



2016 Liver Transplantation: Global view

## Liver transplantation: Current status and challenges

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### Abstract

Great progress has been made in the field of liver transplantation over the past two decades. This

progress, however, also brings up the next set of challenges: First, organ shortage remains a major limitation, and accounts for a large proportion of wait list mortality. While living donation has successfully increased the total number of liver transplants done in Asian countries, the total number of such transplants has been stagnant in the western hemisphere. As such, there has been a significant effort over the past decade to increase the existing deceased donor pool. This effort has resulted in a greater use of liver allografts following donation after cardiac death (DCD) along with marginal and extended criteria donors. Improved understanding of the pathophysiology of liver allografts procured after circulatory arrest has not only resulted in better selection and management of DCD donors, but has also helped in the development of mechanical perfusion strategies. Early outcomes demonstrating the clinical applicability of both hypothermic and normothermic perfusion and its potential to impact patient survival and allograft function have generated much interest. Second, long-term outcomes of liver transplant recipients have not improved significantly, as recipients continue to succumb to complications of long-term immunosuppression, such as infection, malignancy and renal failure. Furthermore, recent evidence suggests that chronic immune-mediated injury to the liver may also impact graft function.

**Key words:** Donation after cardiac death; Mechanical perfusion; Renal-sparing immunosuppression; Antibody-mediated rejection

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**Core tip:** Organ shortage remains a major limitation in liver transplantation, and there has been a significant effort over the past decade to increase the existing deceased donor pool. Recent advances have included better selection and management

of donors after circulatory arrest, application of hypothermic and normothermic perfusion, minimization of standard immunosuppression and use of new immunosuppressive medications. Additionally, there has been renewed emphasis and understanding of liver immunology and the impact of antibody-mediated rejection. Together, these advances have allowed for expansion of the donor pool with concurrent improved patient outcomes.

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## INTRODUCTION

Over the last several decades, the field of transplantation has witnessed much change yet, among all solid organ transplants, arguably the greatest advances have been in liver transplantation. Today, liver transplantation is universally accepted as the only treatment option for end-stage liver disease, acute fulminant hepatic failure, hepatocellular carcinoma, hilar cholangiocarcinoma and several metabolic disorders. Advancements in surgical technique, perioperative management and immunosuppressive therapy have yielded excellent short-term graft and patient survival outcomes which have become the expected norm. With these advances comes the next set of challenges: organ shortage and improving long-term outcomes of the liver transplant recipients.

## ORGAN SHORTAGE

The disparity between the number of available liver allografts and transplant candidates continue to grow worldwide. In Asia, this problem has been successfully addressed by ever-increasing numbers of living-donor liver transplantation (LDLT). In the western countries, however, the number of LDLT has not seen a significant change for over a decade, and the demand for deceased donor liver allografts continue to increase. Thus, substantial effort has been put in to expand the existing deceased donor pool.

