Chapter 2
Living Donors for Fulminant Hepatic Failure in Children

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Keywords Pediatric acute liver failure (PALF) · Living donors · Ethics · Liver transplantation

Abbreviations

ALF	Acute liver failure
DDLT	Deceased-donor liver transplant
HRQOL	Health-related quality of life
KCHC	Kings College Hospital Criteria
LDLT	Living donor liver transplant
LKD	Living kidney donors
NPV	Negative predictive value
NRD	Non-related donors
PALF	Pediatric acute liver failure
PELD	Pediatric end-stage liver disease score
PPV	Positive predictive value
PRISM	Pediatric risk score of mortality
SPLIT	Studies of pediatric liver transplant
UNOS	United network for organ sharing

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2.1 Introduction

This chapter reviews and addresses the ethical aspects of living donor liver transplantation (LDLT) for pediatric acute liver failure (PALF) patients. PALF is a rare, rapidly progressing and life-threatening diagnosis for which liver transplantation is often the only life-saving treatment. Once the diagnosis of PALF and its aetiology are established, there are very limited directed medical treatments available. Thus, the risk of rapid progression and poor natural history in PALF drives decision making about early liver transplantation. There is no guarantee that a deceased-donor liver transplant (DDLT) will become available in time, so LDLT is considered as an alternative when available. However, the use of LDLT requires careful consideration of the ethical issues. The probability of a good outcome with liver transplantation (LT) may not be high enough to justify the risks to the living donor—but who should make this judgement? Is it fair to ask potential donors to make such a big decision in a time-pressured situation? The high mortality from PALF can also exert internal and external pressure on the candidate donor leading to potentially coercive decisions. As will be discussed, these issues are best managed by a collaborative interdisciplinary team with extensive experience and success in LDLT.

This chapter will discuss the following issues:

1. Overview of prevalence and etiologies of PALF;
2. The role of transplantation and indications for transplantation in PALF;
3. Types of transplants used for treatment of PALF including deceased whole liver, deceased split liver, and living donor livers, and their relative advantages and disadvantages;
4. Discussion of wait list issues for children with PALF;
5. Explanation of the evaluation process for living donors for PALF patients;
6. Ethical arguments for and against LDLT in PALF.

2.2 Overview of Pediatric Acute Liver Failure (PALF)

PALF presents as a multisystem disorder with severe liver injury, with or without encephalopathy, and no previous history of liver disease. Without treatment, PALF often progresses to death from multisystem organ failure and/or cerebral anoxia. Supportive care includes the provision of intravenously administered vitamin K to correct abnormal INR, occasional and cautious administration of fresh frozen plasma, cryoprecipitate or platelet infusions to decrease risk of bleeding at time of interventional procedures, and treatment with prophylactic antibiotics to prevent sepsis [1]. It is vital to try to determine the cause of liver failure in order to provide

as early as possible the cause-directed treatments that are discussed below. Children with PALF should also be referred to an experienced pediatric liver transplant centre for coordinated evaluation and management can be conducted. Considering the above issues, the transplant team's role is to:

1. Expeditiously ensure a thorough work-up has been completed
2. Determine the cause of PALF
3. Ensure cause-directed medical therapy is provided whenever possible
4. Rule out PALF etiologies that have a poor outcome with LT
5. List for transplantation if this is deemed the best treatment option, and
6. Explore the option of live donation, when appropriate.

2.3 Role of Liver Transplantation in the Treatment of PALF

2.3.1 Decision to Transplant and Recipient Selection Criteria

The LT decision is complex and should proceed deliberately and thoughtfully despite the inherent uncertainties associated with the fact that PALF is a clinically diverse, multi-faceted and dynamic condition. Treatment generally supportive unless a specific diagnosis responsive to targeted therapy is identified. The dynamic nature of PALF challenges our ability to predict outcome. All scoring systems used to predict mortality in non-transplanted patients with acute liver failure, including the Kings College Hospital Criteria (KCHC), the Clichy score, Pediatric Risk Score of Mortality (PRISM), and Pediatric End-Stage Liver Disease (PELD) score have limitations. Thus, when applied to PALF transplant candidacy decisions, these measures provide helpful clinical guidance, but the final decision to offer transplantation requires experienced clinical judgment [2].

LT holds the greatest lifesaving potential, but it carries with it potential complications related to surgery and immunosuppression [3, 4]. Albeit rarely, some children listed for LT who would have received an organ had one become available, are removed from the list due to clinical improvement. It is difficult to predict which children may improve clinically, and thus need not be exposed to the risk of transplantation. Vigilance must be maintained to ensure that children requiring LT survive, and ongoing efforts to identify clinical models that reliably predict patient death and survival. The challenges of when to apply living donor liver transplantation in PALF are herein discussed [5–7].

2.3.2 *Organ Allocation and Different Surgical Options for Liver Transplantation*

Estimates of annual incidence rate of PALF in the United States are at 2800 cases per annum with an average mortality rate of up to 50 % [8, 9]. Outside of countries that solely use living donation for all transplantation, the main source of liver transplants are deceased-donor organs. Unfortunately, the deceased-donor pool is always insufficient to meet all demands and the lack of control over the timing of obtaining a good quality organ for a child with PALF can result in death while on the wait list.

