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Role of Liver Transplantation in Acute Liver Failure

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1. Introduction

Orthotopic liver transplantation (OLT) was initially developed in the 1960s as treatment for individuals dying of end-stage liver disease. It began to be utilized in the 1980s as salvage therapy in the setting of acute liver failure (ALF). Prior to the use of OLT, ALF mortality rates reached 80-85%, and the early post-transplant survival rates were much lower than those following transplantation for chronic liver diseases (Bernuau et al., 1986a). Over the past thirty years, however, with advances in critical care management and in the field of liver transplantation, 1-year survival rates following OLT for ALF have improved to 60-80% (Bismuth et al., 1995; DeVictor et al., 1992; Hoofnagle et al., 1995; W Lee, 2003; O'Grady et al., 1988). ALF is one of the few conditions for which a patient can be listed as a United Network for Organ Sharing (UNOS) status 1A (urgent) patient in the United States and "super urgent" in the United Kingdom. Although about half of ALF patients undergo OLT, ALF accounts for less than 10% of US transplants and approximately 11% in Europe (Freeman et al., 2008).

2. Prognosis and prognostic models

It is essential to quickly and accurately identify those patients most likely to benefit from emergent OLT. In the setting of organ shortage, it is also important to identify and even delist patients who are too ill to benefit from OLT. To minimize the risk of unnecessarily committing individuals to lifelong immunosuppression, one must balance the desire to delay transplantation to allow for the potential of spontaneous recovery against the risk of death with that delay and the risk of the surgery itself. Many ALF patients who have been listed for OLT will recover spontaneously without transplantation and it is estimated that as many as 20% of patients may be transplanted needlessly. In addition, a significant number of ALF patients listed for OLT will die awaiting a donor organ. In the United Kingdom, about 30% of patients initially considered for OLT ultimately become untransplantable following the development of complications (i.e., cerebral edema, sepsis, hemodynamic abnormalities, multiorgan system failure) (Bernal et al., 1998). Additionally, many patients have medical or psychosocial contraindications to transplantation, including irreversible brain injury, underlying cardiovascular disease, infection/sepsis, alcohol or drug abuse, poorly controlled psychiatric disease, or inadequate family support (Simpson

et al., 2009). Thus, it is important to identify and delist patients who are too ill to benefit from OLT.

It is crucial that reliable predictive models of survival and the need for OLT be developed. Successfully predicting outcome would allow more judicious use of scarce organs and spare those who will ultimately recover the need for lifelong immunosuppression. There are at present no standardized criteria to predict who should be listed for OLT. Several prognostic models have been developed to help identify appropriate patients for transplantation. Unfortunately, these prognostic models have limitations, and their predictive accuracy varies (Blei, 2005; Anand et al., 1997).

2.1 Predictors of prognosis

Many factors may help determine which ALF patients are more likely to die; however, they are generally unreliable in predicting who will ultimately survive or require transplantation.

2.1.1 Etiology

The etiology of ALF is one of the most important predictors of spontaneous outcome (Ostapowicz et al., 2002). The lowest mortality is seen with ALF secondary to acetaminophen (N-acetyl-p-aminophenol; APAP) toxicity (~30%), hepatitis A virus infection (~50%), shock liver, and pregnancy-related ALF (Larson et al., 2005; Ostapowicz et al., 2002; Schiodt et al., 2003). In contrast, the non-transplant mortality for the remainder of causes, including ALF secondary to drug-induced liver injury, remains abysmal (80% to 100%) (O'Grady et al., 1988; Ostapowicz et al., 2002). Therefore, understanding which causes of ALF predominate in a particular region can help lead to the early evaluation and listing of these latter cases for OLT.

ALF secondary to drug-induced liver injury (DILI) predominates in Europe and North America, with a high prevalence of APAP-induced ALF in the US and United Kingdom (Hoofnagle et al., 1995; Larson et al., 2005; Ostapowicz et al., 2002; Schiodt et al., 1999; Williams, 1996). Viral hepatitis predominates in developing countries. The US ALF study group looked at 1198 patients with ALF over an 11 year period and a total of 133 (11.1%) subjects were deemed by expert opinion to have DILI ALF. Transplant-free (3-week) survival was poor (27.1%), but with successful transplantation in 42.1%, overall survival was 66.2%. Transplant-free survival in DILI ALF is determined by the degree of liver dysfunction, specifically baseline levels of bilirubin, prothrombin time/international normalized ratio (PT/INR), and Model for End-Stage Liver Disease (MELD) scores (Reuben et al., 2010).

In the United Kingdom, the number of patients with APAP ALF has declined due to legislative changes in drug packaging, leading to an increase in the relative number of cryptogenic or seronegative cases (16% of all ALF). The majority (88%) of these latter ALF patients met King's College transplant criteria (see below), reflecting the low likelihood of spontaneous recovery (Wigg et al., 2005). A recent study from the UK suggested that OLT is a more favorable approach to managing patients with non-APAP induced ALF compared to patients with APAP induced ALF. This was predominantly due to the frequent psychosocial contraindications in patients with APAP induced ALF (Simpson et al., 2009).

