donor kidney transplantation

This accounts for approximately 1000 kidney transplants annu ally in the UK, which is approximately one-third of the total renal transplant programme. Living donors may be related, unrelated, altruistic or part of a donor exchange scheme (for ABO blood g roup or HLA incompatibility). Potential live donors undergo extensive assessment that includes urine and Robert Lich Jr , urologist, Louisville, KY , USA. Willy Grégoir , Chef de Clinique Urologique, Brussels, Belgium (1962–1987). phy (if indicated) and CT angiography or MRA for the assess - ment of renal vascular anatomy . Renal function is measured by an accurate isotope GFR technique and must be above evidence-based age- and gender-specific safety thresholds for donation. Following unilateral nephrectomy , there is consid - erable compensation by the remaining kidney and donors are usually left with 70% of their predonation GFR. The mortality from donor nephrectomy is approximately 1:3000 and major morbidity occurs in <5%. Donation increases the risks of hypertension, r enal failure and pregnancy-related complications.

Muscle Mucosa Figure 88.14 Ureteric implantation by direct anastomosis to a small cystotomy: Lich–Grégoir technique.

Mammalian target of rapamycin (mTOR) inhibitors

Mammalian target of rapamycin (mTOR) inhibitors

The mTOR inhibitors rapamycin and everolimus act by bind ing to and inhibiting a cytoplasmic kinase enzyme complex called mTOR. This prevents intracellular signalling from the IL-2 receptor. The downstream e ff ect is arrest of T-cell division at the G1–S phase. The cell cycle e ff ects of mTOR inhibitors are not limited to lymphocytes and their side-e ff ect profile includes severe mouth ulceration, poor wound healing and lymphocele formation. This limits the use of mTOR inhibitors in the first few weeks post transplantation. However, mTOR inhibitors are not nephrotoxic and they may be used 3 /uni00A0 months or more after transplantation as an alternative to CNIs to minimise CNI-associated renal dysfunction.

Minimally invasive donor nephrectomy

Minimally invasive donor nephrectomy

Laparoscopic surgery is now widely established and there are a number of techniques. After a fully laparoscopic trans- peritoneal dissection (Figure 88.15), the kidney is removed through a small retrieval incision. Hand-assisted laparoscopic nephrectomy is also used widely . A hand port is used to aid the dissection and for extraction of the kidney . This technique is easier to learn and can be safely performed by surgeons with less laparoscopic experience.

Normothermic machine perfusion

Normothermic machine perfusion

Normothermic machine perfusion (NMP) utilises the prin - ciples of cardiopulmonary bypass technology and has been used for heart, lung, liver and kidney preservation. Warmed and oxygenated red blood cell-based perfusate is circulated thr ough the donor organ (Figure 88.5). This provides a more physiological environment that restores graft function ex vivo and replenishes depleted ATP levels. NMP restores organ func - tion ex vivo and this allows for assessment of allograft quality and viability . This has led to increased utility of marginal organs that would previously have been discarded on the basis of adverse clinical parameters. NMP may also improve early allograft function and is being developed as a platform for the delivery of pretransplant therapies.

Figure 88.5 Donor kidney undergoing normothermic machine perfu sion.

Normothermic regional perfusion

Normothermic regional perfusion

This technique has been developed for donation after circu latory arrest. A cardiopulmonary bypass system is used to recirculate the donor’s own blood through the thoracic and abdominal organs for 2 hours. The under lying principle is to avoid early cold ischaemia injury . The early experience of normothermic regional perfusion in DCD liver preservation and transplantation shows reduced rates of early allograft dysfunction.