Deceased donor liver allocation for children with PALF is evolving. In North America these decisions are based on a recipient disease severity score, or on PELD score for children with chronic liver disease. Children with acute liver failure are listed with Status 1A by United Network for Organ Sharing (UNOS). The criteria for 1A listing are as follows:

1. Onset of hepatic encephalopathy within eight weeks of the first symptoms of liver disease,
2. Absence of pre-existing liver disease,
3. AND one of:

   (a) Ventilator dependence
   (b) Need for dialysis, continuous venous hemofiltration, or continuous venovenous hemodialysis
   (c) INR > 2.0

Based on a weekly reassessment, the child can be either kept on the deceased-donor waiting list, removed from the list if he/she becomes too ill to undergo transplantation or improves, or can be demoted from Status 1A and listed according to the disease severity score.

Several different types of donor grafts can be used to transplant pediatric patients with ALF. Sized-matched pediatric grafts from deceased organs provide excellent outcomes. However, advancements in surgical techniques have also made it possible to transplant different parts of the liver from an adult. Options include segments 2 and 3—also known as the left lateral segment liver graft, the entire left lobe or the right lobe transplants. The use of these techniques increases graft availability for all recipients, thereby improving survival rates in PALF patients [10]. Following live donation, the donor's remaining liver regenerates to a near normal volume and the recipient liver also undergoes hyperplasia (growth) or apoptosis (shrinkage) in volume to match the recipient's size. Partial deceased-donor grafts and live donor grafts have higher or comparable patient survival rates to that of whole deceased-donor grafts [11].

2.3.3 *Shortage of Donors and Magnitude of Death on the Wait List*

The deceased-donor pool remains insufficient to meet all demands. The lack of control over the availability of a good quality organ for a child with PALF can result in death while on the wait list. This can be ameliorated by using living donor grafts. A large series of pediatric liver transplant cases in the United States revealed that of 442 pediatric transplants performed between 1993 and 2006, a total of 49 or 11 %, were from living donors [12].

More than 6000 liver transplants are performed annually in the United States. According to the 2012 US Organ Procurement and Transplantation Network report, each year over 600 children were listed for liver transplant, and on average 540 received a transplant. However, annually, more than 40 children die waiting for a donor liver and approximately 14 became too sick to transplant [13]. This resulted in pre-transplant mortality of 5.8 deaths per 100 wait-list years [13].

Patients with acute liver failure have the highest pre-transplant mortality rates of all patients with end stage liver disease [13]. Of 1621 pediatric patients listed for transplantation, 11.2 % (n = 182) had PALF and about 18 % of these children died waiting for a donor organ [13]. Despite these statistics, LDLT only account for a small proportion of all liver transplants performed [13]. Success rates, concerns, and barriers to LDLT are discussed below.

2.4 Overall Outcomes of Liver Transplantation in Children

Thomas Starzl performed the first liver transplant from a deceased-donor in 1963. Steady advances in surgical technique and improvements in outcomes ensued in the decades to follow. The first reduced-size deceased-donor liver graft was transplanted into a child patient in Belgium in the 1980s. The first pediatric living donor liver transplants were carried out in Brazil in 1989 [14], followed by transplants in the United States and Japan [15, 16].

During the 2000s, the PELD allocation system was introduced, along with increased regulation of living donor (LD) organ allocation, with specific United Network for Organ Sharing (UNOS—a private, non-profit organization that manages the US's organ transplant system under contract with the federal government) centre requirements for LDLT and government oversight of living donor transplantation [17].

Liver transplantation with a cadaveric whole and split or living donor organ is a highly successful treatment for PALF. Survival rates of children with PALF who do not undergo a transplant range from 10 to 30 %, whereas children with PALF who undergo a liver transplant have survival rates in excess of 80 % [18]. The outcomes of transplantation for PALF have been steadily improving. The Studies of Pediatric

Liver Transplant (SPLIT) consortium reported 4-year post-transplant patient survival rates of 69.4 % for children with PALF [18, 19]. In a 2010 report of 57 more recent transplants the survival rate exceeded 80 % at 10 years [5]. Several retrospective series have identified adverse factors that affect outcome of transplantation for PALF [3, 7, 20, 21]. These factors include, but are not limited to: age less than one year, need for pre-transplant dialysis, and idiopathic PALF etiology [7, 22]. Morbidity-related complications of pediatric liver transplantation include infection, hepatic arterial thrombosis, and biliary strictures.

Children with PALF who undergo a liver transplant have worse outcomes than those who are transplanted for chronic liver diseases. There are several reasons for this, including their poorer condition at the time of transplantation, and the fact that postoperative infections and the risk of aplastic anemia are more common than in other transplant recipients, perhaps as a result of intrinsic immune deficits [23, 24].

2.5 Outcomes of Living Donor Liver Transplantation

2.5.1 Recipient Outcomes

The principle advantage of live liver donation is the opportunity to avoid or minimize the risks of waiting for a deceased-donor organ [3]. Other advantages of LDLT for PALF include thorough donor screening leading to a high quality liver graft and brief preservation times [25–27].