2.1.2 Clinical and laboratory criteria

The clinical criteria most commonly used to exclude a patient from OLT vary by transplant center but may include age older than 70 years, the presence of certain malignancies outside of the liver, severe cardiac, lung, or multiple organ failure, severe infection, uncontrolled septic shock and brain death (Table 1) (Samuel & Bismuth, 2001). Patients with grade 3-4 encephalopathy and fixed pupils, cerebral perfusion pressure <40 mmHg, sustained elevation in intracranial pressure >50 mmHg, or seizures are at high risk for postoperative neurologic complications or brain death. They are usually not deemed candidates for OLT (Bismuth et al., 1995). As long as the pupils remain active and the patient does not have posturing movements, liver transplantation can still be considered (Daas et al., 1995). The degree of serum aminotransferase elevation and the rate of its recovery do not predict prognosis. In fact, improvement of aminotransferase levels in conjunction with worsening bilirubin, hepatic encephalopathy, and coagulopathy (INR) signals complete liver failure and is a particularly ominous sign.

Common Exclusion Criteria
Age >70 years old (relative)
Certain malignancies outside of the liver
Severe cardiac, lung, or multiple organ failure
Severe infection
Uncontrolled septic shock
Brain death
UNOS Status 1a Listing Criteria for ALF
Age ≥ 18 years
Life expectancy without a liver transplant of <7 days
Onset of encephalopathy within 8 weeks of the first symptoms of liver disease
Absence of pre-existing liver disease (except for the diagnosis of fulminant Wilson's disease)
Residence in the intensive care unit
At least one of the following: ventilator dependence, renal replacement therapy, or INR >2.0

Table 1. Exclusion and Listing Criteria for Transplantation for Acute Liver Failure. INR-international normalized ratio

2.1.3 Multiorgan failure

The severity of multiorgan failure at the time of OLT is also a predictor of post-transplant survival. Decreased renal function is associated with worse spontaneous survival in non-APAP-induced liver injury. In a multivariate analysis of UNOS data (1988–2003), four risk factors predicting post-transplant survival were identified: pretransplant use of life support, recipient age >50 years, recipient body mass index ≥30 kg/m2, and serum creatinine >2 mg/dL. If an individual had all of these risk factors, the 5-year post-transplant survival was only 44–47%. Whereas, if none of these features were present, the 5-year post-transplant survival was 82–83% (Barshes et al., 2006).

2.1.4 Hepatic encephalopathy

Mortality rates correlate with the severity of hepatic encephalopathy (HE), reported at 30% for grade 2, 45-50% for grade 3 and 80-90% for grade 4 HE (Daas et al., 1995; Hoofnagle et al., 1995). A multicenter US series, in which 39% participants had APAP hepatotoxicity, showed a 52% 3-week transplant-free survival in patients with grade 1-2 encephalopathy, but only 33% with grade 3-4 HE survived without transplant (Ostopowicz et al., 2002). Conversely, 85% of patients with non-APAP ALF without HE experienced spontaneous recovery (Elinav et al., 2005). Paradoxically, those with more rapid development of HE (i.e., APAP-induced) appear to have a better outcome than those with a longer interval between the development of symptoms and HE (i.e., DILI) (Bernuau et al., 1986a; O'Grady et al., 1989; O'Grady et al., 1993). A distinctive feature ALF-induced HE is the development of cerebral edema, the complete pathophysiology of which remains poorly understood. Cerebral edema develops in nearly 80% of patients who progress to grade 4 HE, leading to intracranial hypertension with subsequent ischemic brain damage or brainstem herniation, accounting for up to 50% of ALF mortality (Clemmensen et al., 1999; Jalan et al., 2003). Intracranial pressure (ICP) monitoring is more often utilized in patients who are deemed candidates for OLT, and ICP may be more aggressively managed in these cases. ICP monitors may also be of significant value during the transplant operation, when fluctuations in ICP are common (Philips et al., 1998). ICP monitoring is associated with up to a 10% risk of intracranial hemorrhage, and it has not been shown to change 30 day post-OLT survival (Gasco et al., 2010). Thus, the indication and timing of use of ICP monitoring devices remain controversial (Vaquero et al., 2005). Intracranial hypertension may persist during the first 10-12 hours following liver transplantation, thus ICP monitoring, if utilized, should continue during and after surgery (Bismuth et al., 1995; Jalan et al., 2003).

2.1.5 Infection

ALF-induced hemodynamic changes can be difficult to distinguish from infection and sepsis and are complicated by the fact that ALF patients may not develop leukocytosis or fever. Bacterial infection is the cause of death in up to 37%, with the most common sites of infection being pulmonary (47%), blood (26%), and urine (23%) (Bernal et al., 2003). Fungal infections, especially Candida sp., are seen in up to 32%, occur later in the course of disease, particularly after use of antibiotics or in the setting of renal dysfunction, and are often associated with bacterial infection (Rolando et al., 1991; Vaquero et al., 2003). Active infection is a contraindication to OLT. The empiric use of antibiotics is controversial. Prophylactic antibiotics decrease the number of infections, but do not change overall outcome (Rolando et al., 1990; Rolando et al., 1996; Stravitz et al., 2007). Some centers administer anti-infectives (antibacterial and antifungal) to patients who have significant isolates on surveillance cultures, have progression to Stage 3-4 HE, have refractory hypotension, or have clinical evidence of systemic inflammatory response syndrome (Stravitz et al., 2007). Periodic surveillance cultures and frequent chest radiographs can help detect bacterial and fungal infections early.

2.1.6 Psychosocial predictors

The burden of medical follow-up after OLT can be substantial, and quality of life can be significantly affected. Therefore, the decision to offer OLT to an individual patient also

needs to consider more controversial issues such as psychosocial factors (i.e., adequacy of social support and substance and/or alcohol abuse), and adequacy of medical insurance coverage. For example, in one study, four patients (12%) died in the post-transplant follow-up period from deliberate self-harm (Bernal et al., 1998).

