

Organ transplantation: historical perspective and current practice

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Editor's key points

- There has always been a shortfall in numbers of suitable donor organs available for transplant.
- Advances in immunosuppression have reduced the incidence of acute rejection but have not affected chronic immune damage.
- Current research is directed at techniques to improve organ preservation.

Summary. Over the course of the last century, organ transplantation has overcome major technical limitations to become the success it is today. The breakthroughs include developing techniques for vascular anastomoses, managing the immune response (initially by avoiding it with the use of identical twins and subsequently controlling it with chemical immunosuppressants), and devising preservation solutions that enable prolonged periods of *ex vivo* storage while preserving function. One challenge that has remained from the outset is to overcome the shortage of suitable donor organs. The results of organ transplantation continue to improve, both as a consequence of the above innovations and the improvements in peri- and postoperative management. This review describes some of the achievements and challenges of organ transplantation.

Keywords: immunosuppressants; organ preservation; organ preservation solutions; organ transplantation; tissue and organ procurement

A brief history of transplantation

Kidney transplantation

Since Jaboulay and Carrel developed the techniques required to perform vascular anastomoses at the turn of the last century, there has been a desire to treat organ failure by transplantation. Jaboulay was the first to attempt this in 1906, treating two patients with renal failure by transplanting a goat kidney into one and a pig kidney into the other; in both cases, he joined the renal vessels to the brachial vessels.¹ Both transplants failed and both patients died. At that time, there was no alternative to death if renal failure developed, and it would be another 38 yr before the first haemodialysis machine was invented. The first use of a human kidney for transplantation followed in 1936 when Yu Yu Voronoy, a Ukrainian surgeon working in Kiev, performed the first in a series of six transplants to treat patients dying from acute renal failure secondary to mercury poisoning, ingested by its victims in an attempt to commit suicide. All the transplants failed, in large part because of a failure to appreciate the deleterious effect of warm ischaemia; the first kidney was retrieved 6 h after the donor died.

One limitation to transplantation then, as now, was the lack of suitable donor organs. The initial pioneers had used animal organs or organs from long deceased humans. In the 1950s, there came a realization of the need to avoid

excessive ischaemic injury and kidneys from live donors began to be used. Some of these were from the relatives of the recipient; others were unrelated patients having a good kidney removed for other reasons. The surgical technique also needed refinement; while a kidney based on the thigh or arm vessels might be technically straightforward, and possibly adequate for the short-term treatment of acute renal failure, it was not a realistic solution for the long term. That solution came from France in 1951 and involved placing the kidney extraperitoneally in an iliac *fossa*, where the external iliac vessels are easy to access and the bladder is close by for anastomosis to the donor ureter; this is the technique still used today.

Having overcome the technical issues of vascular anastomosis and placement of the kidney, there remained the problem of the immune response. Medawar's work during and after the Second World War studying the rejection of skin grafts had demonstrated the potency of the immune system.² At that time, attempts to control the immune system using irradiation had proved either ineffectual or lethal. The first successful transplant therefore came about by avoiding an immune response altogether, which Joseph Murray's team achieved by performing a kidney transplant between identical twins.³ There then followed a series of identical twin transplants around the world, with the first in the UK being performed in Edinburgh by Woodruff and colleagues⁴ in 1960.

Liver transplantation

Success in clinical liver transplantation took longer to realize than kidney transplantation. The recipient is usually much sicker than a renal transplant recipient, and the operation is a more formidable undertaking and is usually performed in the presence of a significant coagulopathy. Initial attempts at liver transplantation in 1963 by Starzl⁵ in Denver were unsuccessful, but following a move to Pittsburgh in 1967, his results improved. The first transplant in Europe was performed by Calne in Cambridge the following year.⁶

Starzl had preceded his clinical attempts with extensive animal work during which he identified the need to cool the liver before transplantation and to maintain venous return to the heart using veno-veno bypass to shunt blood from the inferior vena cava (IVC) and portal circulation to the superior vena cava. In spite of these innovations, it would be another two decades, following improvements in patient selection, perioperative management, and post-operative immunosuppression, before liver transplantation could be considered a successful treatment for patients in liver failure.

Heart transplantation

The pioneer in cardiac transplantation was the American surgeon Norman Shumway working in Palo Alto. A series of animal experiments had enabled him to work out the operative strategy, which involved cooling the heart and leaving part of the atria *in situ* to reduce the number of anastomoses required.⁷ However, it was Christiaan Barnard, working in Cape Town and having visited Shumway's unit, who performed the first human heart transplant in 1967.⁸ The following year, on the same day that Calne performed the first liver transplantation in the UK, Ross⁹ performed the first heart transplant, at the National Heart Hospital in London. During the 12 months after Barnard's transplant, more than 100 cardiac transplants were performed at centres around the world. Results were very poor, with few patients surviving to leave hospital. Over the next decade, only Shumway's group and that of Cabrol in Paris remained active. A key advance was the introduction of endomyocardial biopsy by Caves in 1973 and the classification of histological rejection by Billingham.¹⁰ Only with the introduction of ciclosporin in the early 1980s did cardiac transplantation become widespread. By 1986, more than 2000 procedures annually were being reported to the Registry of the International Society for Heart and Lung Transplantation (ISHLT). A decade later, this had more than doubled, although there has subsequently been a decline from that peak in all parts of the world.¹¹ UK numbers similarly were at their highest in the mid-1990s, with more than 300 transplants shared between seven centres, but have now decreased to less than half that number.

The first lung transplant was performed by Hardy, in 1964. Although the patient died of renal failure after 3 weeks, the case is notable because the lung was donated after circulatory death (DCD) and early function of the lung was

excellent.¹² Progress over the next 15 yr was dogged by airway healing complications and the longest survivor, that of Derom in Belgium, lived only 6 months. Reitz and colleagues¹³ performed the first successful heart–lung transplant in 1981 and the Toronto group achieved successful single-lung transplantation a few years later. The bilateral lung transplant, with separate hilar anastomoses, was introduced in 1992¹⁴ and is now the standard procedure for the majority of patients.

Immunosuppression

Historical background

In the 1950s, success in bone marrow transplantation between siblings had been achieved using total body irradiation,¹⁵ and for a while, this was pursued in kidney transplantation but with little success, although two recipients of kidneys from a non-identical twin did achieve some long-term function.¹⁶ ¹⁷ The real breakthrough came with the introduction of chemical immunosuppression that could suppress the immune system sufficient to permit engraftment of the transplant, while at the same time being suitably specific such that other protective immune responses remained intact. The first successful agent was azathioprine, a purine analogue and less toxic derivative of 6-mercaptopurine which had itself been shown to be effective in permitting long survival of dog kidney transplants.¹⁸ Azathioprine is thought to act by inhibiting DNA replication and thus blocking proliferation of lymphocytes. Coupled with prednisolone, azathioprine enabled transplantation of unrelated donor kidneys with around 50% still functioning at 1 yr, a significant achievement in an era when dialysis was still in its infancy and renal failure was usually a death sentence.