LDLT provides excellent outcomes in children [7, 28, 29, 30]. Most of the surgical techniques for these procedures were developed and refined in Japan and Korea where deceased donation is uncommon or unavailable. A study by Baliga and the SPLIT group from centers in the US and Canada, suggests that LDLT accounts for about 14 % of all pediatric liver transplants in the United States and Canada [19]. Liu et al. in Hong Kong reported that right lobe LDLT offers superior survival rates to DDLT in adults [28, 29]. A study by Bourdeaux et al. [28] compared 1010 children who received LDLT to 135 children treated with a DDLT. Although only 16 of the patients were treated for PALF, this study showed a superior survival rate at 1 and 5 years of 94 and 92 % in LDLT group, versus 93 and 91 % after whole DDLT group, 83 and 79 % after reduced-size DDLT, and 90 and 83 % after split DDLT, respectively ($p = 0.169$) (see Fig. 2.1). The chance to obtain a high-quality graft with LDLT is counterbalanced by a slightly higher rate of vascular and biliary complications. Because of these offsetting benefits and risks, transplantation graft survival rates are similar for DDLT and LDLT after ten years [12].

A recent decision analysis compared the costs of DDLT and LDLT. The authors concluded that the addition of LDLT to a standard waiting list for DDLT prevents waiting list deaths and improves recipient survival and, but at greater cost [31]. The cost of being listed for DDLT only was quantified with an Incremental Cost-Effectiveness Ratio (ICER) of $35,000. In comparison, being listed for DDLT

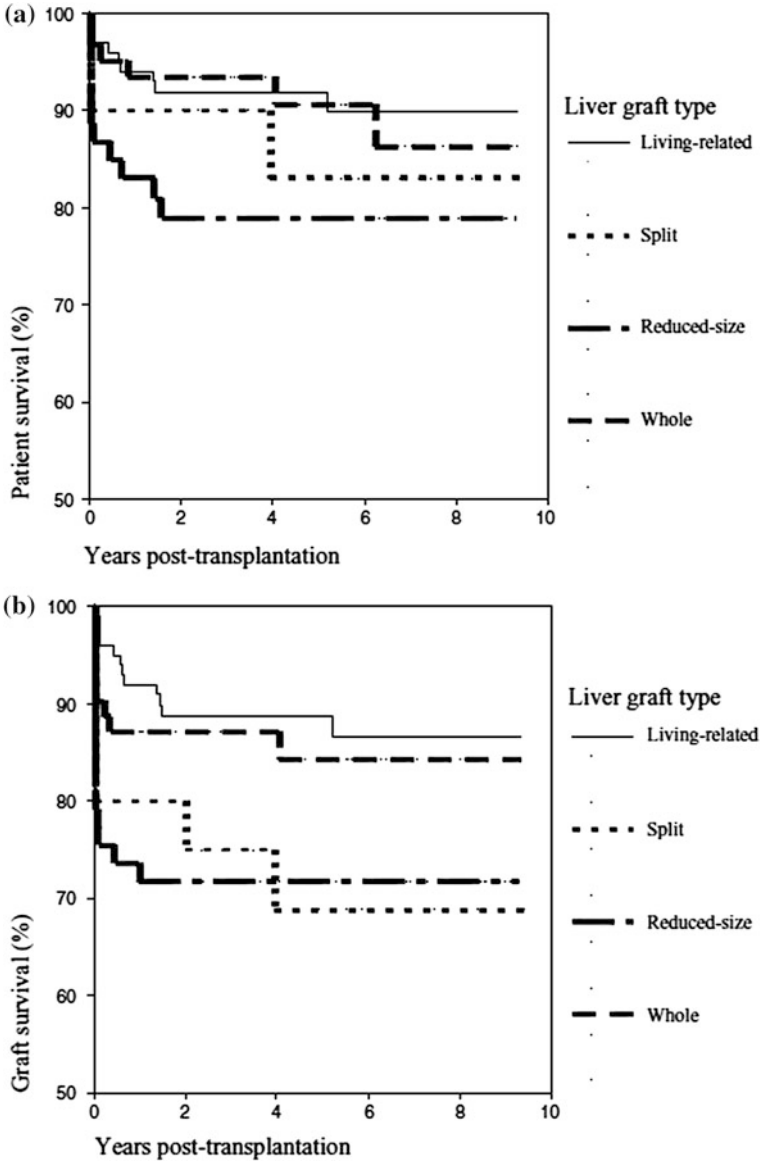

Fig. 2.1 Similar post transplant overall survival but superior graft survival from living donor liver transplantation in 235 children who received either living donor (n = 100) or deceased-donor (n = 135) liver transplant from 1993 to 2002 in a Single Centre. Adapted from Bourdeaux et al. [28]. *Note* Five-year patient survival rates were 92 and 85 % for groups LD and DD, respectively ($p = 0.181$), the corresponding graft survival rates being 89 and 77 % ($p = 0.033$)

with the LDLT option carried an ICER of $106,000, both measured over a 10-year time frame [31]. These costs examined in this study included costs to the donor, the recipient, the health care system, as well as the costs of complications and loss of life.