2.2 Prognostic models

Multiple prognostic models have been proposed to help determine the likelihood of spontaneous survival (Table 2) (Antoniades et al., 2007; Bailey et al., 2003; Bernuau et al., 1986b; Bernuau, 1993; Craig et al., 2010; Harrison et al., 1990; Itai et al., 1997; O'Grady et al., 1989; Pereira et al., 1992; Rolando et al., 2000; Schiodt et al., 2005; Van Thiel, 1993). However, many of these models are methodologically flawed and subject to bias. In addition, many equate OLT with death, which falsely elevates the positive predictive value of these prognostic systems (Craig et al., 2010).

Variable	**Clichy**	**King's Criteria APAP**	**King's Criteria non-APAP**	**APACHE II**	**MELD**
Factor V Level	X				
Age	X		X	X	
Hepatic Encephalopathy	X	X		X	
Arterial pH		X		X	
INR		X	X		X
Serum Creatinine		X		X	X
Etiology			X		
Serum Bilirubin			X		X
Duration of Jaundice			X		
Vital Signs (T, BP, HR, RR)				X	
Oxygenation				X	
Serum Na & K				X	
WBC				X	
Hematocrit				X	

Table 2. Comparison Between the Various Prognostic Scoring Systems for Acute Liver Failure APAP-acetaminophen; MELD-model for end-stage liver disease; INR-international normalized ratio; T-temperature; BP-blood pressure; HR-heart rate; RR-respiratory rate; Na-sodium, K-potassium; WBC-white blood cell count. Clichy (Bernuau et al, 1986); King's Criteria (Bernal et al., 2002; O'Grady et al., 1989), Apache II (Mitchell et al., 1998); MELD (Schmidt & Larsen, 2007; Villamil et al., 2007; Wiesner, 2004; Yantorno et al., 2004; Zaman et al., 2006)

2.2.1 King's college hospital criteria

The most widely applied prognostic system are the King's College Hospital criteria (King's criteria) developed from a retrospective cohort of nearly 600 patients (Bernal et al., 2002;

O'Grady et al., 1989). The Kings criteria incorporate both the etiology of ALF (APAP- versus non-APAP induced ALF) and clinical parameters of disease (O'Grady et al., 1989). In a meta-analysis of studies using the Kings criteria, the pooled sensitivity and specificity was 69% and 92%, respectively (Bailey et al., 2003). The Kings criteria appear to have high positive predictive values (80% in APAP induced ALF and 70-90% in non-APAP induced ALF) but poorer negative predictive values (70-90% and 25-50%, respectively). A recent meta-analysis found that the Kings criteria for non-APAP induced ALF have good specificity, especially for patients with high grade encephalopathy (McPhail et al., 2005). The Kings criteria are helpful in identifying those who may need OLT, but up to 20% of those meeting criteria potentially could have survived without OLT, and those not meeting criteria may still require transplantation. The addition of arterial blood lactate levels to the model has improved its sensitivity (Bernal et al., 2002; MacQuillan et al. 2005).

2.2.2 Other models and predictors

Other Models and Predictors. The Clichy criteria were developed in a cohort of French patients with acute hepatitis B virus infection (Bernuau et al., 1986b). These criteria suggest that a serum factor V level of <20% in patients younger than 30 years or <30% in any patient with grade 3-4 HE has validity as a marker of mortality. The criteria predicted a poor outcome with a sensitivity and specificity of 86% and 76%, respectively. Factor V level measurements are less readily available to the clinician than are the measures in the Kings criteria, therefore, this prognostic model is not commonly utilized (Izumi et al., 1996; Pauwels et al., 1993). In addition, this model has not been validated in the non-HBV population. A factor V <10% has been shown to predict a poor outcome with a sensitivity of 91% and a specificity of 100%; while a factor VIII : V ratio of >30 similarly predicts outcome (91% sensitivity, 91% specificity) (Pereira et al., 1992). The admission Acute Physiology and Chronic Health Evaluation (APACHE) II is ineffective in predicting who will survive without transplantation, since many patients who do not meet the severity criteria will ultimately die of subsequent complications (Mitchell et al., 1998).

Elevated arterial ammonia levels increase the risk of developing intracranial hypertension. A level of >150 μmol/L predicts development of intracranial hypertension with a sensitivity of 60% and a specificity of 84% (Kitzberger et al., 2009). Concentrations of more than 100-150 μmol/L have been positively correlated with cerebral herniation (Bernal et al., 2007; Bhatia et al., 2006; Clemmensen et al., 1999; Toftent et al., 2006).

Serum alpha-fetoprotein (AFP) is generally considered a marker of hepatocellular regeneration. There has been no consistent correlation seen between the absolute AFP level and outcome in ALF (Tofteng et al., 2006). However, an increasing AFP level has been strongly associated with a more favorable outcome (Schiodt et al., 2006; Yang et al., 2002). A threshold AFP of ≤3.9 μg/L at 24 hours following the peak ALT identified nonsurvivors with a sensitivity and specificity of 100% and 74%, respectively, and a negative predictive value of 100% (Schmidt et al., 2005). In addition, it has been shown that a rising AFP level between day 1 and day 3 from presentation predicted survival without transplantation, whereas a decreasing level was seen in 80% of those who died (Schiodt et al., 2006).

