Therapeutic issues in transplant patients

Mark C Bellamy
Alexander Scott

Abstract
Patients who have undergone previous organ transplantation represent a considerable therapeutic challenge to the anaesthetist. Although a transplant may have restored normal or near-normal function for that organ, the original underlying pathology often persists. In addition, undesirable effects of immunosuppressant drugs, particularly calcineurin inhibitors, may give rise to damage to other organs and organ systems. Diabetes, hyperlipidaemia and accelerated vascular and renal damage are a common feature. The majority of post-transplant patients require treatment for these phenomena. Common medications include statins, antihypertensives and sometimes prophylaxis against nosocomial infection. When managing post-transplant patients, both drugs and pathology have to be taken into account. Non-steroidal anti-inflammatory drugs pose a particular hazard.

Keywords General anaesthesia; heart transplantation; kidney transplantation; liver transplantation; lung transplantation; postoperative analgesia

Scope of the problem
An ever-increasing population of patients survive long term following transplantation. These patients may present for anaesthesia and surgery either because of problems relating to their original disease or for unrelated treatments for intercurrent illness. The anaesthetic challenges can be broadly divided into general issues common to all transplant recipients (generally immunosuppressant related) and organ-specific considerations.

The numbers of such patients presenting to the general anaesthetist outside specialist transplant units is growing. Patients may present for elective treatment, when there is adequate time to prepare both the patient and therapeutic environment, or for emergency unplanned intervention. In anaesthetic terms, a number of factors need to be taken into consideration, such as the organ transplanted and its current function, which may vary dramatically. For example, long-term outcomes following liver transplantation tend to be very good, with normal liver function, but this depends on the original pathology. Some pathologies can recur in the transplanted organ. Outcomes following kidney transplantation are likewise generally very good in the early stages, although there is a gradual and progressive reduction in function in many transplanted kidneys over a period of years. The underlying condition (e.g. diabetes) or the toxic effects of immunosuppressant and other drugs (e.g. ciclosporin or tacrolimus) may exacerbate this.

Heart transplant patients may have arterial occlusive disease in the graft because of vascular rejection, or accelerated atherosclerosis. Following lung transplantation patients exhibit a variable interval of good health before declining organ function. Outcomes for heart transplantation and liver transplantation represent the most stable long-term graft function, whereas lung transplantation and small bowel transplantation exhibit the most rapid decline in function of the transplanted organ (Figure 1).

Transplant recipients may appear relatively healthy. Those patients who enjoy good organ function may demonstrate similar levels of health to members of the general population. Although this situation may change over time in an organ-specific fashion, post-transplant patients also have a number of generic health problems with direct relevance to anaesthesia.

The general anaesthetist is most likely to encounter kidney transplant recipients. Liver transplant recipients represent the second most common surviving patient group, followed by heart and then lung recipients. Other solid organ recipients (pancreas, small bowel, multivisceral) are relatively rare. The number of people living with a functioning graft has almost doubled over the last 10 years (Figure 2).

Immunosuppression-related issues
Post-transplant immunosuppression has been subject to significant change in recent years. Changes to practice have centred around both novel monoclonal therapies and in application of reformulated generic agents, with future developments likely to include the use of targeted delivery systems. A wider range of regimens are in use or development, and the anaesthetist may encounter patients with widely varying immunosuppressive strategies.

Calcineurin inhibitors
Ciclosporin and tacrolimus are structurally unrelated. However, they share a common action, binding to the immunophilins (cytosolic proteins). This complex inhibits calcineurin, an inducer

Learning objectives
After reading this article, you should:

- be able to identify three key therapeutic challenges following solid organ transplantation
- understand what immunosuppressant, cardiovascular and general therapeutic agents are in use post-transplantation, and their main implications for organ function
- know how organ function and post-transplant drugs impact on (i) anaesthesia, (ii) cardiovascular status, (iii) analgesic regimens, (iv) risk and (v) perioperative care of the post-transplant patient

Mark C Bellamy MA MB BS FRCA FFICM is Consultant in Intensive Care and Transplant Anaesthesia in the Leeds Teaching Hospitals, UK, and Honorary Professor of Critical Care Anaesthesia in the University of Leeds, UK. Conflicts of interest: none declared.