2.5.2 Donor Outcomes

Living donation (LD) is an imperfect solution to the problem of organ shortage, because of the risks for the donor. Even in the best of hands, this surgery is associated with a small but significant risk of permanent morbidity or mortality [32–36]. By offering "unnecessary" surgery to a healthy person, LD violates the classic Hippocratic oath of doctors to "abstain from doing harm" [37]. In the modern era, the focus of medical ethics is on the efforts to prevent or minimize harm while trying to help the patient. A key concept is the principle of non-maleficence, defined by Beauchamp and Childress, as not inflicting evil or harm [38]. With live donation, the risk of serious complications or death is directly proportional to the amount of liver that is removed. The estimated mortality risk for a donor of a left lateral liver segment (about 25 % of the liver volume) is about 0.15 %, whereas the estimated mortality risk for a donor of a right lobe liver donation (about 68 % of the liver volume) is 0.30 %. Thus, serious complications or death are rare after LD but when they do occur, the outcomes are devastating for the donor, recipient, the family and the clinicians involved.

The largest review of living donor hepatectomy outcomes examined a total of 214 studies on all adult and child LDLT performed up to year 2004 [36]. The authors estimated that approximately 6000 living donor liver transplantations had been performed worldwide, with a mortality rate of 12–13 in 6000, or 0.2 %. Of ten early donor deaths, 1 was in a donor of left lateral segment, 1 of left lobe, and 5 of right lobe donations. Specifically, donor mortality in adult to child LDLT ranged from 3 to 7 per 3500, or 0.09 to 0.2 % [36]. This study reported a median donor morbidity rate of 16.1 % (ranging from 0 to 100 %), with biliary complications and infections being the most common, at 6.2 % (range 0–38.6 %). Other complications included infections at a median rate of 5.8 %, and need for transfusion at a median rate of 1.9 %. The most common morbidities were biliary leaks and strictures (median 6 %; range 0–39 %) and infections (median 6 %; range 0–29 %). Other reported complications included incisional hernias, pleural effusion requiring intervention, and neuropraxia [39]. Nearly all donors had returned to normal function by three to six months.

A more recent large study examined late complications among 4111 LDs in the United States from 1994 to 2012 and compared their mortality rates to the participants in the National Health and Nutrition Examination Survey III (NHANES III). The risk of long-term mortality did not differ from that of healthy, matched individuals over a mean of 7.6 years [40].

A key ethical issue is whether the risks to the donor described above are outweighed by the benefits of helping a loved one and preventing death. We will analyze this ethical issue in more detail in the following sections.

2.5.3 *Urgent Live Donor Work-Ups for PALF Recipients: The Challenges*

LDLT for acute liver failure presents many serious ethical, medical, logistic, and economic issues. In cases where the recipient has subacute liver disease, a live donor work-up takes 4–6 weeks to complete. This provides the donor physicians with ample time to complete all of the required tests and provides the potential donor with a "cooling-off period" to decide if he/she truly wishes to proceed with this operation [41]. In contrast, the donor and recipient work-up for a LDLT for PALF must be completed within hours or a few days. The rapidity of this work-up makes it more difficult to obtain voluntary and fully informed consent [42]. Notwithstanding this concern, we believe that an ethical and timely work-up of a potential donor is possible if several considerations are met. The first step is to ensure the recipient is a good candidate for liver transplantation. The second step is to confirm that a transplant is the best treatment option. The third step is to undertake a well-defined protocol for the donor work-up that includes multiple safety checklists to ensure that nothing is overlooked or missed, including both clinical and ethical issues, including informed consent and prevention of coercion. Several such protocols have been developed and used worldwide and a sample protocol is shown in Fig. 2.2 [43–47]. Undertaking this work-up requires adequate hospital resources and personnel to complete a thorough medical and psychosocial evaluation; and to provide the potential donor with detailed information about all possible surgical complications including mortality, morbidity, and long-term quality-of-life impact, as well as the risk of recipient mortality despite LDLT. Because of the physician's *prima facie* duty to his or her patient—in this case a child with PALF, it is important that there are separate clinical teams working up to the donor and the recipient in order to avoid perceived or real conflicts of interest [48] (Table 2.1).

The assessment of a living donor for a PALF recipient requires confirmation of a compatible blood group, excellent general global health (physical, mental, and social well-being), the absence of any medical co-morbidities that might increase the risks of surgery, exclusion of transmissible malignancy or infections, and confirmation of suitable liver anatomy. Determining the psychosocial status of the donor and social support is a particularly important part of this process. The presence of inherited metabolic disease in the recipient child may not preclude parental donation when the donor is an asymptomatic heterozygote carrier. An estimation of steatosis ("fattiness") of the liver is essential in the selection process for donors with a higher than normal body mass index (BMI); with modern imaging and liver function tests a liver biopsy is only required when screening tests are abnormal.