Persistently elevated phosphate levels may be associated with a poorer prognosis in the setting of acetaminophen-induced ALF. A serum phosphate level >1.2 mmol/L on day 2 or

3 following APAP overdose carries a sensitivity of 89% and a specificity of 100% for predicting poor outcome (Baquerizo et al., 2003; Chung et al., 2003; Schmidt et al., 2003). The level of Gc-globulin, a protein which is markedly reduced in the setting of tissue injury, has not been shown to reliably predict survival in those with APAP-induced ALF. In non-APAP ALF; however, using a cutoff value of ≤80 mg/L, the Gc-globulin level carries a positive predictive value of 74% and a negative predictive value of 81% (Schiodt et al., 2005; Schiodt et al., 2007)). An elevated arterial blood lactate level following volume resuscitation predicts worse survival in APAP-induced ALF (Bernal et al., 2002; Cholongitas et al., 2008; MacQuillan et al. 2005).

The model for end-stage liver disease (MELD) scoring system, is an excellent prognostic model for chronic liver disease (Schmidt & Larsen, 2007; Villamil et al., 2007; Wiesner, 2004; Yantorno et al., 2004; Zaman et al., 2006). However, it has been limited as a prognostic model in ALF, because it does not account for most of the extremely important outcome predictors in ALF, including age, etiology of ALF and duration of jaundice. The MELD score has a sensitivity and specificity of <75% for predicting outcome in all forms of ALF (Bernal et al., 2007; Dhiman et al., 2007; Riorden & Williams, 2003). Whether modification of the MELD with these important factors would improve the MELD as standard scoring system in prognosis of ALF remains to be seen. Dhiman and colleagues compared clinical predictors of MELD and Kings criteria in patients with ALF. Clinical predictors were superior to both MELD and Kings criteria in predicting prognosis of ALF. Significant factors included age >50 years, jaundice to encephalopathy time greater than 7 days, grade 3-4 encephalopathy, cerebral edema, prothrombin time ≥35 seconds, and serum creatinine ≥1.5mg/dL) are associated with a poor prognosis. The presence of 3 or more of these factors is associated with a poorer prognosis (Dhiman et al., 2007; O'Grady et al., 2007). Molecular markers of cell apoptosis have also been found to be helpful prognostic factors. Bechmann looked at replacing the bilirubin value in the MELD score with the ratio of CK18/M65, a marker of cell death. This model was found to be associated with higher sensitivity and specificity. Although this study was limited by a small number of patients, the idea of using molecular markers of cell death in predicting prognosis of ALF is promising and needs to be studied in larger cohorts (Bechmann et al., 2010). Cytokeratin 18-based modification of the MELD score improves prediction of spontaneous survival after acute liver injury.

In effort to develop a functional scoring model for non-APAP induced ALF, Miyaki and colleagues looked at 4 prognostic factors – etiology of ALF, hepatic coma grade (III or IV), systemic inflammatory response syndrome, and ratio of total to direct bilirubin (>2.0). The authors found these factors to be predictors of 2-week outcome with high positive and negative predictive values, 93.3%, and 81.8%, respectively (Miyake et al., 2005). This prognostic model would help the clinician predict prognosis and consideration for liver transplantation for patients with non-APAP ALF, however it requires validation before it can be widely clinically applied.

A liver volume of <1000 mL on computed tomography (CT) imaging is also associated with a high mortality rate, a finding which has been validated (Shakil et al., 2000; Yamagishi et al., 2009). Based upon these findings, a prognostic formula has been proposed, but is not widely utilized. Liver biopsy may also be helpful in determining the cause of the ALF and, theoretically, the severity and extent of liver damage. Hepatic necrosis of more than 70% was associated with a transplant free survival of <10% in one analysis (Scotto et al., 1973).

However, there is a great degree of sampling error, and more recently, a multivariate analysis of 97 consecutive patients found that the amount of necrosis was not predictive of mortality (Miraglia et al., 2006; Voigt et al., 2007).

Based upon the available data, the current prognostic scoring systems have not consistently demonstrated reliable accuracy in predicting outcome from ALF and the subsequent need for OLT. Therefore, the American Association for the Study of Liver Diseases (AASLD) does not recommend reliance on any one of these systems (W Lee & Larson, 2005).

3. Liver transplantation

As previously noted, advances in critical care management of ALF patients has improved the spontaneous survival from 10-20% to about 40% without transplantation (Ostapowicz et al., 2002). For those who will not spontaneously recover; however, OLT remains the only treatment modality that improves survival. With the advent of use of OLT in this setting, overall survival rates have further improved to about 60%.

3.1 Transplant listing criteria

Candidacy for liver transplantation must be determined quickly in the setting of ALF, given the rapid progression of the syndrome. In the US, ALF is one of the few conditions for which a patient can be listed as a United Network for Organ Sharing (UNOS) status 1A (urgent) patient (available at http://www.unos.org) (Table 1). ALF patients may be listed in the "super urgent" category in the United Kingdom. Approximately half of ALF patients undergo liver transplantation; however, ALF accounts for less than 10% of US transplant and 11% in Europe (Freeman et al., 2008; Organ Procurement & Transplantation Network [OPTN], 2009).

3.2 Types of liver transplantation

In addition to whole-organ deceased donor liver transplantation (DDLT), which is preferred, various types of liver transplantation may be considered depending on the situation: living donor liver transplants, ABO-compatible transplants, ABO-incompatible transplants and auxiliary liver transplants. In the setting of organ shortage, the risk of mortality awaiting an organ should be weighed against the risk of complications or failure using an alternative graft (Table 3).