### **Use of donation after cardiac death liver allografts**

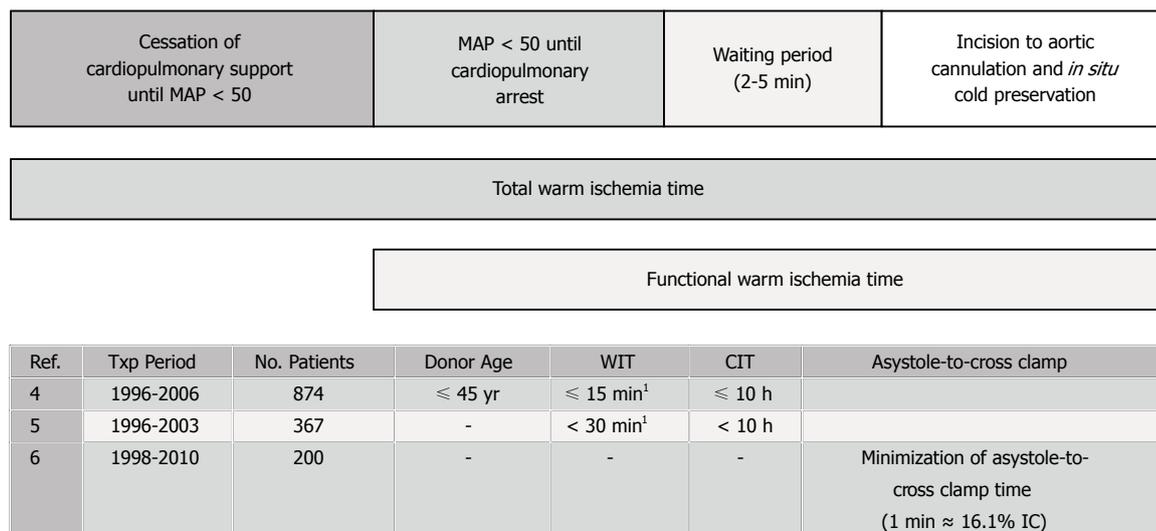
In the early 1990s, the use of livers procured from donation after cardiac death (DCD) donors was an early attempt to narrow the disparity between organs and recipients in need<sup>[1]</sup>. The early experience with DCD livers was not favorable, as prolonged donor warm ischemia time and ischemia-reperfusion injury likely played a large role in the high rate of primary

non-function, hepatic artery thrombosis, ischemic cholangiopathy, and allograft failure<sup>[2,3]</sup>. With increasing experience, however, factors associated with improved outcomes have been identified and more centers have begun to use these donors<sup>[4-6]</sup>.

To date, there have been several large retrospective analyses which have identified DCD donor-related variables associated with recipient outcomes (Figure 1). Young age ( $45 \pm 10$  years old), short donor warm ischemia time (less than thirty minutes), and limited cold ischemia time (less than ten hours) have been shown to improve allograft outcomes<sup>[4-6]</sup>. In the Mayo Clinic experience, every minute added to the warm ischemia period between asystole and cross-clamp was found to be associated with a 16.1 percent increase in the odds of ischemic cholangiopathy<sup>[6]</sup>. Recipient factors associated with improved DCD outcomes generally concentrate on avoidance of sicker patients: excluding patients requiring retransplantation, patients with renal failure (creatinine > 2.0 mg/dL) and patients on life support<sup>[5]</sup>. The correlation between these factors and outcomes is likely related to minimization of both cold ischemia time and further allograft injury through recipient instability. As a result, by applying these donor and recipient criteria, DCD outcomes have improved considerably with recipient survival and allograft function similar to that of donation after brain death (DBD) donors<sup>[4-6]</sup>.

### **Mechanical perfusion of deceased donor liver allografts**

Despite these improved outcomes, many DCD livers continue to go unused as a result of unacceptable donor parameters and concern for poor allograft function. The concept of mechanical perfusion for solid organ transplantation was originally introduced in the late 1960s by Belzer *et al*<sup>[7]</sup> and renewed interest returned following a report by Moers *et al*<sup>[8]</sup> in 2000 which, through a prospective randomized control trial, demonstrated a decreased incidence of delayed graft function and improved graft survival in kidney transplant recipients. Since then, hypothermic machine perfusion in kidney transplantation has gained a widespread use. Although suboptimal, static hypothermic cold storage remains the primary method for liver preservation, largely because of its cost effectiveness, simplicity, and logistics. At present, there is a large and apparent need to optimize preservation particularly for DCD, marginal, and extended-criteria donor organs. These allografts are subject to a greater risk of ischemia-reperfusion injury which occurs as a result of donor warm ischemia time, aortic cross-clamping and initiation of cold ischemia, rewarming during graft implantation, and finally full reperfusion (Figure 1). It is here that the utility of mechanical perfusion has emerged as potential solution to this problem.