Modern immunosuppression

Ciclosporin

The modern immunosuppressive era came with the discovery of the immunosuppressant effects of ciclosporin in the mid-1970s. Initially developed as an antifungal drug, ciclosporin was found to be toxic in rodents, although curiously, it was noted to permit skin grafts between them.¹⁹ Two years later, the drug had undergone its first clinical trials in Cambridge and been shown to be a potent immunosuppressant.²⁰ Ciclosporin improved dramatically the results of kidney transplantation such that today 90–95% of kidney transplants on ciclosporin survive 1 yr; it also provided sufficient immunosuppression to permit successful liver, pancreas, heart, and lung transplantation.

Ciclosporin inhibits T cell proliferation by blocking activation. When foreign peptide antigen is presented to the recipient's T cell, binding to the antigen-binding groove of the major histocompatibility complex (MHC) triggers activation of the T cell. The rate-limiting step in the activation cascade is a serine–threonine phosphatase called calcineurin. When ciclosporin enters a lymphocyte, it binds to an immunophilin called cyclophilin. This ciclosporin–

cyclophilin complex inhibits calcineurin and so arrests T cell activation. Its principal side-effects are [neurotoxicity](#), [nephrotoxicity](#), and [diabetogenesis](#), although it also has other metabolic effects. In spite of careful monitoring of ciclosporin blood levels, up to 5% of patients who take ciclosporin will become diabetic, and a significant proportion will develop renal impairment. Calcineurin inhibitor (CNI) nephrotoxicity also causes renal failure in the native kidneys of many recipients of non-renal transplants, its incidence being highest in those receiving cardiothoracic organs.

[Tacrolimus](#)

Like ciclosporin, tacrolimus is a [fermentation](#) product of a bacterium, and also acts by inhibiting [calcineurin](#). However, tacrolimus binds a different immunophilin, the 12 kDa FK506 binding protein (FKBP12). The tacrolimus–FKBP12 complex binds to a different site on calcineurin to achieve the same effect as ciclosporin. It is more powerful than ciclosporin, and has proved superior in most forms of organ transplantation; it has also permitted intestinal transplantation to be successfully undertaken. It shares the same principle toxicities as ciclosporin, although the incidence of diabetes and neurotoxicity are higher. The two CNI drugs have different cosmetic effects, with ciclosporin causing hypertrichosis and gingival hypertrophy while tacrolimus can cause alopecia.

[Sirolimus and everolimus: inhibitors of the mammalian target of rapamycin](#)

[Sirolimus](#), formerly known as [rapamycin](#), is one of a class of drugs that inhibit the mammalian target of rapamycin (mTOR). Sirolimus was discovered as a fermentation product of a micro-organism originally isolated in soil samples from [Easter Island](#) (known locally as [Rapa Nui](#)); everolimus is a chemical modification of sirolimus which has improved its oral bioavailability and reduced its half-life from around 60 h to nearer [24 h](#).

mTOR is a serine/threonine protein kinase that is involved in the regulation of cell growth and proliferation and acts as a central mediator of protein synthesis and ribosome biogenesis. Blockade of mTOR inhibits the cellular proliferation response to a variety of signals, including cytokines such as interleukin 2. These effects are not limited to lymphoid tissue, so that blockade can also interfere with [wound healing](#) by impairing the normal fibroblast response to fibroblast growth factor. Sirolimus and everolimus achieve their effects by first binding the FKBP12 immunophilin, and it is this complex that inhibits the mTOR pathway.

mTOR inhibitors are [less nephrotoxic](#) than CNIs, although they do have glomerular effects and can cause [massive proteinuria](#); they can also cause diabetes but not as commonly as the CNI inhibitors. More importantly, the mTOR inhibitors can cause a [life-threatening pneumonitis](#),²¹ which resolves on treatment withdrawal. They are generally used as alternatives to CNIs in patients with impaired renal function, but in heart transplantation, mTOR inhibitors have been shown to

reduce immune-mediated [vasculopathy](#).²² In addition, mTOR inhibitors appear to have some anti-tumour properties, so have been used in patients transplanted for tumour (such as primary hepatocellular carcinoma) or who develop malignant tumours post-transplant, such as Kaposi's sarcoma.²³ Indeed, temsirolimus, another analogue of sirolimus, has been developed as an anti-neoplastic agent and is licensed for use in advanced renal carcinoma.²⁴

[Mycophenolic acid](#)

[Mycophenolic acid](#) (MPA) is the active component of mycophenolate mofetil and mycophenolate sodium. MPA blocks inosine monophosphate dehydrogenase, an enzyme required for the *de novo* synthesis of guanosine nucleotides. While other cells have salvage pathways by which guanosine nucleotides may be synthesized, lymphocytes do not. MPA thus blocks lymphocyte proliferation by blocking DNA synthesis. It is more potent than azathioprine and is associated with a greater reduction in acute rejection; however, it is not as potent as mTOR or CNIs, and is generally used in [combination](#) with one of those drug classes. Its main toxicity is in the gastrointestinal tract, with [diarrhoea](#) often being dose limiting.

[Induction therapy](#)

Immunosuppression is required for as long as the graft functions; if it is stopped, then rejection occurs and the graft is lost. However, the intensity of immunosuppression is not constant. [High](#) levels of immunosuppression are required soon [after](#) transplant, but thereafter doses can be [reduced](#) to a lower maintenance level. Immunosuppression in that initial period after transplantation is often [enhanced](#) by the use of a biological agent, such as a [monoclonal](#) or polyclonal antibody, many of which may be started intraoperatively or given immediately before surgery. Historically, anti-lymphocyte globulin, produced by inoculating horses or rabbits with human thymocytes and lymphocytes, was used, but this has been largely superseded by [monoclonal](#) antibodies that target specific [lymphocyte subsets](#). One such example is basiliximab, a chimeric monoclonal antibody to the CD25 antigen on the alpha chain of the interleukin 2 receptor, which is only expressed on activated T cells. Basiliximab therefore targets only activated T cells, and in the context of transplantation, these are the ones involved in allorecognition and initiation of an immune response. It has been shown to significantly reduce the incidence of graft rejection, although it is unclear whether it affects long-term survival. [Alemtuzumab](#) is another monoclonal antibody that is increasingly being used, and acts by depleting circulating T and B cells. Like the polyclonal anti-lymphocyte globulins, the first dose of alemtuzumab is associated with massive [cell lysis](#) and [release](#) of cytokines that can cause [dramatic haemodynamic instability](#), an important consideration if administration occurs in the peri-operative period. This can be reduced by [prior](#) administration of [steroids](#) and an [antihistamine](#).