ORGAN DONATION Donation after brainstem death

ORGAN DONATION Donation after brainstem death

Brainstem death occurs after severe brain injury as a result of either trauma or a cerebrovascular accident. Potential DBD donors are in an apnoeic coma that requires mechanical ventilation on the intensive care unit (ICU). There must be a known cause of irreversible brain damage demonstrated by a computerised tomography (CT) scan. Brainstem death is defined as the permanent loss of the capacity for consciousness and spontaneous breathing. These two essential functions are controlled by the brainstem. The reticular activating formation controls consciousness and is di ff use throughout the brainstem; the respiratory centre is in the medulla oblongata. In this situation the circulation can be maintained for a period of time after death and DBD donors were formerly called heart-beating donors. In most countries it is accepted that brainstem death equates in medical, legal and religious ter ms to the death of the patient. Before brainstem death testing can be considered, all reversible causes of coma must be excluded. These include: hypothermia, muscle relaxants, drugs with central nervous system depressive e ff ects, alcohol intoxication, hypothyroid - - ism, uraemic encephalopathy , hepatic encephalopathy , hypo - glycaemia and hyponatraemia. When these preconditions are met then formal brainstem death testing can be undertaken (Table 88.1). The UK guidelines state that the tests should be perf ormed twice by two clinicians who are independent of the transplant team. One of them should be a consultant and the other must have been registered with the General Medical Council for at least 5 years.

The main indications for organ transplantation • The surgical principles of organ transplantation • The expected outcomes after transplantation • The potential future developments in transplantation • TABLE 88.1 Clinical testing for brainstem death. Cranial nerve 1. Pupillary re /f_l ex (cranial nerves II and III) re /f_l exes 2. Corneal re /f_l ex (cranial nerves V and VII) 1 3. Oculocephalic (doll’s eyes movements – cranial nerves III, IV and VI) 4. Vestibulo-ocular (cranial nerves VIII, III and VI) 5. Cough/gag re /f_l ex (cranial nerves IX and X) 6. It is not possible to test cranial nerves I and XII in unconscious individuals Absence of cranial nerve motor response to Motor supraorbital pressure (cranial nerves V and VII) response and absence of motor response in the cranial nerve distribution to adequate stimulation of any somatic area (commonly nail-bed pressure) After preoxygenation with 100% oxygen the Apnoea test patient is disconnected from the ventilator for >5 minutes in order to achieve a PaCO 2 ≥ 6.0 /uni00A0 kPa (and pH<7.4). If there are no respiratory movements in response to the progressive hypercarbia then the test con /f_i rms that the brainstem respiratory centre has been destroyed. To prevent hypoxia during the apnoeic period, O (6 /uni00A0 L/min) is delivered via an 2 endotracheal catheter , partial pressure of carbon dioxide. PaCO 2

oxygenated blood during the procurement surgery . The thor acic and abdominal organs are accessed through a median sternotomy and a midline laparotomy incision and their inflow vessels are cannulated. The organs to be recovered are usually dissected and mobilised with the heart beating. Ice-cold cardio plegia solution is then perfused into the coronary arteries via a cannula in the ascending aorta to stop the heart. At the same time the abdominal organs are perfused with ice-cold preser vation solution via cannulae in the abdominal aorta and the portal vein. Each organ is removed and stored in fresh preser va tion solution and then packed in crushed ice for transport.

ORGAN PRESERVATION

ORGAN PRESERVATION

Transplant organs need to be stored and preserved in the period between procurement from the donor and transplan - tation into the recipient. Static cold storage is the traditional - method of organ preservation, but more recently there have been developments in preservation b y machine perfusion. Le Foie: Études anatomiques et

Middle hepatic vein Left hepatic vein II I IV III Umbilical vein (remnant) Hepatic duct Inferior vena cava Hepatic artery Portal vein Bile duct