**Figure 1 Favorable donation after cardiac death donor criteria.** <sup>1</sup>From time of cessation of cardiopulmonary support to with loss of hemodynamic and respiratory function up to the *in situ* initiation of cold preservation solution. MAP: Mean arterial pressure; WIT: Warm ischemia time; IC: Ischemia cholangiopathy.

Table 1 Comparison of hypothermic and normothermic mechanical perfusion		
	Hypothermic mechanical perfusion	Normothermic mechanical perfusion
Temperature	4 °C	37 °C
Pathophysiology	Reduced cellular metabolism Non-functioning liver during preservation	Continued cellular metabolism Functioning liver during preservation
Perfusate	No specific requirements, oxygen can be used	Continuous delivery of nutrients and oxygen needs to be maintained
Logistics	Similar to that of hypothermic mechanical perfusion currently used for renal allografts	More complex
Benefits	Logistically easier  May provide benefit in marginal livers	Allows for the assessment of metabolic and synthetic function during preservation May provide benefit in marginal livers Potential use in steatotic livers Felt to reduce ischemia reperfusion injury

### Hypothermic perfusion

Hypothermia slows cellular metabolism and prolongs the amount of time an organ can be deprived of oxygen without loss of viability (Table 1). In liver transplantation, hypothermic perfusion has shown similar benefits. Authors Guarrera *et al.*<sup>[9]</sup> have demonstrated that hypothermic perfusion decreases the extent of graft injury and subsequent clinical studies by the same group have shown improved allograft function, lower serum transaminases and decreased hospital stay as compared to matched historic cold storage liver allografts from DBD donors<sup>[10,11]</sup>. Equally beneficial results have been reported in DCD liver allografts<sup>[12,13]</sup>. In a trial using human DCD livers, Hypothermic Oxygenated PERfusion (HOPE) was applied for 1 to 2 h prior to implantation<sup>[12]</sup>. Functional warm ischemia time (MAP < 50 mmHg to cold flush) in this group ranged from 22 to 41 min and postoperative allograft function was normal in the entire cohort. In a follow-up period of 8.5 mo, no evidence of intrahepatic biliary complications was noted. As a continuation to this study, authors Dutkowski *et al.*<sup>[13]</sup> recently published

their results evaluating DCD livers treated with HOPE along with matched static cold storage DCD livers. As anticipated, results for DCD livers subjected to HOPE were superior with decreased graft injury, decreased intrahepatic cholangiopathy and biliary complications and improved 1-year graft survival<sup>[13]</sup>. Similarly, hypothermic machine perfusion has also been applied to extended criteria DBD donor liver allografts with encouraging outcomes, such as decreased allograft dysfunction (19% vs 30%), improved patient survival at one year (84% vs 80%) and a reduction in biliary complications (13% vs 43%)<sup>[11]</sup>.

### Normothermic perfusion

Normothermic perfusion is technically more demanding, as it requires a continuous delivery of nutrients and oxygen in order to maintain ongoing cellular metabolism<sup>[14]</sup>. In theory, this setup reduces the ischemia-reperfusion injury and may thereby allow for the safe transplantation of marginal liver allografts. Normothermic mechanical perfusion can also allow for the assessment of liver function during the pre-

implantation period (Table 1). Although these advantages are notable, historically, there have been difficulties in maintaining stable perfusion<sup>[15]</sup>. In a preclinical work by op den Dries *et al.*<sup>[16]</sup>, discarded DCD human donor livers were subjected to normothermic mechanical perfusion following cold ischemia times of  $6.9 \pm 1.9$  h (WIT  $15.5 \pm 2.4$  min). After six hours of normothermic perfusion ( $37^\circ\text{C}$ ), bile production was observed and histological examination showed well-preserved liver morphology without signs of hepatocellular ischemia, biliary injury, or sinusoidal damage<sup>[16]</sup>. Currently, there are several human trials underway comparing normothermic liver preservation with static cold storage. The first Phase I, non-randomized, prospective trial using the normothermic mechanical perfusion unit enrolled twenty transplanted livers in United Kingdom and was completed in 2014. Results from this trial demonstrated the safety and feasibility of normothermic machine preservation in human liver allografts (personal communication). In the interim, a multicenter, randomized controlled trial with enrollment plan for 260 liver allografts (130 using OrganOx<sup>®</sup>; 130 using static cold storage) is under way.