Alexander Scott MB ChB BSc FRCA is a Specialty Registrar in Anaesthesia and Intensive Care Medicine in the West Yorkshire Deanery, UK. Conflicts of interest: none declared.
of interleukin-2 (IL-2) transcription. Additionally, there is an inhibitory effect on other lymphokines. This leads to widespread suppression of T-cell function. Calcineurin inhibitors are among the most widely used immunosuppressant agents, with a side-effect profile that potentially limits their use. Both ciclosporin and tacrolimus are associated with renal failure (exacerbated by non-steroidal anti-inflammatory drugs; NSAIDs) and neurotoxicity (including altered consciousness and fitting), they are diabetogenic and can induce hyperlipidaemia. Tacrolimus has also been associated with cardiomyopathy, particularly in higher doses.

The anaesthetist will encounter patients on either agent as maintenance therapy post-transplant. However, as experience is gained with tacrolimus, there is a growing trend for its use in maintenance immunosuppression over ciclosporin. Ciclosporin is still favoured in elderly liver transplant recipients, and those with hepatitis C.

It is the authors’ practice to discontinue calcineurin inhibitors in the immediate perioperative period.

**Anti-metabolites**

The first-developed compound in this class is azathioprine. This is a pro-drug which is broken down to mercaptopurine, a purine analogue. It gives rise to competitive inhibition of DNA synthesis, which prevents lymphocyte clonal expansion, down-regulating the induction phase of the immune response. However, as a purine analogue, it also induces non-specific marrow suppression. Although all cell lines are affected, in clinical practice, thrombocytopenia is the most significant feature. The use of azathioprine is declining in modern regimes, in favour of the newer agent mycophenolate.

Mycophenolate mofetil is more selective than azathioprine. There are two pathways for guanosine nucleotide synthesis: the de novo pathway and the recycling pathway. Mycophenolate selectively inhibits the de novo pathway via inosine monophosphate dehydrogenase. Lymphocytes are uniquely dependent on this pathway, and so proliferation of clonal lines is prevented, while preserving production of other ‘high-turnover’ cell lines, such as megakaryocytes (platelet production).

The side effects of mycophenolate include diarrhoea, nausea and vomiting. Leucopenia and opportunistic infections may also occur.

**Monoclonal therapies**

The induction phase of immunotherapy has seen considerable change in recent years with the introduction of monoclonal antibody therapies. These are beginning to take over from older polyclonal preparations. The principal agents used are daclizumab, basiliximab and alemtuzumab.

Daclizumab and basiliximab are monoclonal antibodies specific for the α chain of the IL-2 receptor expressed on T-cell activation. They do not cause T- or B-cell depletion. Their principal adverse effects are through hypersensitivity reactions, both to initial doses and subsequent administration, and gastrointestinal upset including nausea, vomiting and diarrhoea, with a slight excess burden over background events in the transplant population.

Alemtuzumab is the subject of several current studies. It is a humanized monoclonal antibody, specific for the lymphocyte-
expressed CD52 receptor, which is itself expressed only the mature lymphocyte and not the relevant stem cell line. Acute adverse reactions are described in the administration of alemtuzumab, both hypersensitivity reactions and cytokine release effects, leading to hypotension, rigors, fever, difficulty in breathing and cutaneous manifestations. In the recipient population, these effects may be significant and require intervention during anaesthesia or postoperative care, with particular reference to profound hypotension in the arteriopath.

Other agents
Rapamycin, also known as sirolimus, is a macrolide synthesized from the bacterium Streptomyces hygroscopicus. Initially developed as an antibiotic, its use as such was abandoned when its potent immunosuppressive action was discovered. Despite its similar name to tacrolimus, it has no inhibitory effect on calcineurin, instead blocking IL-2 response pathways. Although promising, rapamycin has not gained the acceptance expected, due to highly variable bioavailability profiles and a profound antifibrinolysis leading to postoperative wound dehiscence.

The use of N-acetylcysteine infusion in harvested organs has received attention; recent research is completed and publication of results is awaited.

Emerging therapies
There still remains a need for immunosuppressive agents with fewer adverse consequences, probably with a novel mechanism of action. Current research is centred around ‘biologics’, those compounds isolated from natural sources, protein-based and produced by biotechnological methods.

Betalaccep is a humanized monoclonal antibody developed for use in renal transplant. It inhibits co-stimulation of T-cells by antigen-presenting cells, blocking CD80/86 interaction with CD28, downregulating the immune response and causing apoptosis of T-cells. Early trials have demonstrated enhanced renal graft function compared with conventional regimes, complicated by increased rates of lymphoproliferative disease.

Alfagee is an antagonist of the CD2 receptor, inhibiting lymphocyte activation. It was initially designed for autoimmune disease, but is now being studied for immunosuppression.

Eculizumab is a recombinant human monoclonal that binds the complement component C5, blocking complement-mediated cell lysis, a major contribution to antibody-mediated rejection. Investigation is underway.