In the absence of oxygen, organs switch from aerobic to anaerobic metabolism. The mitochondrial electron transport chain cannot function without oxygen as the final electron acceptor. Oxidative phosphorylation ceases and, in consequence, so does the tricarboxylic acid (Krebs) cycle and the link reaction (conversion of pyruvate to acetyl coenzyme A). This leaves glycolysis as the only source of adenosine triphosphate (ATP). Anaerobic metabolism of one glucose molecule produces only two ATP molecules compared with the 36 ATP molecules that are produced during aerobic metabolism. Consumption of ATP rapidly exceeds production, + + leading to depletion of cellular ATP . Na /K ATPase pumps + are disabled and this leads to an influx of Na ions into the + cell down their concentration gradient. Na ions are followed by H O by osmosis and this causes swelling and disruption 2 of membrane-bound intracellular organelles and lysis of the cell membrane. Anaerobic glycolysis generates lactate and promotes intracellular acidosis. At low pH phospholipase and protease enzymes are activated and cause lysosomal damage and eventually cell death. ATP-dependent active transport of calcium out of cells is impeded, leading to the 2+ intracellular accumulation of Ca ions and activation of the calcium-dependent processes. This leads to breakdown of the cytoskeleton and loss of cell structure.

Outcomes after renal transplantation

Outcomes after renal transplantation

Patient and graft survivals vary according to donor type and are presented in Table 88.4 . Overall, kidney transplantation is a highly successful treatment for ESRD. Living donor trans - plants yield better results than deceased donor transplants. Causes of long-term graft dysfunction /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF DBD and DCD kidney transplants have comparable patient and graft survival. Although these survival analyses are helpful, most patients want to know how long their transplant can be expected to last. This is best expressed by graft half-life (t) data (median ½ graft survival). The current overall t for live donor transplants ½ is approximately 25 years and for deceased donor transplants approximately 15 years. For all types of kidney , increasing donor age is the most important risk factor for poorer graft survival. Long cold isch aemic time (>12 hours for DCD kidneys and >24 hours for DBD kidneys) is also associated with reduced graft survival. Graft survival also decr eases as the number of HLA mis matches increases.

Immunological Chronic AMR Acute CMR or AMR, which can occur at any time Non-immunological Pre-existing damage in the donor kidney (especially relevant to DCD and extended criteria donor kidneys) Early ischaemia–reperfusion injury Chronic calcineurin nephrotoxicity Ureteric or bladder out /f_l ow obstruction Recurrent urinary tract infection or pyelonephritis BK polyomavirus nephropathy Recurrent native disease: glomerulonephritis; focal segmental glomerulosclerosis; immunoglobulin A nephropathy Renal artery stenosis Poorly controlled hypertension Dyslipidaemia transplantation. 10-year 5-year 10-year 5-year Type of graft graft patient patient allograft survival survival survival survival (donor source) Live donor 95% 90% 90% 80% Deceased 90% 80% 85% 75% donor Deceased donor includes both DBD and DCD results, which are comparable.

RENAL TRANSPLANT SURGERY Preparation of the donor

RENAL TRANSPLANT SURGERY Preparation of the donor kidney

The donor kidney must be examined and prepared on the back-table in order to check that it is suitable to be transplanted. Multiple renal arteries are present in up to 25% of kidneys and, if present, may require reconstructive bench surgery to simplify implantation. The renal arteries are end arteries, so it is important whenever possible to preserve all branches (Figure 88.12).

(a) (b) Figure 88.13 Renal allograft implantation techniques. (a) Anastomosis of the renal artery on a donor aortic patch end to side to the external iliac artery. (b) Anastomosis of the renal artery end to end to the divided internal iliac artery. artery end to end to the internal iliac artery and the

renal vein end to side to the external iliac vein. Figure 88.12 Deceased donor renal transplant with three arteries that have been reconstructed using a patch of donor aorta and anastomo

sed to the external iliac artery.

Rationale for kidney transplantation

Rationale for kidney transplantation

- Kidney transplantation improves life expectancy and quality of life when compared with dialysis. However, only approxi - mately one-third of patients with ESRD are fit enough to with - stand transplant surgery and long-term immunosuppression. Successful transplantation frees patients from the rigors of dialysis and eliminates uraemic symptoms . Transplant kidneys produce normal levels of erythropoietin and this reverses the anaemia of chronic renal disease. Transplant patients therefore have more energy and better exercise capacity than patients on dialysis. There are also no fluid or dietary restrictions after transplantation. Importantly , for women of child-bearing age pregnancy is also possible after a successful kidney transplant. Life expectancy is higher in the transplant population with 5-year survival of >85% compared with <50% for patients on dialysis. However, these figures cannot be directly compared as there is selection bias because only relatively fit patients are o ff ered transplantation.