#### **Steatotic liver allografts and mechanical perfusion**

The application of mechanical perfusion to marginal donors is foreseeable as hepatic steatosis has become increasingly common in the United States and the incidence of deceased donors with steatotic livers has concurrently increased. Allografts with severe steatosis, defined as greater than sixty percent of the parenchyma, are known to carry a high risk of primary non-function<sup>[17,18]</sup>. On the contrary, liver allografts with mild steatosis (< 30%) yield results similar to those of non-steatotic liver allografts<sup>[17,18]</sup>. The outcomes of liver allografts with moderate steatosis (30% to 60%) remain variable, and often depend upon additional factors such as recipient stability, ischemia time, and mechanism of donation (*i.e.*, DBD vs DCD). Impaired microcirculation secondary to increased hepatocyte volume is theorized to be responsible for the relative susceptibility of steatotic livers to ischemia<sup>[19]</sup>. Cellular edema accompanying ischemia-reperfusion likely results in further obstruction of the sinusoids, thereby exacerbating this injury. Accordingly, steatotic DCD liver allografts are generally discarded as these scenarios combine several risk factors. As such, the application of mechanical perfusion may help salvage steatotic livers. At present, preclinical and clinical studies are lacking however Bessems *et al.*<sup>[20]</sup> evaluated mechanical perfusion using a steatotic rat model in which they compared static cold storage and hypothermic oxygenated mechanical perfusion. Results from this animal model found that preservation of steatotic livers stored in standard cold storage resulted in more cellular injury. By comparison, the steatotic livers subjected to hypothermic oxygenated mechanical perfusion showed improved bile production

and higher ATP levels<sup>[20]</sup>.

## **IMPROVING LONG-TERM LIVER TRANSPLANTATION OUTCOMES**

Although the short-term outcomes after liver transplantation have been excellent worldwide, long-term outcomes remain suboptimal. The top causes of late mortality after liver transplantation are allograft failure, cardiovascular events, infection, malignancy and renal failure<sup>[21]</sup>. There is a clear and direct link between these and the long-term use of immunosuppressive medications. As a result, in the past decade, a significant effort has been put forth to minimize immunosuppression in liver transplantation.

#### **Renal sparing protocols**

Renal insufficiency is the strongest predictor of late mortality following liver transplantation<sup>[21]</sup>. Because of this, the use of renal sparing immunosuppression protocols both during the induction and maintenance periods following liver transplantation has been introduced into the clinical practice over the past decade.

#### **Mammalian target of rapamycin inhibitors:**

A number of large trials evaluated the role of mammalian target of rapamycin inhibitors (mTOR) in liver transplantation. The Preservation of Renal Function in Liver Transplant Recipients with Certican Therapy (PROTECT) study<sup>[22]</sup>, a randomized controlled trial sought to evaluate the effect of conversion from calcineurin inhibitors (CNI) to everolimus starting four weeks following liver transplantation. Unfortunately, at one year, the study results proved to be inconclusive. No difference in glomerular filtration rate (GFR) was noted using the Cockcroft-Gault formula. Moreover, despite lack of clear benefit, the study did, however, observe a higher rate of infections, anemia, leukopenia and hyperlipidemia in the Everolimus treatment group<sup>[22]</sup>.