Immunosuppressive regimens

Immunosuppression is normally given as a combination of agents with different sites of action and different side-effect profiles, following similar principles to antimicrobial and anti-neoplastic chemotherapy. The most common regimen used today in kidney transplantation is a CD25 monoclonal antibody such as basiliximab, followed by a combination of tacrolimus, mycophenolate, and steroids.²⁵ The regimen will vary according to the perceived immunosuppressive challenge that the transplant poses, with more powerful immunosuppression being used where the risk of rejection is perceived to be highest. Similarly different organs and different diseases require different protocols.

Complications of immunosuppression

In addition to individual drug side-effects, patients who are immunosuppressed have a higher risk of infection and malignancy. Commonly encountered infections include pneumocystis jiroveci and cytomegalovirus, although other unusual pathogens such as aspergillus are also more common in transplant recipients. Patients are usually given anti-microbial prophylaxis for the first 3–6 months, after which the effects of the induction immunosuppression have worn off and the baseline immunosuppression has been reduced.

While the incidence of all malignancies is higher in immunosuppressed patients, those with a possible viral aetiology are very high. Hence, post-transplant lymphoma due to EB virus affects around 2% of recipients, and non-melanoma skin cancer is particularly high, with human papilloma virus implicated.²⁶

Future possibilities in immunosuppression

Advances in immunosuppression have reduced the incidence of acute rejection, but have not affected the incidence of chronic immune damage in any organ, although the demonstration that everolimus inhibits coronary allograft vasculopathy in heart transplant recipients may be a step towards this.²² The goal of transplantation is the induction of tolerance, a state of specific unresponsiveness towards the donor. While this is readily and reliably achieved in animal models, it is rarely achieved clinically. Some patients who have discontinued their medication (often due to non-compliance) do appear to develop tolerance. This seems to be most common after liver transplantation, but has been reported after other organ transplants.²⁷ Nevertheless, such a state appears to be brittle, and readily broken when the immune system is challenged, for instance, by an intercurrent infection such as influenza. It may be more realistic to aim for a state of 'almost tolerance', where minimal immunosuppression is required.^{28 29}

Trends in organ donation

Since the start of transplantation, there has been a shortfall in the number of suitable donor organs available, and as the numbers of patients on the waiting lists has progressively increased, so too has the number of patients who are denied

access to the waiting lists. At the end of March 2010, there were almost 8000 patients on the national waiting lists for an organ transplant in the UK, with more than 7000 waiting for a kidney or combined kidney and pancreas, 360 a liver, 254 a lung, and 144 a heart or heart and lungs.³⁰ Patients are generally considered for listing for a transplant if they have a better than 50% chance of surviving 5 yr after transplant, although the actual recipient survival after transplantation of all organ-types transplants is far better than this (Figs 2–6). Greater availability of suitable donor organs would allow these arbitrary thresholds to be relaxed.

Death while awaiting a transplant

A significant number of patients fortunate enough to be on the transplant waiting list will die or be removed from the list at a later date, usually because they become too unfit for transplantation (Table 1). Hence while 62% of patients awaiting a heart will be transplanted within a year, 12% will die and a further 7% will be removed from the waiting list in the same year. The situation is worse for lungs where 27% of patients will either die or be removed from the waiting list in the first year of listing, while only 31% will be transplanted; only a half of those patients listed for a lung transplant will ever be transplanted.

Extending the envelope: live donors and less than ideal donors

In an effort to address the widening gap between demand and supply of donor organs, there has been an increase in the numbers of live donors, such that there are now more live donors than deceased donors per year in the UK, as there are in the USA.³⁰ The numbers of deceased organ donors have increased recently, but largely through increases in DCD which has increased 10-fold in the last decade and now comprises one-third of all deceased organ donors (Fig. 1).³¹

In addition to the increases in the numbers of DCD donors, there has been an increase in the use of organs from donors that would previously have been considered to be inappropriate. For example, the proportion of deceased donors who were aged >60 yr has increased from 14% in 2000–1 to 26% in 2009–2010, and the proportion with a BMI of ≥ 30 kg m⁻² has increased from 13% to 24% over the same period. There has also been a change in the common causes of donor death, with fewer donors dying after head injury and more after intracranial haemorrhage, organs from the latter being associated with less good transplant outcomes than the former. Recipients now have some difficult choices: turn down an organ which has associated risks in order to wait for the possibility of a better one, while risking death without a transplant, or alternatively accept a transplant from a live donor putting them at risk of death, a risk that may be as high as one in 200 for live donation of a liver lobe.

Table 1 Outcomes of UK patients placed on the waiting list for transplants (for the heart, lung, and pancreas, transplant data are for adult non-urgent patients listed between April 1, 2006, and March 31, 2007; for livers, data are for adult non-urgent patients listed between April 1, 2007, and March 31, 2008; and for kidneys, data relate to adult patients listed between April 1, 2004, and March 31, 2005). Data from NHS Blood and Transplant Activity Report 2009/2010. *For livers, the data are for 1 and 2 yr, not 1 and 3 yr

Organ	Proportion of patients at 1 yr				Proportion of patients at 3 yr*			
	Transplanted (%)	Still waiting (%)	Died (%)	Removed (%)	Transplanted (%)	Still waiting (%)	Died (%)	Removed (%)
Heart	62	19	12	7	69	4	16	12
Lung	31	42	21	6	51	6	30	13
Liver	69	11	10	9	75	2	11	12
Kidney	25	71	2	2	47	41	7	5
Pancreas	64	30	3	3	78	12	3	7

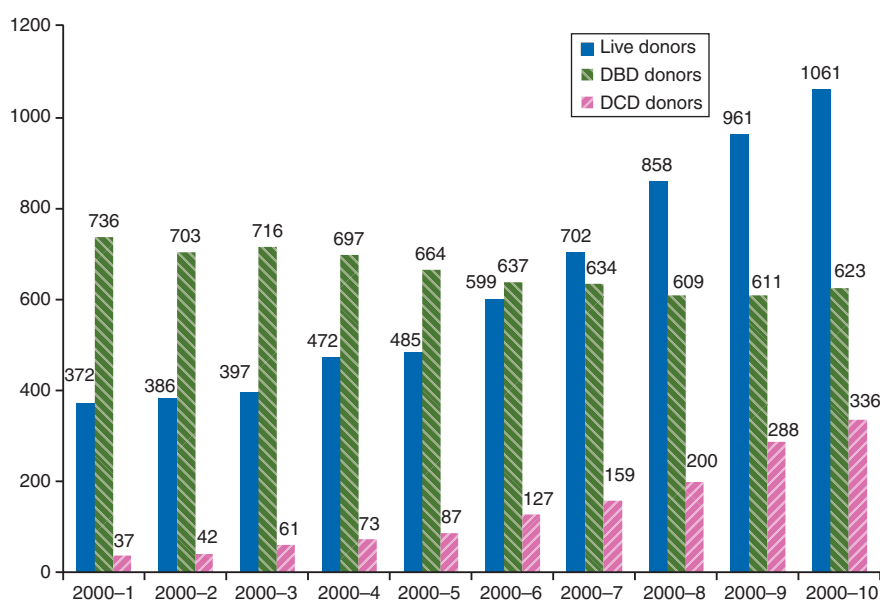


Fig 1 Trends in organ donors in the UK, 2000-10. The figure shows the change in the numbers of different types of organ donor in the last 10 yr. There are now more live donors in the UK, most of whom give a single kidney, although around 20 liver lobes are donated each year. The number of donors after circulatory death (DCD) has also increased nine-fold in the last 10 yr, while there has been little change in the number of DBD in the last 3 yr. This itself is notable given the decreasing numbers of DBD donors until 2007-8.