Renal transplant operative technique

Renal transplant operative technique

The donor kidney is transplanted heterotopically into one of the iliac fossae via a curvilinear incision. The peritoneum should be kept intact and swept upwards to reveal the iliac vasculature. The transplant renal vein is anastomosed end to side to the external or common iliac vein. The renal artery is anastomosed either end to side to the external or common iliac artery or end to end to the divided internal iliac artery (Figure 88.13). The internal iliac artery is used more commonly for live donor kidneys because of the lack of an aortic patch. There are several

(c) Transplant kidney Renal artery Internal Renal vein iliac artery External iliac vein (c) Operative photograph of anastomosis of the renal

arteries, but it is best to minimise the number of anastomoses by careful bench surgery . For example, equal-sized arteries can be ‘trousered’ to create a single ostium for anastomosis. Upper or lower polar arteries may also be anastomosed to the divided inferior epigastric artery . It is especially important to anastomose lower polar arteries as these may provide the only blood supply to the ureter. After revascularisation of the transplant kidney the ureter is anastomosed to the bladder as an extravesical onlay (the Lich–Grégoir technique) (Figure 88.14). It is now routine practice to place a double-J stent across the ureteric anastomosis. The stent is removed by flexible cystoscopy under local anaesthesia after a few weeks. Before closing the wound it is important to ensure that the kidney is lying in a satisfactory position without kinking of the renal blood vessels.

Renal transplantation in children

Renal transplantation in children

In children with established renal failure, kidney transplanta tion facilitates their growth and development and markedly improves the quality of life of the child and their parents. In young children there is often a size mismatch between the donor kidney , which may be from an adult, and the recipient. In this case the kidney is transplanted intraperitoneally with anastomosis of the renal artery to the distal aorta and the renal vein to the inferior vena cava or common iliac vein.

Selection of patients for transplantation

Selection of patients for transplantation

- Potential transplant recipients undergo a rigorous work-up process to identify major comorbidities that would preclude transplant surgery . Age per se is not a contraindication to renal transplantation and it is now common to transplant patients in their seventies as long as they have the necessary cardiovascular fitness. Uncontrolled infection and most malignancies are contraindications to transplantation. Patients with ESRD have a greatly increased risk of cardiovascular disease and require a chest radiograph, electrocardiogram (ECG) and, if indicated, an echocardiogram. Patients with a history of diabetes or isch - aemic heart disease should undergo a stress echocardiogram and sometimes coronary angiography . There are a number of technical considerations before a patient is deemed suitable for transplanta tion. The iliac blood vessels must be suitable for anastomosis and there must be a means of draining the transplant ureter. In patients with a history of vascular disease or deep venous thrombosis, the iliac arterial and venous system should be assessed by Doppler ultrasound scanning and possibly also MRA or CT angiography . Patients who have been anuric for a number - of years may have a small non-compliant bladder and this should be assessed by urodynamics. In patients with polycystic kidney disease, the size of the native kidneys should be assessed clinically to make sure that there is su ffi cient room for a kidney transplant in at least one iliac fossa. If there is inadequate space on both sides, then a pretransplant native nephrectomy will be necessary (Figure 88.11). With the exclusion of non-melanotic skin cancer, patients who have had a malignant disease should be deferred for a disease-free period of at least 2 /uni00A0 years. Where possible patients should be listed for transplantation pre-emptively when they are within 6 months of requiring dialysis. This equates to an estimated glomerular filtration rate 2 (eGFR) of 10–15 /uni00A0 mL/min/1.73m .

Figure 88.11 Computed tomography scan of a patient with very large polycystic kidneys that extend well into both iliac fossae. The patient requires removal of one of the polycystic kidneys to make room for a subsequent renal transplant. Nephrectomy should be performed several weeks before transplantation.