By comparison, a second trial by Masetti *et al.*<sup>[23]</sup> in 2010 showed some benefit in using mTOR inhibitors in liver transplantation. In this randomized control trial, cyclosporine (CsA) was used for ten days following liver transplantation. Patients were then randomized to Everolimus or cyclosporine plus mycophenolate mofetil (MMF). At twelve months, GFR was better in the Everolimus group and no differences were noted in patient survival, acute rejection or hepatic artery thrombosis<sup>[23]</sup>. Among the patients with a GFR less than 60 mL/min per 1.73 m<sup>2</sup>, the Everolimus treatment group showed a benefit. Accordingly, conclusions of the study were that early withdrawal of CsA followed by Everolimus monotherapy in de novo liver transplant patients was associated with an improvement in renal function, although, a criticism of the study has been the baseline difference between

the two groups with regard to the starting GFR.

In Spare-the-Nephron Trial<sup>[24]</sup>, patients on CNI/MMF for the first four weeks post-transplant were randomized to either continue the same regimen or convert to Sirolimus/MMF. A mean increase in patient GFR was noted in the Sirolimus group, however the composite endpoint demonstrated non-inferiority of Sirolimus to CNIs when used with MMF<sup>[24]</sup>. Review of other smaller studies evaluating the conversion from CNI to mTOR inhibitors in liver transplant patients with renal insufficiency reveals similar variable results<sup>[25-28]</sup>. A meta-analysis of the use of Sirolimus in liver transplant recipients with CNI-induced renal insufficiency found no significant improvement in GFR, risk of death or graft failure<sup>[29]</sup>. Findings were, however, significant for an increased risk of infection, mouth ulcers and treatment discontinuation<sup>[29]</sup>. Given this variability, the role of mTOR inhibitors continues to evolve with much indecision and hesitancy surrounding their use for renal insufficiency. Newer roles, specifically with regard to benefit in hepatocellular carcinoma, likewise remain to be fully realized.

**Induction therapy and delayed introduction of calcineurin inhibitors:** Delayed introduction of CNI following liver transplantation may, theoretically, help decrease the negative impact of CNI on renal function<sup>[30-33]</sup>. Among *de novo* liver transplant recipients who had pre-existing renal insufficiency, Thymoglobulin induction and delayed introduction of CNI resulted in lower serum creatinine, a higher estimated GFR, and less dependence on dialysis at twelve months<sup>[30]</sup>. Similar strategies have been employed using newer generation anti-interleukin-2-receptor antibodies (Basiliximab, Daclizumab) for induction<sup>[32,33]</sup>. The ReSpECT trial, comparing standard Tacrolimus vs reduced-dose Tacrolimus and Daclizumab induction and delayed reduced-dose Tacrolimus<sup>[34]</sup>, demonstrated that the greatest decline in eGFR was seen in the standard Tacrolimus group with the least decline noted in the Daclizumab induction and delayed reduced-dose Tacrolimus group. Currently, at Mayo Clinic, Basiliximab induction is used in patients with renal insufficiency so as to delay initiation of CNI post-transplant.

**Immunosuppression minimization/withdrawal:** Of all the solid organs that are transplanted routinely, liver allograft appears to be unique, as approximately 19 percent of the recipients can achieve "operational" tolerance (off immunosuppression incidentally or obligatorily)<sup>[35,36]</sup>. Given these findings, several recent trials investigated elective withdrawal of immunosuppression (IS) in liver transplant recipients. In one such trial, 12 out of 20 (60%) pediatric liver transplant recipients were successfully weaned off IS, with no or minimal portal inflammation<sup>[37]</sup>. In a large European multi-center trial of 102 adult deceased donor liver

transplant recipients, 41 (40%) achieved operational tolerance<sup>[38]</sup>. At present, more information is needed so as to better guide clinical decision making and similar trials with long-term follow-up will help identify parameters with predictive and diagnostic value regarding who could be successfully weaned off IS. Longitudinal follow-up of operationally tolerant patients will also further demonstrate whether long-term outcomes improve with limiting the recipients' cumulative exposure to IS, particularly CNI.