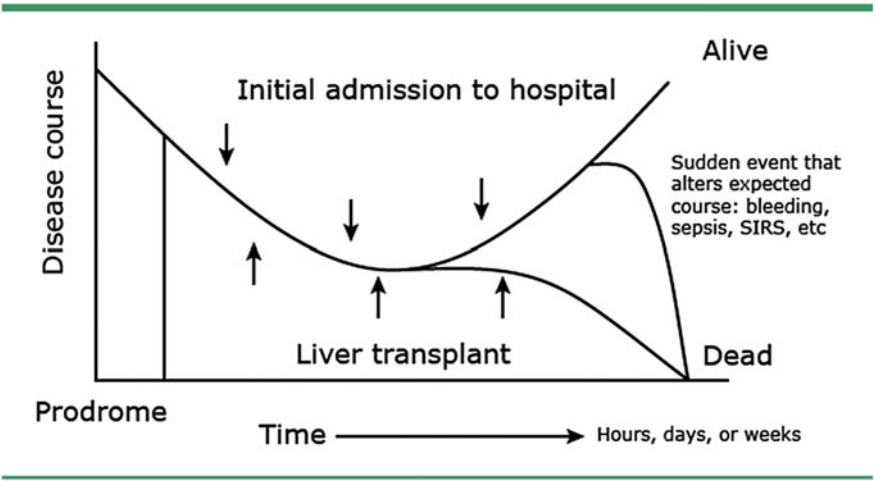

Fig. 2.2 Schematic model of the natural course and outcome of acute liver failure in children. *SIRS* Systemic inflammatory response syndrome. Reproduced from Squires and Alonso [49]. Copyright © 2012 Cambridge University Press

Table 2.1 Pros and cons of living donor liver donation to children with PALF

PRO	CON
Autonomy of the donors is supported by donation if they have strong emotional links to the sick child with PALF (i.e. are parents, adult siblings or other family members and care-givers)	Post-operative complications and potential mortality to donors
Quality of life of the child and the family is improved with LDLT if no deceased organ is available	Increased costs and difficulty coping with child's illness for parent donors who are also healing from donor surgery
Utilitarian argument—LDLT decreases wait time in a rapidly deteriorating child with PALF and wait times of other children on the deceased organ wait list are not affected	Additional costs and affects to other family members in the home, such as siblings, if parents are unable to care for them
Not donating might impart long-term negative effects on the parents and family members if the child with PALF was a transplant candidate but did not receive an organ and had serious sequellae including mortality	The challenge of accurate and objective quantification of risk-benefit ratio for the donor, including their psychosocial and physical postoperative risks, the effects that not donating might impart long term, and the effects that postoperative complications of the recipient child can have

When considering a donor for a child with PALF, the goal is to complete the donor work-up within 24–48 h [47]. A suggested evaluation protocol for a potential living donor for a child with PALF is shown in Table 2.2. During this process, the

physician responsible for the donor work-up must be readily available to provide education and psychological support, and to ensure that the assessment process is free of pressure or coercion to donate. The donor assessment team is completely independent from the recipient assessment team. Challenges in communication between donor and recipient parties should follow the pre-established program guidelines and consider the guiding principles discussed in Sect. 2.7. With these strict criteria and well-defined processes, donor rejection rates are significant, ranging from 29 to 86 % [47, 48, 50, 51].

Table 2.2 Suggested evaluation protocol for potential living liver donors for children with PALF[a]

Step 1	
	– History and physical examination – Laboratory investigations: blood group, hematological tests, chemistry, coagulation profile, C-reactive protein, pregnancy test in females – Serology for Hepatitis A, B, C, HIV, CMV, HSV, EBV – Cross sectional imaging with CT scan and MRI to delineate vascular and biliary anatomy – Liver biopsy (in select cases based on suspicion for steatosis or other liver pathology) – Psychosocial evaluation – If no contraindications proceed to Step 2
Step 2	
	– Surgical risk assessment for comorbidities: ECG, chest X-ray – Laboratory: thyroid function tests (TSH, T3, T4), immunoglobulins IgA, IgG, IgM, iron, transferrin, ferritin, alpha-1-antitrypsin, ceruloplasmin, tumor markers (CEA, AFP, Ca19-9), factors V, VII and VIII, protein C and S, APCR, and urine sediment – Pulmonary function tests, echocardiography, stress testing if suspicion for cardiopumonary disease – Select consultations if needed – Hepatitis B vaccination – If no contraindications proceed to Step 3
Step 3	
	– Surgeon assessment – Hepatologist assessment – Second psychosocial assessment – If no contraindications proceed to Step 4
Step 4	
	– Second Hepatitis B vaccination – Anaesthesia consultation – Ethics board evaluation – Final informed consent
Optional steps	Autologous blood donation, liver function tests: galactose, indocyanine clearance test, lidocaine

HIV human immunodeficiency virus; *CMV* cytomegalovirus; *HSV* herpes simplex virus; *EBV* Epstein-Barr virus; *CT* computed tomography; *ECG* electrocardiogram; *TSH* thyroid-stimulating hormone; *T3* triiodothyronin; *T4* thyroxin; *CEA* carcinoembryonic antigen; *AFP* alpha-fetoprotein; *APCR* activated protein C resistance

[a]Adapted from Valentin-Gamazo et al. [47]