Static cold storage

Static cold storage

Hypothermia suppresses metabolism to maintain organ viability . The first requirement is to flush the donor organs with an appropriate preservation solution at a temperature of approximately 4°C (Figure 88.3). This is normally done in situ via cannulae placed in the donor aorta and portal vein. This process has three e ff ects: (i) it flushes blood out of the microcirculation to prevent thrombosis; (ii) it cools the organs to a temperature of <5°C and so reduces tissue oxygen requirements; (iii) it replaces the normal extracellular fluid with the preservation fluid. Sir Hans Adolf Krebs , 1900–1981, Professor of Biochemistry , University of Oxford, Oxford, UK. electrolytes, an impermeant and a bu ff er. In general, the + ion concentration electrolyte composition mimics the high K + and low Na ion concentration of intracellular fluid. This eliminates ionic fluxes, and therefore the movement of H O 2 across cell membranes. Impermeants such as mannitol, lacto - bionate and ra ffi nose are large osmotically active molecules. They cannot pass through the cell membrane and remain in the extracellular space. Here, the y prevent cellular swelling by counteracting the osmotic force from intracellular proteins. The bu ff er component of preservation fluids is based on either – 3– HCO or PO and acts to maintain a stable physiological pH 3 4 in the extracellular space. A number of di ff erent preservation solutions are available, but the University of Wisconsin (UW) solution is widely regarded as the current gold standard.

Figure 88.3 After removal from the donor, the kidney is /f_l ushed with chilled organ preservation solution and, if necessary, stored brie /f_l y on ice until transplanted into the recipient.

Surgical complications of renal transplantation

Surgical complications of renal transplantation

Haemorrhage A haematoma may develop in the transplant bed in the first few postoperative days. This is often due to bleeding from small unsecured vessels in the renal hilum that were not apparent at the time of surgery . In this situation the patient is haemody namically stable and can be investigated by CT angiography and subsequently re-explored to remove the haematoma. Anastomotic haemorrhage can also occur but is very rare. It presents as haemorrhagic shock associated with a fall in the haemoglobin to <50 /uni00A0 g/L. This is a life-thr eatening situation and the patient should be returned to the operating theatre immediately . It may be possible to repair a defect in an arte rial or venous anastomosis but transplant nephrectomy is often required. Late anastomotic haemorrhage can also occur after some weeks or months owing to the development of a m ycotic aneu rysm. The commonest causative or ganism is donor-derived Candida albicans . A ruptured mycotic aneurysm requires an immediate graft nephrectomy and has a significant mortality . - Although this occurs in <1% of renal transplants, the most common outcome is loss of the allograft. Most cases are due to technical complications at the arterial anastomosis. The usual presentation of renal artery thrombosis is sudden anuria and a rapid decline in renal function. The diagnosis may be missed in patients who have DGF or a normal urine output from their native kidneys. An urgent Doppler ultrasound scan will show an absence of perfusion to the graft. The patient must - be returned to the operating theatre immediately to attempt thrombectomy , but most grafts will already be infarcted and transplant nephrectomy will be required. Renal vein thrombosis Renal vein thrombosis occurs in 1–5% of transplants. It may be due to a technical error such as kinking or torsion of the venous anastomosis, but many cases are idiopathic. The peak incidence occurs at postoperative days 3–7. The presentation is distinctive with sudden pain over the renal transplant associated with frank haematuria. In early cases with partial thrombosis, Doppler ultrasound scanning may demonstrate reversal of arterial blood flow in diastole. In an established renal vein thrombosis Doppler scanning will demonstrate in situ marked swelling of the renal allograft, often with a significant surrounding haematoma due to rupture of the renal capsule. Re-exploration to attempt a thrombectomy is rarely successful and the vast majority of cases lead to graft loss. Urological complications Urological complications occur in approximately 5% of renal transplants but they rarely result in graft loss. After dissection of the ureters at organ retrieval, only the ureteric blood supply from the renal artery is preserved. In consequence, the blood supply of the distal transplant ureter can be poor. Urinary leak Urinary leaks can occur in any part of the urinary drainage system but are commonly due to ischaemic necrosis of the distal ureter. The peak incidence is at the time of urinary catheter removal (day 5) but leaks can be delayed for a few weeks. In early leaks clear fluid discharges through the wound or collects in the drains. Biochemical analysis will show that the fluid is urine (creatinine in the millimolar range) rather than - lymph (creatinine in the micromolar range and equal to the serum