Xenotransplantation

The use of organs from animals has long been seen to be a solution to the shortage of donor organs. In spite of much effort, there is still no successful clinical xenotransplant programme. The pig has long been thought to be the most likely species to provide donor organs, since the organs are physically of similar size to human organs, and the species has a short gestation period, produces many offspring, can be successfully farmed, and can be genetically manipulated. Aside from ethical considerations, there are three main obstacles to successful xenotransplant: physiological, microbiological, and immunological.

Porcine and human physiology differs in a number of important aspects. There are differences in organ perfusion

pressures and core temperatures (the latter being 39°C in the pig). There are also differences in structure and activity of a variety of proteins, particularly those involved in the clotting and complement cascades and cell regulation.³²

The second concern relates to zoonotic infection, particularly from porcine endogenous retroviruses (PERVs).³³ Several PERVs have been identified in the genome of pigs, some of which have been shown to infect human cells in culture. The significance of these in clinical transplantation in an immunosuppressed recipient is unknown, but a cause for concern.

The third challenge is immunological.³⁴ Genetic manipulation of pig endothelium to express human complement regulatory proteins overcomes the immediate threat of

antibody-mediated hyperacute rejection response that would otherwise be a consequence of humans having preformed natural antibodies to porcine antigens. However, the threat of subsequent cell-mediated rejection has proven more resistant to genetic manipulation, with the cellular response to pig antigens that are indirectly presented on human MHC molecules being particularly aggressive. It would appear that xenotransplantation is still some years away from clinical practice.

Organ preservation

In the absence of a circulation, cells rapidly switch from aerobic to anaerobic metabolism, which requires 19 times more glucose substrate to generate adenosine triphosphate (ATP) than aerobic metabolism. The result is rapid consumption of energy substrate, depletion of intracellular energy stores, and accumulation of toxic metabolites and lactic acid. As ionic membrane pumps fail for lack of ATP, the cell membrane depolarizes as sodium enters and potassium leaves the cell. Eventually, cellular integrity is lost. The purpose of organ preservation is to prevent or arrest these changes as quickly as possible. This is achieved primarily by cooling: metabolic rate is halved at temperatures below 10°C, and at 4°C is <10% of that at normal body temperature.

Preservation solutions for the liver, kidney, and pancreas

Preservation solutions have been devised to counter the effects of prolonged ischaemia and minimize injury associated with reperfusion. They contain a physiological buffer to maintain pH in the face of accumulating lactic acid (e.g. phosphate or citrate) and large molecules such as mannitol or raffinose to maintain an intravascular osmotic potential in the absence of blood, thus minimizing cell swelling. In addition, the early fluids had an electrolyte composition more akin to intracellular fluid than extracellular fluid, with high potassium and low sodium concentrations to minimize diffusion. Indeed, the two most commonly used solutions today, Marshall's solution (Soltran, a preservation solution only suitable for kidneys) and the University of Wisconsin solution (ViaSpan, suitable for the kidneys, liver, and pancreas), are high potassium, low sodium solutions.^{35 36} This fluid composition has implications when the organs are reperfused with blood in the recipient, since the preservation solution is washed from the transplanted organ into the circulation carrying with it its potassium load. More recent work suggests that a composition akin to intracellular fluid is not essential, and low potassium, high sodium solutions have been introduced (e.g. Celsior), although they are not widely used in the UK.³⁷

Preservation solutions for the heart and lung

Cardiac preservation solutions tend to be adaptations of cardioplegia solutions, with a high potassium content

ensuring diastolic arrest and rapid reduction of metabolic activity that is added to the effects of cooling. For pulmonary preservation, almost all centres worldwide use a low-potassium/dextran solution (commercially available as Perfadex) to which a prostaglandin vasodilator has been added, and gentle inflation of the lungs to aid perfusate distribution. Additional low-pressure retrograde perfusion via the pulmonary veins is of proven advantage, washing clot and debris out of the arterial side and possibly giving additional cooling via the bronchial circulation.

Cold storage

Different organs exhibit different tolerances to warm and cold ischaemia, in part related to the nature of the organ and in part because of the demands on the organ after transplantation. Hence the heart, which has to function immediately upon transplantation, has the shortest tolerance to cold ischaemia, and each hour beyond the first results in a measurable reduction in survival,³⁸ it should ideally be transplanted in <4 h. This in turn mandates that heart retrieval cannot begin until a suitable recipient has been identified, admitted to transplant centre, and indeed prepared for surgery. Although lungs are slightly more tolerant, with good function to be expected as long as cold ischaemia is <6–8 h, similar principles very often apply.

Kidneys, in contrast, need not work immediately and the recipient can be supported on dialysis until they do work. Nevertheless, there is an increased recognition that even kidneys fare better if transplanted as quickly as possible, and ideally within 18 h. The liver and pancreas lie in between and are best transplanted within 12 h. For DCD organs, those values go down to 12 and 6 h, respectively, for the kidney and liver/pancreas. Registry analysis shows that with each type of organ, the duration of cold ischaemia is one of the more significant variables in determining outcome after transplantation,^{39–41} and one of the only modifiable factors. Moreover, it is a continuous variable, and any period of cold or warm ischaemia is undesirable.

DCD and warm ischaemia

Organ donors in whom death has been certified by neurological criteria (donation after brain death, DBD) are taken to theatre supported on a ventilator with the heart still beating. After mobilization of the organs and administration of heparin, the circulation is stopped by cross-clamping the aortic arch, draining the vena cava, and immediately flushing ice-cold preservation solution through the distal aorta thus keeping warm ischaemia, and accompanying anaerobic metabolism, to a minimum.

The organs retrieved from DCD donors are exposed to a more prolonged period of warm ischaemia than those retrieved from DBD donors. The warm ischaemic time has traditionally been assessed as the time interval between onset of irreversible asystole and subsequent cold

perfusion. This time interval includes the 5 min of continuous observation required to confirm death,⁴² together with time taken to transfer the donor to the operating theatre, perform the initial laparotomy, cannulate the aorta and IVC, and begin cold perfusion. However, it is now recognized that organ hypoperfusion and warm ischaemia begin some considerable time ahead of asystole as cardiovascular and respiratory functions slowly collapse after treatment withdrawal. Thus, while the warm ischaemic time may be 10–30 min, the true 'functional' warm ischaemia may extend beyond an hour. With the exception of the lung (which can be inflated with oxygen immediately after entering the operating theatre), all organs that suffer warm ischaemia tolerate subsequent cold ischaemia very badly.