Non-pharmacological methods
Recent changes in approach have focused on improving the graft function and long-term survival in organ grafts taken from non-heart-beating donors, now also referred to as donation after cardiac death. Grafts harvested in this way have higher rates of acute rejection and may have worse function post-transplant. The use of automated organ-perfusion systems has been established in renal grafts, and has been demonstrated to improve post-transplant function. Systems for hepatic and cardiac transplant are in use, but currently considered experimental.

Infection risk
Immunosuppressant agents give rise to both a general infection risk and a specific risk of opportunistic infections, including cytomegalovirus, Pneumocystis pneumonia, fungal infections and Epstein–Barr virus infection. Epstein–Barr virus may additionally drive the development of polyclonal and, subsequently, monoclonal lymphocyte proliferation, leading to post-transplant lymphoproliferative disorder. Many transplant patients remain on prophylaxis (co-trimoxazole, and occasionally an antifungal agent) in the long term.

Organ-specific issues
Renal transplant recipients
Many pathologies, for example diabetes, give rise to renal failure, subsequently requiring transplantation. Such pathologies generally persist after transplantation, and require ongoing management. They may further give rise to subsequent renal injury in the transplanted organ. Problems include diabetes, hypertension, ischaemic heart disease, hyperlipidaemia and, occasionally, vasculitic processes (beware the patient on steroids or cyclophosphamide — immunosuppressed, electrolyte imbalances, integument injury, low platelet count). Renal transplant patients, in addition to their immunosuppression, are often still on treatment for their primary condition. This requires specific care and consideration by the anaesthetist. Commonly, renal transplant patients require ongoing management of diabetes.

Rarely, patients may have received a renal graft for diabetes or associated renal failure and a pancreas transplant. In general, pancreatic grafting is reserved for patients with additional complications (e.g. severe retinopathy with visual impairment). Paradoxically, patients who additionally receive a pancreas transplant may have normal or near-normal glycaemic control, and consequently be relatively well compared with those who have received a renal transplant alone. Pancreas grafts frequently drain to the bladder, with a risk of conduit ulceration. Long-term protein pump inhibitor drugs and H2-receptor antagonists may be prescribed. Graft survival of the pancreas and of the kidney may differ, leading to various problems. Use of NSAIDs is contraindicated.

Treatment for hypertension is extremely common in the renal transplant population, and is generally multimodal. Antihypertensive medications, especially β-blockers, should be continued in the perioperative period, although caution should be used in the case of angiotensin-converting enzyme (ACE) inhibitors (potential for hypertension) and angiotensin receptor antagonists (the ‘sartan’ series of drugs) which have the potential for severe and potentially intractable intraoperative hypotension. In addition to acute problems in the immediate aftermath of transplantation, there is a gradual reduction in kidney graft function over subsequent years (Figure 1). Moreover, there is emerging evidence that kidneys transplanted from ‘marginal donors’ show a greater attrition rate than those from optimal donors. Several years after transplantation, patients may have significant renal impairment with exacerbated hypertension and arterial disease (particularly coronary artery disease). Depending on the severity of renal impairment, morphine metabolites may accumulate and the action of non-depolarizing muscle relaxants may be prolonged. Moreover, use of NSAIDs or transient hypovolaemia/hypotension may result in exaggerated renal injury.

Liver transplant recipients
Patients on the transplantation waiting list represent a much greater therapeutic challenge than those who have been transplanted. Those on the list often present with end-stage cirrhotic
liver disease, characterized by minimal functional impairment but major symptomatology (e.g. severe pruritus in primary biliary cirrhosis) through to the end-stage liver disease, with coagulopathy or a hypercoagulable state (potentially concurrently), reduced platelet count, portal hypertension, ascites, pleural effusions, hyponatraemia and renal failure. Treatment with β-blockers (propranolol) is common in severe portal hypertension, and those with severe ascites/effusions may also be on a loop diuretic. This can in turn contribute to worsening renal function, and may require discontinuation if there is significant reduction in creatinine clearance. Additionally, antiviral therapies such as interferon or lamivudine may interfere with other drugs. Interferon α-2a and α-2b may prolong elimination of theophylline and increase levels of other antivirals such as zidovudine or lamivudine to potentially toxic values. The combination potentially induces cardiotoxicity, hepatotoxicity and depression of platelet and white cell counts. Partial correction of clotting may be possible by intravenous vitamin K. However, major intraoperative bleeding is more likely to be associated with portal hypertension and coagulopathy. Near-patient monitoring (such as thromboelastography) is the most appropriate strategy to managing such issues. NSAIDs should be avoided in liver transplant recipients, owing to the risk of renal injury and bleeding.