level). Leaks presenting later on when the wound is fully healed present as a peritransplant fluid collection. Initial management is bladder catheterisation and cystography to confirm the diagnosis. The anatomical site and extent of the leak can be deter mined by inserting a percutaneous nephrostomy and performing antegrade pyelography . It - is sometimes possible to place a double-J stent across the leakage point using an antegrade approach. If there has been significant ischaemic necrosis of the distal transplant ureter the leak will not resolve and surgery will be required. There are a - number of alternatives for reconstructing the urinary drainage system. If there is a su ffi cient length of transplant ureter after excision of the necrotic segment, the ureter can be reimplanted directly into the bladder over a new double-J stent. If the to-transplant ureteroureterostomy or ureteropyelostomy can be performed. Finally , if the ipsilateral native ureter is absent, because of a previous nephrectomy , a Boari bladder flap can be fashioned to drain the transplant kidney . Ureteric obstruction This can occur at any time after transplantation (days to years). Early obstruction is usually due to a technical error in the bladder anastomosis. Obstruction occurring after 3 months is invariably due to an ischaemic stricture. BK polyomavirus infection is also a cause of ureteric stricture. Patients present with renal dysfunction and investigation by ultrasound scanning reveals hydronephrosis. The initial management of choice is to place a percutaneous nephrostomy . An antegrade pyelogram can then be performed to define the site and extent of the stricture. Short strictures may be treated by interventional radiology with antegrade balloon dilatation and placement of a double-J stent across the stricture. Long, tight strictures require surgery and the options for reconstruction are the same as those for a urine leak. Lymphocele The incidence of significant lymphoceles (>3 /uni00A0 cm) that cause complications and need treatment is around 5%. Small lymphoceles (<3 /uni00A0 cm) are more common but asymptomatic and resolve spontaneously . The usual source of a lymph leak is from lymphatics that are divided during dissection of the iliac vessels. Lymph accumulates as a collection because of the extraperitoneal position of the kidney . Large lymphoceles can compress surrounding structures and, in some cases, cause renal vein thrombosis or ureteric obstruction. All large peritransplant collections should be aspirated under ultrasound to exclude a urinary leak. Lymph is charac terised by having the same biochemical profile as serum. Percu taneous drainage, sometimes on a number of occasions, leads to resolution of most lymphoceles. If this fails surgical drain age is required. This is usually performed laparoscopically and involves creating a fenestra tion in the wall of the lymphocele so that it drains into the peritoneal cavity . Transplant renal artery stenosis The incidence of transplant renal artery stenosis (TRAS) is approximately 5%. The usual presentation is refractory hyper tension associated with allograft dysfunction at 3–6 months post transplant. TRAS activates the renin–angiotensin–aldosterone system and may become evident by a sudden increase in serum creatinine after prescribing an angiotensin-conv erting enzyme inhibitor. Doppler scanning is suggestive of TRAS when the arterial peak systolic velocity is >250 /uni00A0 cm/s and the waveform may have the characteristic tardus parvus (Latin for late and small) pattern. MRA or CT angiograph y are useful for anatomical definition. Percutaneous transluminal angioplasty with or without stenting is the preferred treatment. Achille Boari , nineteenth century Italian urological surgeon from Ferrara, described the technique of a bladder flap in dogs in 1894; it was first performed in a patient in 1936. This can be defined as a rise in serum creatinine of >10% from baseline or an absolute rise of ≥ 20 /uni00A0 µmol/L. Common causes are listed in Summary box 88.2 . Allograft dysfunction should be investigated by urinalysis and culture to exclude urinary tract infection, CNI blood levels for drug-mediated nephro - toxicity and Doppler ultrasound scanning to check for arterial perfusion, venous drainage and hydronephrosis due to urinary obstruction. If there is uncertainty about the cause of graft d