Outcomes of organs from DCD donors compared with those from DBD donors

The extra warm ischaemic damage suffered as a consequence of DCD donation manifests in different ways. For kidneys, there is an increased incidence of acute tubular necrosis that results in a delay in resumption of renal function, necessitating post-transplant dialysis in more than half of the recipients. Livers transplanted from DCD donors have a higher incidence of primary non-function requiring urgent retransplantation or resulting in death, and also more anastomotic and intrahepatic biliary strictures which may result in recurrent cholangitis and necessitate retransplantation; DCD livers are also associated with poorer graft and patient survival than DBD livers,⁴³ but superior survival compared with remaining on the waiting list. There are less data for pancreas transplantation, but review of the UK Transplant Registry data suggests a higher incidence of graft thrombosis and pancreas loss with DCD donor pancreases compared with DBD donor grafts. In contrast, lungs transplanted after DCD donation function at least and also standard DBD lungs.⁴⁴ This may be attributed to both the arrest of warm ischaemia (by prompt re-inflation of the lungs with oxygen and the resulting restoration supply of oxygen to the pulmonary alveoli) and the absence of many of the deleterious pulmonary consequences of brain-stem death such as neurogenic pulmonary oedema.

Improving organ preservation

In the last two decades of organ transplantation, the focus has been on improving immunosuppression to achieve prolonged graft survival. Today, the emphasis has changed and organ preservation is being revisited in an attempt to improve outcomes. This has been spurred on by the rapid increase in DCD donation, and the use of more organs from older donors. There are three strategies that are currently being evaluated.

Normothermic regional perfusion of the abdominal organs in DCD donation

Surgeons in Barcelona have pioneered a technique to improve the outcomes of organs retrieved from uncontrolled DCD donors. After death, a double-balloon catheter is passed from the femoral artery into the aorta where the balloons are inflated to isolate the abdominal aorta. Venous outflow is via the ipsilateral femoral vein. The catheters are then connected to an extracorporeal membrane oxygenator (ECMO) circuit to perfuse the abdominal organs with circulating warm, oxygenated blood. This permits recovery from the warm ischaemic injury that occurs around death and early results suggest that it improves the outcomes of kidneys and livers retrieved from such donors.^{44–46} Having replenished ATP, the cells in the organs are then better placed to withstand subsequent cold storage. The technique has been adopted in France and in parts of the USA,⁴⁷ and initial studies are underway in the UK in controlled DCD donors with promising early results. With the numbers of DCD donors, increasing the use of normothermic regional perfusion may become standard practice in these donors.

Cold machine perfusion of the kidney

After removal from the deceased donor, kidneys are usually placed in a bag of preservation solution in a box of ice, keeping the temperature of the organ around 4°C. While such static cold storage has the advantage of being simple and facilitating easy transport of the kidney from donor hospital to recipient hospital, nevertheless it has been argued that the kidney may be better preserved if it is placed on a machine where cold preservation solution is pumped through it, flushing out the small capillaries and the accumulating metabolic products. Particular attention has focused on cold machine perfusion of kidneys from DCD donors, which potentially have most to gain from improved storage. However, two recent randomized controlled trials using the same machines have produced contrary results, so the true value of cold machine perfusion remains to be determined.^{48 49} As yet, there are no commercially available machines for the cold perfusion of non-renal organs.

Normothermic machine perfusion

The liver

Although avoidance of unnecessary warm ischaemia is essential, there is no doubt that cold preservation is also damaging to organs, some more so than others. Steatotic (fatty) livers are particularly susceptible to damage by cold preservation, since the intrahepatic fat globules solidify and damage the hepatocytes and hepatic microcirculation,⁵⁰ accounting in part for the high incidence of non- and poor function in such livers. One solution would be to preserve the livers at normal body temperature.⁵¹ Since metabolism is fully active at 37°C, such preservation needs to involve an oxygenated perfusate. Normothermic perfusion devices for the liver are currently in early trials in the UK and the first clinical transplants with such livers are expected this

year. Preclinical evidence suggests that such a technique will offer considerable advantages over cold preservation, particularly for livers that have experienced significant periods of warm ischaemia as occurs in DCD donation.⁵²

The heart

The ability to extend the safe preservation period for hearts has led to much interest in normothermic perfusion. Such a device perfuses the coronary arteries and the heart itself does not need to contract; this does allow pre-transplant assessment of pump function. One such device, the TransMedics Organ Care System™ is currently undergoing phase 2 trials in the USA (http://www.transmedics.com/wt/page/PROCEED_II) and has been evaluated in Europe, although the results are not yet published.

The kidney

The ability to preserve a kidney in the cold for long periods has removed the incentive to develop normothermic preservation. However, recent work suggests that a period of normothermic preservation immediately before implantation using a red cell-based plasma-free perfusate may reduce reperfusion injury;⁵³ clinical trials of this are currently underway with encouraging early results.

The lung

Ex vivo lung perfusion is probably the furthest advanced of all the normothermic organ preservation techniques. Initial work showed that lungs can be perfused with a blood-based perfusate and assessed *ex vivo* before transplantation.⁵⁴ The lungs are ventilated via a tracheal tube in the trachea/bronchus and perfused via a cannula in the pulmonary artery. After passing through the lungs, the perfusate passes back to an ECMO device where it is deoxygenated by a nitrogen/carbon dioxide-rich gas mixture, warmed to 37°C, and passed from there through a leucocyte filter back to the lungs. The ability of the lungs to oxygenate the perfusate gives an indication of function. There is now considerable evidence that lungs that would otherwise have been considered not suitable for transplantation could be ‘reconditioned’ *ex vivo*, with the potential for making significantly more lungs available for transplantation.^{55–57}

Ischaemic preconditioning

Ischaemic preconditioning, either by rendering the target organ ischaemic (direct ischaemic pre-conditioning) or by rendering a different organ or tissue ischaemic (remote ischaemic preconditioning), may help reduce reperfusion injury after organ transplantation. Although animal work suggests the benefits of such an approach, there have been few large-scale trials to substantiate these observations clinically, particularly with organs from deceased donors, with the studies that have been published offering conflicting results.⁵⁸ In part, this may reflect the very abnormal physiological state that exists after coning in brain-

dead organ donors, and in part because most studies are insufficiently well powered to show any significant difference. A large correctly powered study of remote ischaemic preconditioning in living kidney donation is currently underway in the UK; large properly powered studies in deceased organ donation are awaited.

Clinical results in organ transplantation

The results of transplantation of all solid organs have improved year on year in spite of the fact that fewer ‘ideal’ donor organs are used; instead, donors are now older and more commonly donate after a spontaneous cerebrovascular event rather than after isolated traumatic brain injury.