	OLT	**LDLT**	**ABO-compatible**	**ABO-incompatible**	**Heterotopic auxiliary LT**	**Auxiliary partial LT**
Graft	75	56-90	49-54	39-52		
Patient	82	59-90		30	33	71

Table 3. One-Year Post-Transplant Sruvival Rates for Acute Liver Failure (percent). OLT-orthotopic liver transplantation; LDLT-living donor liver transplantation, LT-liver transplantation. OLT (O'Mahony et al., 2007); LDLT (Ichida et al., 2000; S Lee et al., 2007; Miwa et al., 1999; Uemoto et al., 2000); ABO-Compatible (Bismuth et al., 1996b); ABO-incompatible (Bismuth et al., 1996b; Farges et al., 1995); Heterotopic (Van Hoek et al., 1999); Auxillary Partial (Van Hoek et al., 1999)

3.2.1 Living donor liver transplantation (LDLT)

The use of LDLT in this setting remains controversial (Campsen et al., 2008; Liu et al., 2002; Nishizaki et al., 2002; Uemoto et al., 2000). It is imperative to consider the need for an adequately sized graft for the recipient with the requirement of a sufficient residual liver mass for the donor. Grafts over 40% of the standard liver volume are necessary in the setting of ALF, and outcomes are better with a graft-to-recipient weight ratio greater than 0.8, with 1.0 being ideal (Kawasaki et al., 1998Kiuchi et al., 1999). A graft of <40% of standard liver weight is at risk for the development of small-for-size syndrome – portal hypertension following reperfusion leading to sinusoidal damage and graft injury (Man et al., 2003). In the absence of small-for-size syndrome following OLT, the graft and donor livers regenerate to full size in a matter of 4 weeks (Marcos et al., 2000). Despite these risks, right lobe LDLT improves survival in patients with ALF, with overall 1-year survival rates of between 60-90%, averaging about 75% (Campsen et al., 2008; Ichida et al., 2000; S Lee et al., 2007; Miwa et al., 1999; Uemoto et al., 2000). For children undergoing LDLT, the 1-year survival was 67-89% and death on the waiting list was decreased to 9% (Casas et al., 1999; Emre et al., 1999). In the SPLIT experience of pediatric transplantation, 57% of the recipients with ALF received partial grafts, without a difference in outcome compared to recipients of whole grafts (Baliga et al., 2004).

Unique ethical issues exist in the setting of LDLT. Given the urgent need for an organ in this setting, the donor evaluation must be expedited. The time required for thorough donor medical and psychosocial evaluation may be truncated in the setting of rapid clinical deterioration of the intended recipient (Abouna, 2001). This carries the risk of an incomplete evaluation and the possibility of donor coercion. The 1997 Council of European Recommendations argued against the use of LDLT for ALF due to the theoretical risk of coercion, with the assumption that patients were undergoing transplantation without significant waiting times (Committee of Ministers, 1997). In regions where cadaveric organs are not as readily available, the risk of the recipient's death while waiting for a cadaveric organ must be weighed against the risk to the living donor, including a 0.2% mortality (Ghobrial et al., 2008; Yasutomi et al., 2000). Protocols will likely need to be established to address these concerns (Carlisle et al., 2011; Reding, 2005).

It has been suggested that instead of comparing the donor risks to the recipient benefits, one should compare the donor risks to the donor benefits. Some individuals may feel rewarded by being a donor (such as parent to child donation) (Spital, 2005). Mathematical modeling suggests the sickest patients or those with highest risk of death while on the waiting list would receive more benefit from living donation than those who are less sick (Durand et al., 2006). Donors surveyed in the year following donation (two thirds responded), appeared to be doing well from a psychosocial perspective, but their well-being was linked to recipient outcomes (Kim-Schluger et al., 2002). A prospective German study evaluated the psychological impact on potential donors during evaluation for urgent indications for LDLT. They found that there was more mental stress compared to the general population, explained by the recipient's severity of illness. Donors had more postoperative pain, particularly somatoform pain, and decreased vitality. Three months after LDLT, donor mental quality of life, depression, and anxiety scores were again normal, although they were somewhat linked to recipient outcomes (Erim et al., 2007). The US Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) group reported that 4.1% of all donors

(392) had experienced one or more psychiatric complication. Three had severe psychiatric complications, including suicide, accidental drug overdose, and suicide attempt, despite the well-being of the recipients. Although there was no clear explanation why these donors, despite detailed screening, would be at increased risk for psychiatric problems, they suggested that donors need careful preoperative assessments and perhaps prolonged post-operative monitoring (Trotter et al., 2007).