2.6 Ethical Issues

2.6.1 Donor Health-Related Quality of Life and Psychosocial Health After Live Donor Surgery PALF

Physical complications developing following donor hepatectomy to donors are well documented in many publications, but only a few studies have assessed the health related quality of life (HRQOL) and the psychosocial outcomes after adult-to-child donation. The goals of the donor psychosocial evaluation are to identify issues that might contribute to ill health or decision regret after donation and to ensure that the decision to donate is well informed. The limited studies on psychosocial aspects of adult-to-child LDLT show that the HRQOL for living donors is as good as, or better than that of, the general population. Studies looking at outcomes for donors who are parents versus those who are relatives versus anonymous donors are much needed to explore this further. Interview assessments with family and parent donors for children with non-acute liver failure show nearly uniform absence of regret [52, 53]. In cases where the transplant failed, a re-transplant was needed, or the child recipient died, many donors were comforted in knowing that they did all that could possibly be done to save the child [52]. In these studies the majority of donors were parents, and a much smaller proportion was represented by relatives and grandparents [53]. In contrast, one study assessed the frequency and risk factors for donor ambivalence in adult-to-adult donors, and found that 34 % of donors had some regrets [53]. In this study, donor ambivalence was defined as "simultaneous and contradictory attitudes and/or feelings toward a person (the recipient) or an action [of right hepatic lobe donation]" [54]. Of a total of 45 donors studied, one was a parent, three were friends or relatives, and the remaining 41 were adult children donating to parents [54]. Those donors who reported ambivalence were more likely to be male, over 35 years old, with a higher level of education, and donating to a recipient with hepatitis C or alcohol-related liver disease [54]. Similar findings have not been documented in parent-to-child LDLT.

Living donor liver donation for babies, infants, and young children with PALF most commonly requires resection of a small segment of liver, such as a left lateral lobe, from parents or relatives. Only larger, older children require a larger right-sided graft. The available evidence on psychosocial aspects and consequences of donation, post-donation quality of life, and decisional regret suggest that when the donors are parents or close relatives and are emotionally invested in the well-being of the child, LDLT for PALF has minimal medical/surgical risks, no negative effects on the donor HRQOL, and negligible decisional regret. In situations where right or left lobe donation is needed, a larger segment of liver is resected for an older child with PALF. Notably, most of the positive studies on absence of decisional regret in parent-to-children donors and high levels of post-donation HRQOL are of donors of small segments of liver. Therefore, it is particularly important that the slightly higher morbidity and mortality risks and

potentially greater effect on HRQOL in donors to older children who require right lobe transplants are fully disclosed to potential donors.

2.6.2 *Unique Pediatric Issues Relevant to Living Donation for Children with Acute Liver Failure*

There are several unique social and ethical aspects related to living liver donation for a child with PALF. Unlike adult medicine and surgery, which generally focuses on individual outcomes, caring for a child with PALF requires an understanding of how this condition impacts on the entire family. In this setting caregivers must provide strong psychosocial support to all family members, be aware of the extreme stresses imposed by the need to make vital but expedient healthcare decisions; and recognize the challenges associated with making decisions for a patient who may be unable to provide any independent input, either because of young age, general ill health, or hepatic encephalopathy.

2.7 Ethical Arguments for and Against Urgent Living Donor Liver Transplantation for PALF in Children

In the LDLT assessment process, physicians assessing the donor and recipients must be mindful of their moral and legal fiduciary responsibilities. Fiduciary obligations flow from the relationship of trust between physician and patient and the implicit or explicit understanding that physicians will focus, almost exclusively, on the best interests of the patient using their knowledge and expertise. Thus, caregivers must not only do their best to minimize harm to the donor and recipient. As moral agents in this process, they must also ensure patients are well informed and determine for themselves if the net benefits of LDLT outweigh the net risks. A more detailed analysis of the ethical issues associated with LDLT is provided below.

2.7.1 *Autonomy, Time Pressure and Coercion of Donors*

The principle of autonomy provides a strong ethical foundation supporting urgent LDLT for PALF. We live in a society that allows people to participate in high-risk activities like hang-gliding and enlists young men and women in high-risk military activities. In this context, it seems reasonable to also offer individuals the option of live donation, with relatively low associated risks, in order to save the life of child.

Surveys of the general population and of past donors support that offering LDLT in PALF appeals to the autonomy of the parent donors [53, 55, 56]. In a survey of

150 people recruited at the time of their presentation for a routine medical visit at an internal medicine clinic, thresholds for donation to a loved one were quantified. This was based on hypothetical and not real-life scenarios. This study showed that most laypersons have extremely high thresholds for donation risk and mortality. Sixty percent of the respondents suggested they would prefer to donate and die and have the transplant recipient live rather than forgo donation and have the potential transplant recipient die of liver failure. A personal survival threshold after LDLT was only 79 % and a threshold survival for the loved one after transplantation was only 55 % for them to agree to donate. Only a small proportion of correspondents had a survival threshold that exceeded the estimated risk of donation, as shown in Fig. 2.3. The majority of respondents (82 %) believed that the potential donor, not a physician, should have the final say regarding candidacy for living donation [55]. Survey studies and populations surveyed may have unrecognized biases, so these data should be interpreted cautiously. In addition, the survey was given to people who were not in fact dealing with the realities of these decisions, and who were answering hypothetical questions. Nevertheless, these data suggest that the potential donors' threshold and tolerance of risk is much higher than the actual risks of donation for PALF (and much greater than risks that would be deemed acceptable by most health care professionals). Thus, when evaluating the candidacy of a potential donor, clinicians must recognize the very high value that most people place on taking all possible steps to ensure the survival of a patient with organ failure.