Kidney transplantation

There are around 22 000 patients in the UK alive with a functioning kidney transplant, and a further 25 000 on dialysis, of whom 7000 are active on the kidney transplant waiting list.⁵⁹ Figure 2A illustrates the underlying diagnosis in those patients, while Figure 2B illustrates the long-term outcomes after kidney transplantation. As can be seen for all transplant types, there is an initial rapid decrease in graft (and patient) survival in the first few months post-transplant and thereafter a slow attrition; around 70% of grafts will be functioning at 10 yr. The early graft losses include technical problems such as vascular thrombosis, and also losses due to rejection. Late losses are usually a result of a combination of pre-existing donor disease, recurrence of the recipient’s own disease (e.g. IgA nephropathy), and immunological response to the graft.

Pancreas transplantation

Most pancreas transplants are performed in patients with diabetic nephropathy who either also require (80%) or who have previously received (15%) a kidney transplant. A small number of patients with life-threatening hypoglycaemic unawareness receive a pancreas alone. In this latter group of patients, their symptoms have to be sufficiently troublesome to warrant a major laparotomy and the continued immunosuppression that is involved.

Although the first pancreas transplantation in the UK was in 1978, activity has only increased in the last few years, largely as the result of national commissioning along similar lines to cardiothoracic and liver transplantation. The number of pancreas transplants has increased from around 40 in 2000 to nearly 200 10 yr later. The results of pancreas transplantation have improved rapidly as experience accrued, with the most recent results now as good as those in the USA (Fig. 3).

A proportion of donated pancreases are processed to extract islets for isolated islet transplantation. This is also indicated for patients with life-threatening hypoglycaemic unawareness, and has the advantage that it avoids a significant surgical intervention. However, the extraction, isolation, and transplantation process is not very

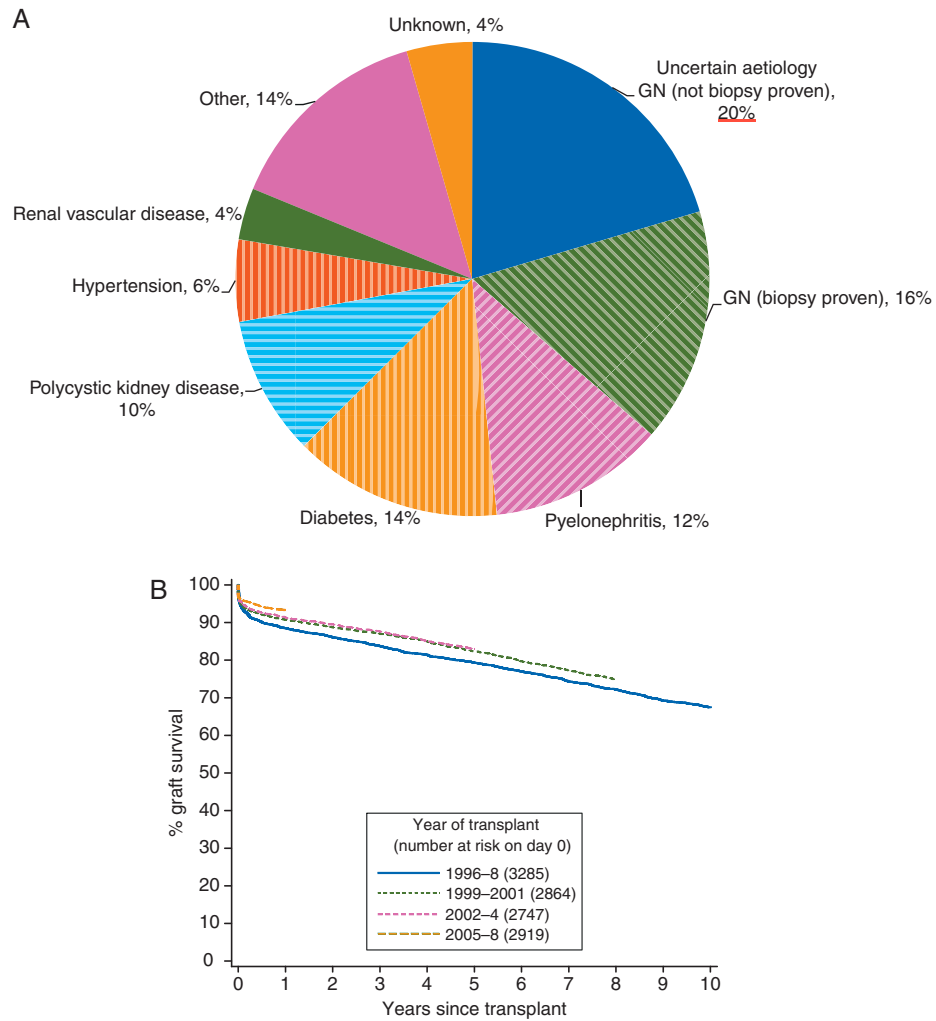


Fig 2 (A) Primary renal disease in prevalent patients on renal replacement therapy in the UK on December 31, 2008 (GN, glomerulonephritis).⁵⁹ (B) Long-term graft survival after first kidney only transplant in the UK from DBD donors, January 1, 1996–December 31, 2008.

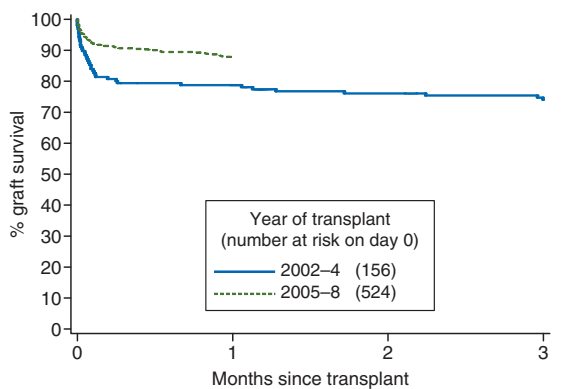


Fig 3 Pancreas graft survival after first combined kidney and pancreas transplant in the UK, January 1, 2002–December 31, 2008.

efficient such that most recipients continue to require insulin afterwards, although they are symptomatically much improved.