3.2.2 ABO-incompatible grafts

Although ABO-identical grafts are preferred, ABO-compatible grafts (e.g., O graft; A recipient) have comparable 1-year patient survival following OLT and 49-54% 1-year graft survival (Bismuth et al., 1996a). However, ABO-incompatible grafts (e.g., A graft, B recipient) have less favorable outcomes and experience diminished 1-year graft survival rates of about 30% (Bismuth et al., 1996a). Patient survival was not affected by ABO compatibility for patients who had ALF, but the grafts suffered a greater incidence of hyperacute rejection (20%), vascular thrombosis, and/or biliary injury (56%). A Canadian group reported overall 5-year graft survival rates of 54–60% and 5-year patient survival rates of 61–77%, although the number of study subjects was small (Toso et al., 2007). The Birmingham group published their experience in liver transplantation for 29 children of < 5 kg weight, five of whom underwent for ABO-incompatible grafts. They found no difference in transplant outcome or survival between ABO- incompatible vs. ABO-compatible graft (Gelas et al., 2011). A recent meta-analysis found that ABO-incompatible grafts have excellent outcome in children but not in adult liver transplantation (Wu et al., 2011). At present, up to 60% survival of the graft is generally seen in ABO-incompatible transplants, likely related to intensive management (use of quadruple immunosuppression, postoperative plasmapheresis, splenectomy, methylprednisolone, or prostaglandin E1) (Egawa et al., 2004; Farges et al., 1995; Hanto et al., 2003; Sugawara & Makuuchi, 2006). Overall, controversy remains as to whether ABO-compatible and ABO-identical OLT leads to equivalent post-transplant outcomes. Some studies have reported no statistical difference in graft survival, while others have demonstrated that patient survival is less in ABO-compatible recipients compared to ABO-identical recipients. ABO-identical OLT is still preferred (Aladag et al., 2006; Bjoro et al., 2003; Koukoutsis et al., 2007); Smith et al., 2000).

3.2.3 Auxiliary transplantation

Auxiliary transplantation leaves the recipient's liver in place and utilizes a partial left or right lobe from the donor which acts as temporary support for the recipient's injured liver. Ideally, once the native liver recovers, immunosuppression may be withdrawn and the graft is either surgically removed or is allowed to atrophy naturally (Bismuth et al., 1996b; Chenard-Neu et al., 1995; Chenard-Neu et al., 1996). The partial graft is placed below the native liver (heterotopic auxiliary transplantation) or replaces a resected right or left native lobe (auxiliary partial liver transplantation.) While easier to perform, implantation of the heterotopic graft onto the infrahepatic vena cava may induce venous outflow obstruction, resulting in slower hepatocyte regeneration, presumably due to cytokine release from residual necrotic liver tissue. There is also an increased incidence of primary graft non-function and portal vein thrombosis with heterotopic auxiliary transplantation compared to auxiliary partial or whole graft OLT (Van Hoek et al., 1999). Despite a similar patient

survival rate compared to conventional OLT, unique postoperative complications may develop following auxiliary transplantation, including biliary and neurologic problems (Azoulay et al., 2001). Portal blood flow is partially diverted from the native liver to the auxiliary graft, therefore, regeneration of the native liver and graft function may be impaired. Moreover, due to the smaller mass of the transplanted liver, cerebral edema and neurologic dysfunction may continue to progress (Bismuth et al., 1996b). In addition, leaving the necrotic graft in situ following immunosuppression withdrawal may lead to the development of multi-system organ failure, or over time, cirrhosis may develop in the native liver (Chenard-Neu et al., 1996; Pereira et al., 1997).

The best outcomes with auxiliary transplantation are in young patients with hyperacute presentations due to a viral or autoimmune disorder, but this group also has the greatest chance of spontaneous recovery (Chenard-Neu et al., 1995; Chenard-Neu et al., 1996; Brandsaeter et al., 2002). Overall patient survival rate for auxiliary transplantation is reported to be between 60% and 65% and up to 85% of these survivors were able to discontinue immunosuppressive therapy by one year following transplantation (Bismuth et al., 1996b; Boudjema et al., 2002; Chenard-Neu et al., 1995; Van Hoek et al., 1999). However, those who had auxiliary partial transplantation have the greater 1-year survival rate, whereas those who underwent heterotopic transplantation had a diminished 1-year survival rate of only 33% (Van Hoek et al., 1999). Fifteen percent of the patients who underwent auxiliary transplantation had to undergo retransplantation for a variety of reasons. More recently, Faraj et al. looked at the long term outcome of 20 children who underwent auxiliary liver transplantation in the UK, the 1 and 10 year survival in this group of children was 85% (Faraj et al., 2010).

4. Transplant outcomes

Unfortunately, medical contraindications may develop quickly over the course of illness, thereby preventing OLT. This was demonstrated in patients with APAP-induced ALF who fulfilled KCH criteria. Thirty percent were not listed due to the rapid development of pre-operative contraindications to surgery and 35% of those who were listed were eventually delisted or not transplanted because of rapid clinical deterioration. The majority (90%) who met transplantation criteria but did not undergo OLT died (Bernal et al., 1998). In the largest US study, 29% of ALF patients underwent OLT but 25% of those listed (10% of the entire group) died prior to receiving an organ (Ostapowicz et al., 2002). In general, about 15-30% of patients die before OLT can be performed, usually due to brain death but other causes include sepsis, hemodynamic instability, multiple organ failure, and gastrointestinal bleeding (Bismuth et al., 1995; Castells et al., 1993).

4.1 Survival with transplantation

There are unique postoperative issues that afflict ALF patients. Despite OLT, elevated ICP and cerebral edema can persist for up to a day or more. In ALF patients who die post-OLT, as many as 13% succumbed to brain death (Barshes et al., 2006). Protective strategies, such as continued ICP monitoring, may be helpful through this period of risk. Although renal function often improves dramatically, patients may require renal replacement therapy for many weeks post-OLT, particularly in the setting of APAP-ALF. Immunosuppressive

strategies that attempt to minimize nephrotoxic agents, such as calcineurin inhibitors, in this critical recovery period may be necessary. Nearly one third of post-OLT deaths in this setting are from bacterial or fungal infections (Barshes et al., 2006). The majority of these deaths occur within the first 2–3 months following the transplantation, usually due to neurologic complications or sepsis (Bismuth et al., 1995; DeVictor et al., 1992; Hoofnagle et al., 1995; W Lee, 2003; O'Grady et al., 1988; Russo et al., 2004; Wigg et al., 2005). In the largest Canadian study (60 patients transplanted between 1994-2007); the wait-list mortality rate was 6% with mean waiting time of 2.7 days. The perioperative mortality rate was 15%, and complications included neurological problems (13%), biliary problems (10%), and hepatic artery thrombosis (5%) (Chan et al., 2009). The Canadian data suggested that cerebral edema and extended criteria donor graft are associated with worse outcome.