### **Chronic antibody-mediated injury**

Historically, liver allografts were thought to be spared from the HLA antibody-mediated injury, however recent findings have challenged this concept. The Baylor group initially reported their observation in liver recipients with chronic rejection, who had circulating donor-specific HLA-antibody (DSA) more often than in patients with no rejection<sup>[39]</sup>. Subsequently, they found that multiple IgG subclasses were found in the sera of chronic rejection patients, and the IgG3 subclass was associated with increased risk of graft loss<sup>[40]</sup>. A definitive cause-and-effect relationship remains to be demonstrated however, as these studies used post-transplant DSA for analyses and did not include protocol biopsies. In our own observation at Mayo Clinic, we did not find any DSA-mediated graft injury in the first year after transplantation<sup>[41]</sup>, and over the long term, *de novo* DSA formation was preceded by liver allograft dysfunction (*e.g.*, recurrent HCV cirrhosis)<sup>[42]</sup>.

Based on these new observations, it appears that DSA may indeed cause chronic liver allograft injury, although less frequently than in kidney or heart transplantation. In order to better understand the impact of DSA on both early and late outcomes in liver transplantation, longitudinal prospective studies, similar to those done in kidney transplantation, correlating DSA (both pre- and posttransplant at routine intervals) with clinical outcomes and graft histology through protocol biopsies will need to be done. These studies will ideally be designed to analyze DSA in detail, target antigen expression in the allograft, and take into account immunosuppression and compliance issues in the recipients. In addition, histologic and genetic evidence of endothelial cell injury and microvascular inflammation (hallmark of DSA-mediated injury in kidney allografts) will need to be investigated in liver transplant recipients with circulating DSA (Table 2)<sup>[43-58]</sup>.

## **CONCLUSION**

Along with the advances made in liver transplantation over the past thirty years have come a new set of challenges. As the demand for liver transplantation continues to grow worldwide, more collaborative studies are needed to narrow the disparity between the number of available deceased donor liver allografts and wait-listed patients, and to improve the long-term

**Table 2** Current data for donor-specific HLA-antibody-associated injuries in kidney and liver transplantation

	Kidney transplantation	Liver transplantation
DSA specificity and levels	↑ risk hyperacute rejection <sup>[44]</sup> ; ↑ DSA in new onset late kidney allograft dysfunction <sup>[45]</sup> ; acute AMR is associated with high posttransplant DSA levels <sup>[45]</sup>	↑ DSA in recipients with CR, presence of IgG3 subclass associated with ↑ risk of graft loss <sup>[40]</sup>
C4d deposition in microvasculature	Graft failure significantly worse in the presence of C4d+ staining <sup>[44]</sup> ; C4d+ is a marker of antibody-mediated injury <sup>[44,46]</sup>	C4d+ staining nonspecific; In the presence of DSA, linear portal capillary and sinusoidal staining observed in ACR; DSA negative C4d+ staining found in biliary strictures and recurrent liver disease <sup>[47]</sup>
DSA subtypes, C1q binding	↓ graft survival and ↑ risk for AMR with C1q-binding DSA <sup>[48,49]</sup>	Limited data <sup>[50]</sup>
Microvascular inflammation	Peritubular capillaritis is a possible predictor of chronic AMR <sup>[51]</sup> ; subclinical AMR may contribute to development of CAN <sup>[52]</sup>	No current data
EC activation by light microscopy	EC and BM ultrastructural abnormalities in glomerular and peritubular capillaries are early markers of TXG <sup>[53]</sup>	No current data
Gene expression profile of chronic AMR	Defined genetic profile in AMR <sup>[54,55]</sup>	No current data
Therapeutic-trials to prevent DSA-associated injury	Bortezomib (plasma cell-targeted therapy) as a possible antihumoral therapy <sup>[56]</sup> ; plasma exchange for AMR <sup>[57,58]</sup>	No current data

Modified from Ref. 43. AMR: Antibody-mediated rejection; CAN: Chronic allograft nephropathy; EC: Endothelial cell; BM: Basement membrane; DSA: Donor-specific HLA-antibody; TXG: Transplant glomerulonephropathy.

outcomes of the liver recipients.

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