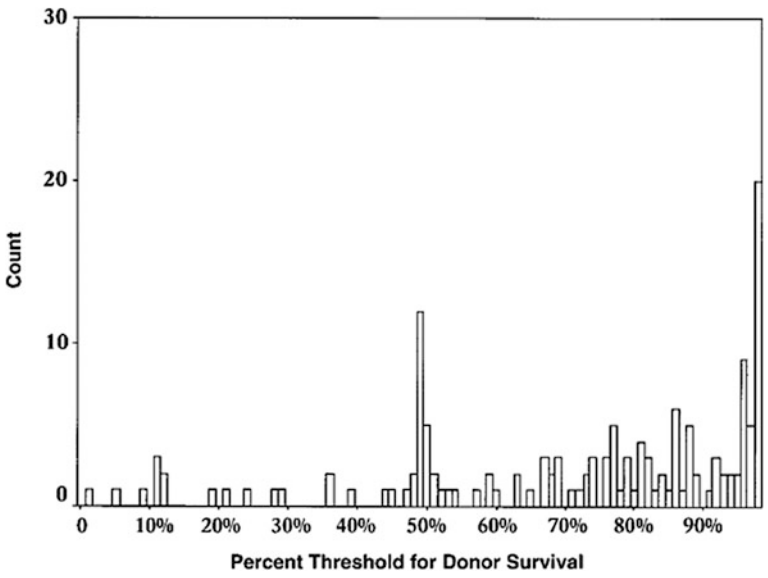

Fig. 2.3 Survey of 150 non-donor persons recruited from an internal medicine clinic suggests that only a small proportion reported their threshold for mortality for donation to a loved one to exceed the actual risk of donation. Adapted from Cotler et al. [55]

2.7.2 Principles of Non-maleficence and Beneficence and as They Apply to LDLT for PALF

The principle of non-maleficence, or doing no harm to the donor, is potentially violated if the measures of harm are solely the physical consequences, such as pain, scarring, temporary lack of mobility and potential development of post-operative complications, including death. On the other hand, it can also be argued that these are minor risks compared with the harm that might be posed to parents, close family members, or friends if they were forced to stand by watching a child die knowing that his or her life might be saved through live donation.

The concept of beneficence also generally supports live liver donation. The principle of beneficence refers to the moral obligation to act for the benefit of others, and not merely refrain from harming them [38]. In a society that does not support deceased donation, the principle of beneficence with LDLT is easily met because the acutely ill child with PALF will otherwise die. At first glance, the principle of beneficence is more difficult to invoke when offering LDLT for a sick child with PALF if the option of deceased donation exists. However, LDLT may still be justified if the probability of getting a suitable donor organ in time is small.

LDLT has several other attributes supporting the principle of beneficence. First, live donation offers an opportunity for families to forego the sense of helplessness that is associated with waiting for a deceased-donor organ by taking active control of this process. Most often the donor is a parent or very close relative and so the potential benefit psychologically is high. Second, when donating a part of one's liver to a child with PALF, the donor benefits from the continued survival of the recipient and from the increased self-esteem derived from actively contributing to a child's survival. One study documenting these benefits examined the stress for donors in urgent situations by comparing living donors for hepatocellular carcinoma (HCC) versus those for recipients with ALF. Before surgery, the donors for recipients with ALF had much lower health related quality of life (HRQOL) scores than the donors for recipients with HCC, indicating that they were under severe stress [56]. After surgery, the ALF donors showed the largest improvement in HRQOL scores, supporting the notion that LDLT for PALF helps relieve stress and brings fulfillment to the donor. In addition, LDLT for a child with PALF provides benefit to the family unit, other parent, and the siblings, which further increases the benefit to the donor.

2.7.3 Utilitarian Perspective

Utilitarian arguments also favour LDLT for PALF. LDLT not only directly benefits the sick child with PALF, but it also allows children on the waiting list and their families who do not have a live donor to benefit from the addition of an extra donor organ that would not otherwise be available. In addition, the risk of donation for

living donors is much lower than the risk of waiting for a deceased organ for a child with PALF. Also, the benefit of the donation is higher when the donors are parents or anyone emotionally invested in the well-being of the sick child.

Indeed, using statistical models, Durand et al. [57] found that LDLT is most effective for overcoming the consequences of organ shortage when performed in patients at high risk of death on the waiting list, including those who are acutely ill but can still withstand the stress of transplantation. On one hand, it can be argued that putting living donors at risk should only be justified if the expected benefit for the recipient is maximal. In that view, low-risk patients, those whose condition is less severe, should be preferentially oriented to LDLT while the sicker individual should be kept on the waiting list for DDLT with a reduced waiting time (strategy 1). On the other hand, it can also be argued that the potential risk for the donor would be better justified if the recipient's risk of death on the waiting list for DDLT were high. In this view, the sickest patients should be preferentially oriented to LDLT (strategy 2). They embarked on a study to determine which of the two strategies was superior in reducing death on wait lists and maximizing survival after transplantation. After comparing these two strategies using the existing mortality statistics on both high-risk and low-risk patients, they found that LDLT was more effective for overcoming the consequences of organ shortage when used in high-risk patients [57]. Findings included a superior 3-year survival for strategy 2 of 17 % versus 8 % for strategy 1 and strategy 2. Even though the one-year survival after LDLT was lower for high-risk patients their one-year survival benefit with LDLT was 75 % versus zero survival benefit in low-risk patients who received LDLT. Notably, this study was performed on adult patients so its applicability to PALF patients might be limited. Nonetheless, it does challenge the notion that patients at high-risk of death on the waiting list who are acutely ill should receive a timely transplant, in order to provide the maximum utility and survival benefit for all patients on the wait list.