The severity of multi-organ failure at the time of OLT is a good predictor of post-transplant survival (Devlin et al., 1995). Decreased renal function is also associated with worse spontaneous survival in non-APAP induced liver injury (Moore et al., 1991). In a multivariate analysis of UNOS data (1988-2003), four risk factors predicting post transplant survival were identified: history of life support, recipient age >50 years, recipient body mass index ≥30 kg/m2, and serum creatinine >2 mg/dL. If an individual had all of these risk factors, the 5-year post transplant survival was only 44-47%. Whereas, if none of these features were present, the 5-year post transplant survival was 82-83% (Barshes et al., 2006). The quality of the graft also impacts post-transplant outcome (Bismuth et al., 1995). Graft steatosis, reduced graft size, and ABO-incompatible grafts have all been shown in multivariate analyses to lead to decreased patient and graft survival (Bernal et al., 1998; Bismuth et al., 1995). On multivariate analysis of data from the United Kingdom, the strongest predictor of early mortality in seronegative ALF was higher donor body mass index (BMI), which may be a marker for donor graft steatosis (Wigg et al., 2005). This group found an odds ratio (OR) of 1.2 for every unit increase in donor BMI relative to a normal donor (BMI 25 kg/m2). For example, the OR for early death following OLT with a liver from an obese donor (BMI 35 kg/m2) is 1.2 to the power of 10 or 1.2^{10} which is an OR of 6.2. The next most predictive variables were recipient age >50 years (OR 4.2) and non-Caucasian ethnicity (OR 4.9) Additional factors which have been reported to influence survival in ALF include recipient age >60 years, donor age >60 years, and mechanical ventilation at the time of transplant (O'Mahony et al., 2007; Mas et al., 2010). Unfortunately, graft quality needs to be weighed against the time factor, since patients may deteriorate while waiting for optimal grafts, sometimes to the point when they are no longer feasible candidates. Suboptimal grafts may fail; however, leading to the need for retransplantation.

Some advocate the use of venovenous bypass during the operation, but this is not uniformly practiced. Bypass is thought to minimize changes in cerebral perfusion pressure during the clamping of the inferior vena cava and portal vein as well as during reperfusion (Bismuth et al., 1996a; Jalan et al., 2003). Hepatectomy of the native liver with temporary portocaval anastamosis in certain patients may achieve temporary hemodynamic stabilization, with the expectation that a suitable graft will be available within the next 24-28 hours (Ejlersen et al., 1994; Ringe et al., 1993).

In infants with ALF transplanted between 1986 and 2000, only 24% had spontaneous recovery. Nearly half (47%) succumbed to sepsis or multiorgan failure, and 29% underwent

OLT, of which half were still alive at a mean follow-up of 5 years. The authors concluded that infants had worse prognosis with ALF, since the etiology was more commonly an inborn error of metabolism. Extrahepatic disease sometimes excluded OLT as a means of treatment (Durand et al., 2001). The Studies of Pediatric Liver Transplantation (SPLIT) Research Group found that 13% of all primary transplants performed between 1995 and 2002 in children were done for ALF and that the majority of these cases were from unknown (indeterminate) causes (89%). The 3-month spontaneous survival was markedly diminished for children with ALF compared to those without (59% vs. 96%) and 6-month post-transplant survival was lower (76% vs. 91%, respectively). The majority of children with ALF (80%) die from brainstem herniation. On multivariate evaluation, risk factors for post-transplant mortality included grade 4 HE, age less than 1 year, and use of pre-transplant dialysis (Baliga et al., 2004).

Over the past thirty years, however, with advances in the field of liver transplantation and critical care management, the US 1-year survival rates following OLT for ALF have improved to 60-80% and 1-year post-transplant graft survival rates have improved from 63% to 75% (Bismuth et al., 1995; DeVictor et al., 1992; Hoofnagle et al., 1995; W Lee, 2003; O'Grady et al., 1988; Wigg et al., 2005). In Spain, Portugal, Belgium, and Italy, where the majority of ALF cases are induced by hepatitis B infection or cryptogenic causes, 1-year post-transplant survival is 61-79% (Areia et al., 2007; Detry et al., 2007; Escorsell et al., 2007; Montalti et al., 2005). These 1-year survival rates are less than the 1-year survival seen in patients who have been transplanted for chronic liver failure (80–90%) (Farmer et al., 2003; Freeman et al., 2008). However, by 1–4 years following transplantation this trend has reversed, and ALF patients have a better survival than those transplanted for chronic liver disease. Chan et al. reported the Canadian experience with 5- and 10-year patient survival rates of 76% and 69%, respectively, and graft survival rates of 65% and 59% (Chan et al., 2009). Poorer outcomes are seen in centers performing less than 25 liver transplants per year and less than 20 split-liver grafts per year for those doing living donor liver transplantation (Adam et al., 2000).