Liver transplantation

The most common indication for liver transplantation today is hepatocellular carcinoma (hepatoma) occurring in a cirrhotic liver (Fig. 4A). The hepatoma(s) must be small and confined to the liver; current guidelines indicate that patients with a single tumour under 5 cm or no more than 5 tumours all under 3 cm are suitable candidates with least chance of recurrence or extra-hepatic spread of the tumour. The majority of these hepatomas occur against a background of hepatitis C-induced cirrhosis, which also accounts for 14% of transplants in patients without tumours. Alcoholic liver disease is the next most common indication for liver transplantation. Potential

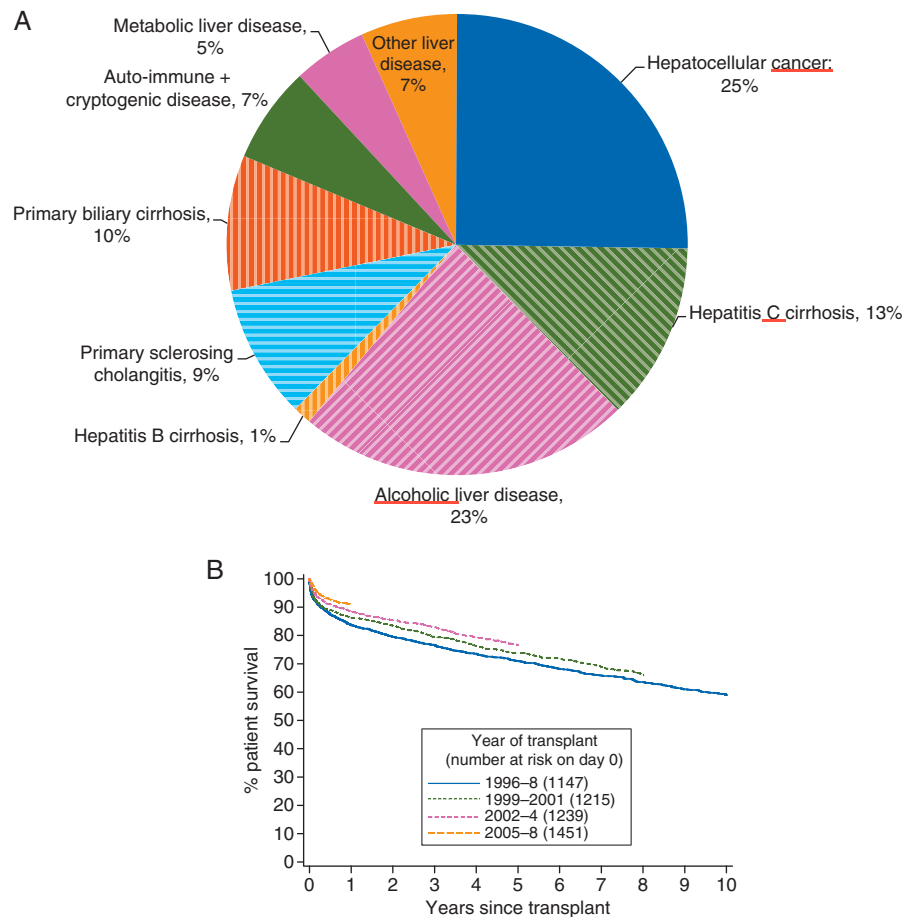


Fig 4 (A) Indications for elective liver transplantation in the UK, January 1, 2008–December 31, 2010. (B) Long-term patient survival after first elective liver transplant in adults in the UK from DBD donors, January 1, 1996–December 31, 2008.

recipients must have abstained from alcohol for 6 months before listing, a period of time that may allow significant recovery if there is an element of alcoholic hepatitis. Auto-immune disease represents most of the other indications. Hepatitis B, once a common indication for transplantation, now only accounts for 1% of liver transplants, reflecting the impact of the new anti-viral treatments for that disease. It is hoped that the anti-viral drugs against hepatitis C that are currently in development will have a similar effect on the current hepatitis C epidemic.⁶⁰ Acute liver failure represents about 10% of transplants performed in the UK. Although such patients are prioritized for a liver via the national allocation scheme, one-third will die before a suitable graft can be identified.

After non-urgent liver transplantation, the long-term outcomes are good (Fig. 4B), with a 10 yr patient survival in excess of 60%, and likely to approach 70% for the most recently transplanted patients.

Heart transplantation

In both adult and paediatric practice, the most common indication for transplantation is idiopathic dilated

cardiomyopathy (Fig. 5A). Most other paediatric recipients will have complex congenital heart disease and often come to surgery after a number of previous palliative procedures. Problems of pre-sensitization to HLA antigens add to the substantial technical difficulties, and these patients are very challenging. Outcomes have been improving in recent years (Fig. 5B).

Across the board, a 1 yr survival of 80–85% can be expected, with a subsequent attrition rate of perhaps 4% annually. Late deaths are most commonly the result of graft vasculopathy. The endothelium of the graft coronary circulation represents the zone of contact between host and recipient. Endothelial dysfunction can be detected as early as 6 weeks post-transplant. It is likely that ongoing immune injury is the stimulus for sub-intimal thickening that eventually results in diffuse coronary arterial narrowing. Post-transplant rejection episodes, dyslipidaemia, and continued smoking are all predictors of worse disease. In addition, donor age and pre-existing coronary disease are also important. Most other deaths are the consequence of prolonged immunosuppression, with malignancy and renal failure prominent. Functional

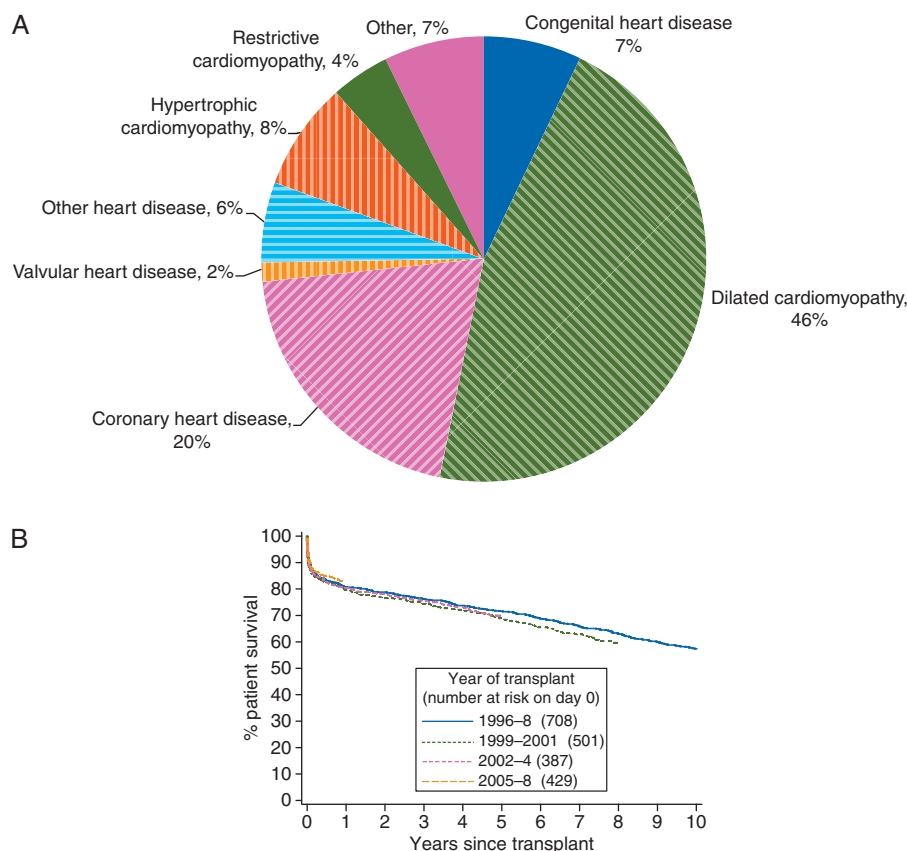


Fig 5 (A) Indications for adult non-urgent heart only transplantation in the UK, January 1, 2008–December 31, 2010. (B) Long-term patient survival after first heart only transplant in adults in the UK, January 1, 1996–December 31, 2008.

outcome is excellent, with very good quality of life and return to normal activities after successful transplantation.