ysfunction, a percutaneous needle-core transplant biopsy should be performed to establish whether allograft rejection is present. Summary box 88.2 Causes of early graft dysfunction /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Long-term allograft dysfunction There are immunological and non-immunological causes for a progressive decline in renal allograft function over a period - of months or years (Summary box 88.3). The commonest - cause of long-term renal allograft damage and subsequent loss is chronic AMR. This is often related to inadequate compli - - ance with immunosuppressive medication. There is no proven treatment for chronic AMR. Non-immunological causes are also significant risk factors for chronic allograft damage. Irrespective of the cause , chronic transplant injury leads to interstitial fibrosis and tubular atr o - phy . Once established these changes are irreversible and will eventually lead to failure of the transplant. - The two most important factors in maintaining good long - term allograft function are meticulous adherence to immuno - suppressive medication and good b lood pressure control (<130/80 /uni00A0 mmHg).

Any rise in serum creatinine of >10% of baseline or ≥ 20 /uni00A0 µmol/L should be considered as acute allograft dysfunction that requires investigation. Possible causes are: Acute rejection (antibody mediated or cell mediated) Calcineurin inhibitor toxicity Dehydration Urinary tract infection or pyelonephritis Any other source of sepsis Renal vein or renal artery thrombosis Ureteric obstruction or urine leak

TRANSPLANT REJECTION

TRANSPLANT REJECTION

Allograft rejection can be divided into distinct types. - -

The immune response to a transplanted organ

The immune response to a transplanted organ

The main immune cells involved in transplant immunology are APCs and T and B lymphocytes. These cell types interact by a series of specific surface molecules that are designated by CD (cluster of di ff erentiation) numbers. Cell surface receptors can only interact if they have the correct complementary three-dimensional structures. The immune response to an allograft is orchestrated by T lymphocytes. When T cells encounter foreign transplant HLA antigens they become activated and then proliferate into clones of cells that attack the allograft. Full T-cell activation requires a number of signals (Figure 88.6). Transplant antigen). -

CD4 A TCR MHC II CD3 H Signal 1: antigen APC T presentation CD28 CD80/86 Signal 2: co-stimulation Figure 88.6 Interaction between an antigen-presenting cell and a CD4+ T-helper cell. A, antigen; APC, antigen-presenting cell; CD, cluster of differentiation; MHC II, major histocompatibility complex

H class II; TCR, T-cell receptor; T , T-helper cell. (Adapted with permis

sion from Clatworthy M, Watson C, Allison M, Dark J. Transplantation at a glance . John Wiley and Sons Ltd, 2012.)

molecules by specialised APCs. The class II/peptide antigen complex is recognised by the T-cell receptor (signal 1). CD4+ T-helper cell activation also requires a co-stimulatory signal involving the interaction of pairs of molecules, one on the sur face of the T cell and the other on the surface of the APC (signal 2). An example of signal 2 is the interaction of T-cell CD28 with CD80 on the APC. When both signal 1 and signal 2 are received the CD4+ T-helper cell will upregulate expres sion of the interleukin-2 (IL-2) receptor (CD25) on its cell sur face. Binding of IL-2 to its receptor causes further activation of the T cell (signal 3). The T cell will then proliferate and release more IL-2, which, in turn, leads to activation and clonal proliferation of T-killer cells (CD8+). These cytotoxic killer cells infiltrate the allograft and cause cell death by the release of molecules called perforin and granzyme. Perforin punches holes in the target cell membrane and this allows passive dif fusion of granzyme into the cell, where it activates caspase enzymes and causes cell death by apoptosis.