Paracetamol appears safe and is widely used. Following liver transplantation, recipients rapidly recover from the effects of liver failure, including rapid resolution (within days or weeks) of portal hypertension, ascites and pleural effusions. A right-sided pleural effusion is common after liver transplantation for the first few days, but rapidly resolves as secondary hyperaldosteronism is corrected, and protein synthesis returns to normal. Likewise, encephalopathy, pulmonary hypertension, hepatopulmonary syndrome (shunting and hypoxia associated with liver failure) and the hepatorenal syndrome resolve in the majority over the ensuing weeks or months. Consequently, patients presenting for anaesthesia and surgery after recovery from liver transplantation generally enjoy relatively good health. This is subject to the caveats regarding recurrence of some primary pathologies. For example, recurrence of viral hepatitis is relatively common, although this may be a slow and insidious process. This is particularly an issue in patients with hepatitis C. In this condition, despite recent advances in antiviral therapy, many patients are either intolerant of treatment or resistant to it. After a primary hepatitis C infection, not all patients go on to the chronic state; in those who do, and who subsequently develop cirrhosis, an interval of 15 years or more commonly elapses. This is not the case after transplantation; recurrence of hepatitis C cirrhosis may be much more rapid, occurring within 1–2 years.

Primary biliary cirrhosis and autoimmune hepatitis may also recur, although they tend to be delayed and relatively uncommon. This is generally not a concern for the anaesthetist treating a patient for an intermittent condition. Likewise, patients transplanted for alcoholic liver disease may suffer recidivism. A relatively small proportion of these go on to develop cirrhosis in the transplanted liver. Again, the numbers are small; liver function tests and drug disposition are unlikely to be significantly altered until late disease (around 15% or fewer of hepatocytes surviving), so this is very uncommon.

**Heart transplant recipients**

Careful consideration should be given to anatomical issues in transplant recipients (patency of great veins, suitability for central venous cannulation, etc.). Accelerated atherosclerosis may occur, leading to coronary artery disease following transplantation. There is a vogue for performing coronary artery stenting in heart transplant patients with accelerated vascular occlusion. Despite a high primary success rate and deferred recurrence of stenosis, stenting has no impact on graft survival. It impacts the conduct of subsequent anaesthetics because of the use of potent inhibitors of platelet function such as clopidogrel.

Full cardiac assessment should be performed wherever possible, and echocardiography is mandatory for elective patients and highly desirable in all others. Impaired cardiac function, with potential to deteriorate under anaesthesia, may occur in an otherwise asymptomatic patient.

Patients following heart transplantation are likely to be treated with statins, antiplatelet agents and anti-failure agents (e.g. ACE inhibitors), which may have significant implications for haemodynamic stability during anaesthesia, and for the risk of perioperative renal dysfunction. As with other transplant patients, the use of NSAIDs is undesirable, as is even transient hypotension or hypovolaemia.

After heart transplantation, autonomic denervation is present. The predominant effect is loss of vagal innervation, and so there is a fixed resting heart rate which is moderately elevated compared with normal. Despite sympathetic denervation, the heart is still sensitive to circulating catecholamines. In the longer term, there is growing evidence for progressive partial re-innervation of the heart, with recovery of autonomic responsiveness.

Heart transplant recipients may also have significant psychological morbidity, which may require specific treatment. Antidepressants or antipsychotic drugs may occasionally represent part of the drug history.

**Lung transplant recipients**

Lung transplant patients present considerable challenges to the anaesthetist, including potential anatomical derangement. Initially after lung transplantation, there is a dramatic improvement in pulmonary function tests. However, a significant proportion of these patients are at risk of pulmonary infection, particularly with opportunistic organisms potentially related to immunosuppression. Additional problems over time include pulmonary hypertension and progressive bronchiolitis obliterans. The leading causes of death among lung transplantation recipients are respiratory failure, bronchiolitis obliterans syndrome, infection (particularly cytomegalovirus and *Aspergillus fumigatus*) and bronchial anastomosis dehiscence.

By 5 years after transplantation, up to 40% of lung transplant patients develop bronchiolitis obliterans. However, pulmonary function (percentage of predicted forced expiratory volume in 1 second) is well preserved in survivors, remaining stable at around 80% of predicted values up to 6 years after transplantation. Consequently, intraoperative pulmonary function and gas exchange (including exchange of volatile agents) is likely to be clinically normal.

In common with other transplant patients, lung transplant recipients experience a significant decline in renal function, thought to be related to high-dose calcineurin treatment.
REFERENCES


FURTHER READING