Paediatric results have been improving steadily over the past few years, perhaps reflecting the restriction of activity to specialist centres (just two in the UK). In particular, infants presenting with cardiomyopathy may expect a 10 yr survival approaching 90% after transplantation.⁶¹

Lung transplantation

Major indications for lung transplantation include cystic fibrosis, emphysema, and pulmonary fibrosis (Fig. 6A). The last may be best treated with a single-lung transplant, but the bilateral procedure has become the norm for most patients. There are clear-cut advantages in terms of both early and late survival. Very few combined heart and lung transplants are currently performed, and they are largely restricted to patients with complex congenital heart disease and secondary pulmonary hypertension.

There remains a significant early mortality rate (Fig. 6B) which principally relates to primary graft dysfunction and brain-death-induced damage in the donor.⁶² As a result, barely 20% of potential donor

lungs in the UK are currently used for transplant, and while relaxation of donor criteria may permit greater activity, it may also result in more early graft dysfunction and patient mortality.⁶³

Although registry figures continue to suggest a 5 yr survival of only 50–60%, single institution results, particularly in favourable groups such as those with cystic fibrosis, can be much better. Median survivals in excess of 10 yr have recently been reported.⁶⁴ Late attrition is largely related to progressive small-airway narrowing, termed obliterative bronchiolitis. Although it is, in part, a chronic immune injury, early post-implant damage is also a risk factor, and it would seem that a range of immune and non-immune insults set up progressive airway obliteration. The latter include viral infections and gastro-oesophageal reflux. While in some patients, augmented immunosuppression may halt the progress, for others retransplantation is the only option.

Summary

Organ transplantation is a story of remarkable achievement and an ongoing challenge. Immunosuppression needs to be improved to further extend the life of the grafts with

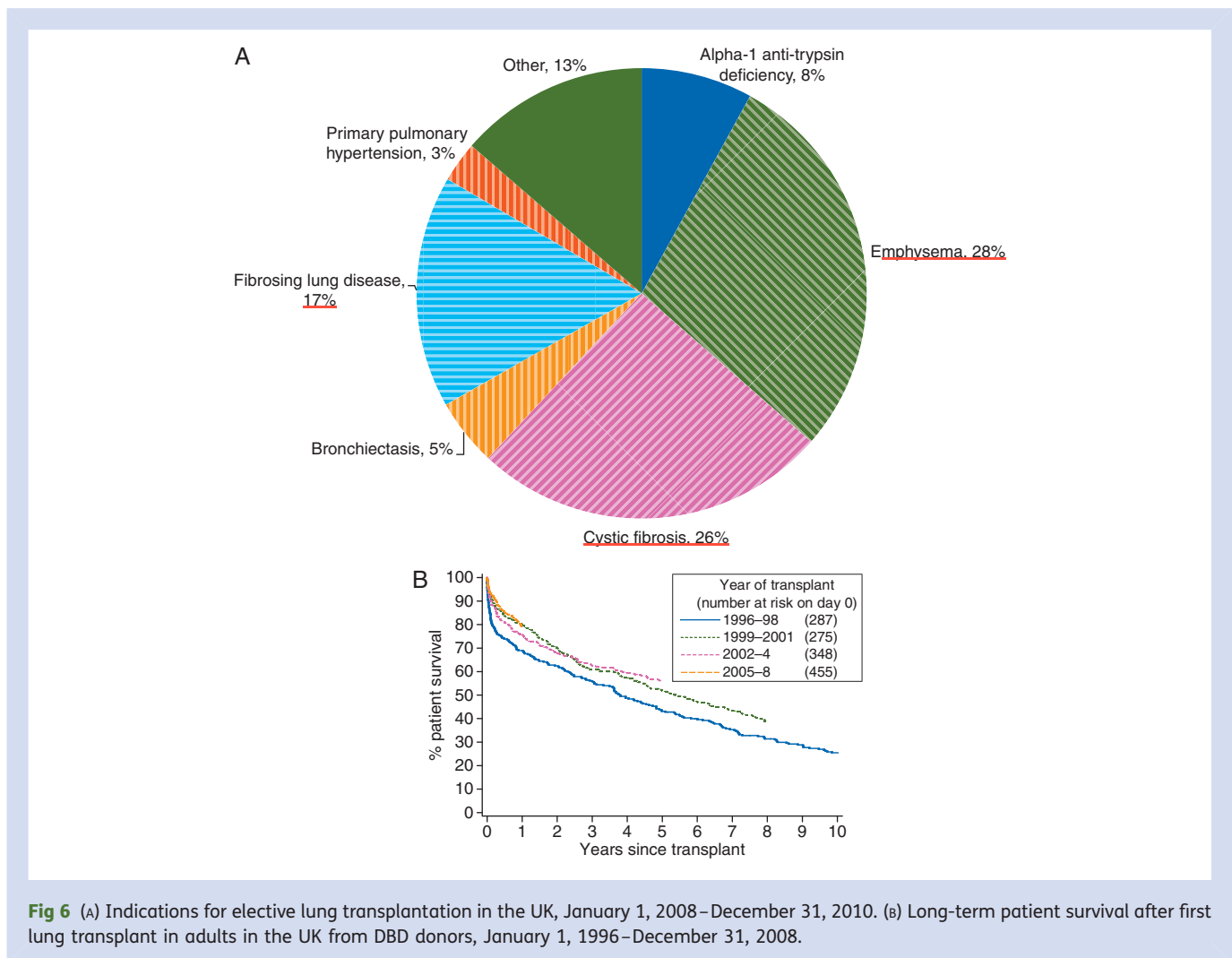


Fig 6 (A) Indications for elective lung transplantation in the UK, January 1, 2008–December 31, 2010. (B) Long-term patient survival after first lung transplant in adults in the UK from DBD donors, January 1, 1996–December 31, 2008.

induction of tolerance still the goal; preservation techniques need to be modified to reduce the ischaemic injury that organs sustain, and which contributes to premature failure. Nevertheless, the main factor limiting the success of transplantation continues to be the shortage of suitable donor organs.

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Declaration of interests

None declared.

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