4.2 Retransplantation

Retransplantation occurs more frequently following emergent OLT (13%) compared to elective OLT (7%). The cause of graft failure is usually secondary to acute cellular rejection, primary graft nonfunction, or intrahepatic biliary strictures, all of which may be related to the quality of graft used or the use of an ABO incompatible graft (Adam et al., 1991; Farges et al., 1995; Gugenheim et al., 1990).

5. Quality of life

Overall, the quality of life and long-term survival among ALF transplant survivors is good, but some differences have been identified. When ALF patients were compared to a matched control group who had undergone OLT for chronic liver disease, both groups complained of memory difficulties but more ALF patients complained of concentration difficulties and as a group scored lower on neuropsychological tests (Jackson et al., 2002). The King's College group initially sent out questionnaires to small sample of ALF and chronic liver disease OLT recipients about 2-3 years following surgery. The ALF patients tended to be younger (35 vs.

59 years), so age may have influenced results. More ALF patients were employed or were in full-time education (50 vs. 26.5%). The mental health scores were slightly lower for those who had ALF (68 vs. 79; p=0.022), which was attributed to the fact that the ALF recipients did not undergo typical preoperative education and psychological support prior to OLT. There was no significant difference in parasuicide quality of life scores between the two groups (Sargent et al., 2006).

ALF patients scored slightly lower in the physical function and role emotion areas compared to normal values, but the values were similar to those who were transplanted for chronic liver disease (Sargent et al., 2006). When more carefully interviewed, six ALF recipients described significant physical inactivity and fatigue for the first 3-6 months following OLT due to weight loss and loss of muscle tone. They also noted a health transition lasting between 3-6 months, during which time dependence on others was present. Pretransplant lifestyles were changed in order to regain independence. Support groups or role models were deemed extremely helpful in coping with the ordeal. The majority felt that they had been given a "second chance at life" and were willing to reciprocate support to other going through the same process (Sargent et al., 2007).

Following spontaneous recovery, ALF patients with psychiatric illness who had taken a deliberate APAP overdose are at risk of repeated overdoses. Risk of repeated overdose appears to be less common; however, if the patient was transplanted, perhaps due to the intensity of postoperative care. In two series from the United Kingdom, APAP-ALF patients who underwent OLT showed similar long-term survival (median 5 years and 9 years) compared with patients transplanted for chronic liver disease (Cooper et al., 2009; Karvellas et al., 2010). Less than 5% of those transplanted for APAP overdose reattempted overdose. There was worse 30-day mortality for the APAP-ALF patients, and a greater probability of post-OLT medical nonadherence and adverse events in those who had taken APAP for deliberate self-harm compared with both non-APAP-ALF patients and chronic liver disease patients (Cooper et al., 2009).

6. Future directions

Hepatocyte transplantation has been studied predominantly in patients with chronic metabolic disorders. There is evidence, however, that partial liver engraftment is possible and there may be improvement in neurological status, as noted in small groups of patients with ALF who have undergone hepatocyte transplantation (Bilir et al., 2000; Habibullah et al., 1994; Strom et al., 1997). Xenotransplantation is an intriguing concept and porcine livers have been used for ex vivo perfusion but in vivo use has not yet proven effective due to problems with transspecies rejection. Bioartificial livers and extracorporeal liver assist devices (ELAD) have been used to bridge patients to transplantation and have demonstrated improved neurologic outcomes. There are two cell-based devices. One uses porcine hepatocytes and did not show survival advantage in one large multicenter study and another uses hepatoblastoma cells which was noted to decrease severity of encephalopathy without change in survival in one study (Demetriou et al., 2004; Ellis et al., 1996). Non-biological systems also exist such as albumin dialysis (MARS) and plasmapheresis, and no survival advantage was found on meta-analysis (Khuroo et al., 2004).

7. Conclusion

Many advances have occurred that have significantly improved outcomes following transplantation for ALF. Prognostic models are helpful, but they are not entirely predictive of which individuals need OLT and which will survive without OLT. In the setting of organ shortage, alternatives to conventional OLT are being increasingly used, including living donor split grafts, ABO incompatible grafts, and auxiliary grafts, with variable outcomes. The risks and benefits to both the donor and the recipient must be considered. Long term outcomes and quality of life for both donors and recipients are good but prolonged monitoring may be helpful to identify those in distress. Newer technologies are being developed and enhanced to improve short term and long term survival after acute liver injury.

8. References

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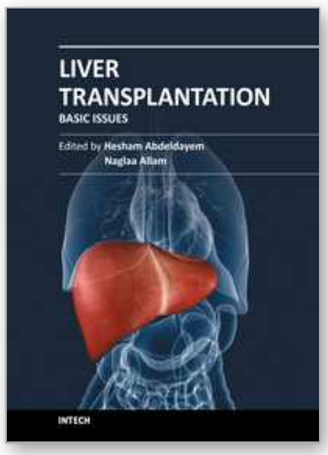

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This book covers a wide spectrum of topics including history of liver transplantation, ischemia-reperfusion injury, immunology of liver transplantation, viral hepatitis and liver transplantation, other indications for liver transplantation, prognostic factors and perioperative period. The authors of the chapters are experts in their respective fields. They are proponents covering different aspects of liver transplantation and come from many centers across the world. The interdisciplinary approach and the authority of the contributors resulted in a valuable reference to anyone interested in developing a global view in liver transplantation including medical students, residents, fellows, nurses, and practicing physicians and surgeons as well as researchers in the field of liver transplantation.

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