Therapeutic issues in transplant patients

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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

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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

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.[1] 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

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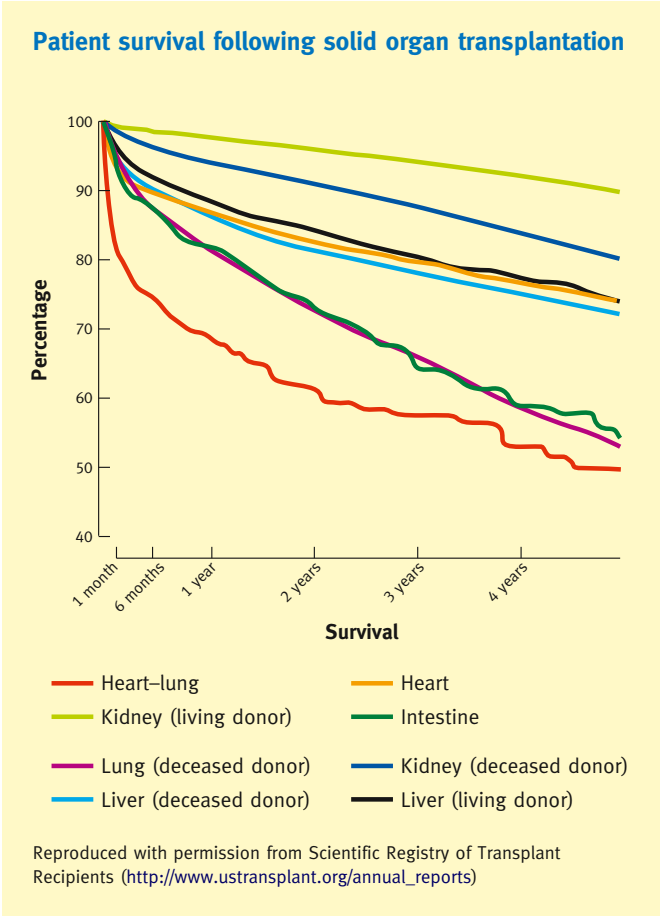

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Figure 1

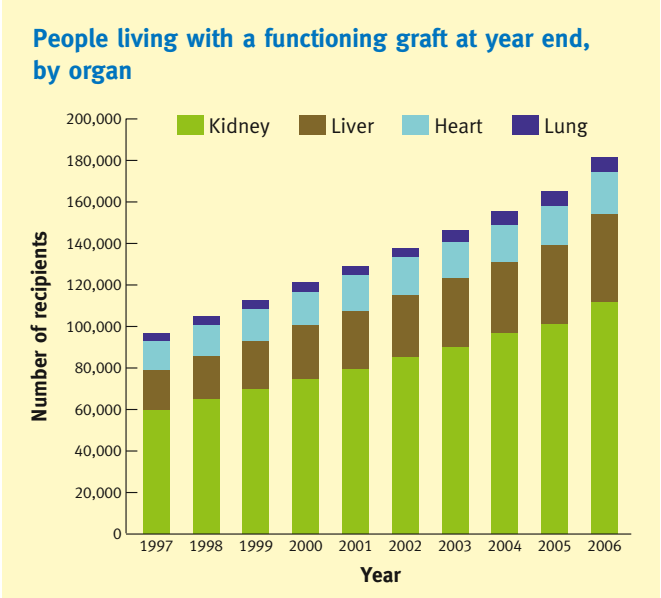

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Figure 2

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 that is broken down to mercaptopurine, a purine analogue. It gives rise to competitive inhibition of DNA synthesis, which prevents lymphocyte clonal expansion, downregulating 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.

Monocolonal 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