In the absence of deceased organs for a child with PALF, LDLT is generally accepted as the best way to overcome death on the waiting list. The rationale for this is its benefit of overcoming death for the child with PALF, which is much higher when waiting for a deceased organ. Due to the high case fatality rate in a shorter period of time for children with PALF compared to those with more chronic conditions needing transplant, providing a living organ when a deceased organ is not available can be life-saving, and delays can result in rapid deterioration and death. While waiting for a deceased organ, children can die from liver failure, or develop conditions that will make them no longer suitable for transplantation, such as advanced encephalopathy, cerebral oedema or sepsis.

2.7.4 Minimizing the Risk of Coercion and Exploitation

Opponents of LDLT for PALF raise concerns about the potential for coercion of vulnerable donors, especially in light of likely time pressures because of the acuity

in the context of PALF diagnosis. Fully informed consent requires that a competent person is given full disclosure of the procedure and all options and their consequences; that he or she understands what is disclosed; and that consent is voluntary [58]. We believe that these requirements can be satisfied with LDLT to PALF provided the donor team uses a robust assessment process that includes intensive psychosocial assessment and support and provides confidential opportunities to opt-out.

We reject the view of those who suggest that coercion is inevitable with live donation for PALF because the situation itself presents families and friends with bleak choices, which are in turn misconstrued as coercion. Situations in which people may feel as though they have no real freedom to choose may present bleak choices, but these choices do not inherently result in coercion. Indeed, studies show that most donors who come forward have made up their mind long before the formal consent process begins [59]. In addition, it is uncommon for potential donors to change their mind during the consent process. Hawkins and Emanuel [60] point out that dire situations not of anyone's doing, such as in the case of a child with acute liver failure, are not a moral problem and are best solved by active informed decisions.

In order for consent to be fully informed, full disclosure of all options and short-term and long-term risks and benefits to the donor of each option must be discussed in detail with the donor. This is a difficult task and the best ways to do this are unclear because there are few studies about the impact of disclosure practices on the outcomes of live liver donation [61]. Survey studies on living kidney donors (LKD) document significant variation in the information disclosed, and wide centre differences in the weight put on certain elements of this discussion. For instance, an international study of 221 transplant professionals from 177 US centers found greater emphasis on disclosure of financial burdens, expenses and loss of income, than non-US centers [62]. According to a study of consent processes for LKD in 132 US centers showed that programs varied in the extent to which all elements of disclosure were discussed with donor candidates, with only 42 % disclosing all elements [63].

Recommended disclosure elements include: (1) description of evaluation, surgical procedure and recovery process; (2) Potential donor mortality and morbidity; (3) medical uncertainties, including potential for long-term complications; (4) short-and long-term follow-up; (5) recipient-specific risks and benefits; (6) expected outcome of transplantation for recipient; (7) expenses for the donor; (8) potential impact on donor's candidacy for health and life insurance; (9) potential impact on donor's lifestyle and prospects for future employment; (10) potential benefits to the donor; (11) alternatives to donation and different donation procedures; (12) center-specific statistics on donor and recipient outcomes; (13) alternative treatments available to the recipient. Beavers et al. [64] found that 64 % of right lobe donors reported complications but stated that they would still choose to undergo the procedure. Of all partial liver donors in their series, 40 % reported adverse events that did not appear in the medical record, meaning that they were not collected or recorded in the medical record but were experienced by the donors.

The findings in this study highlight the need to agree upon the specific adverse events or risks that must be disclosed during the consent process [64].

Based on these findings, we support the view that all elements of informed consent for a potential LD for a child with PALF should be standardized, and practices consistently reevaluated on an institutional or government level. These elements include determination of competence and voluntariness; standardized and explicit disclosure, recommendation and documentation of understanding; and documentation of decision and authorization of the chosen plan [38]. One such example is the US Charlie W. Norwood Living Organ Donation act of 2007, that calls for the Secretary of the Department of Health and Human Services to submit a yearly report detailing the long-term health effects of living organ donation and the disclosure process of informed consent [65].

2.7.5 Optimal "Cooling off" Period

In an effort to safeguard against undue inducement, a mandatory "cooling off' period of one to two weeks from the time of coming forward to donate has been proposed and used in LDLT for chronic liver disease. However, this lengthy period is not feasible for LDLT to most children with PALF [42]. Furthermore, there is little evidence that this period is necessary or makes the donor work-up process more robust. Evidence from qualitative studies of adult-to-child donors for non-acute indications provides helpful insights into donor perceptions and experiences around urgency prior to donation. In a study of adult-to-child living donors by Crowley-Matoka et al. [52] in-depth interviews conducted 3–10 years after donation provided retrospective comments on their decisions to donate. The study participants were mostly parents of the recipients. They perceived their child's need for transplant as an acute crisis. They reported that this perception of urgency prompted an overwhelming desire to save the life of the child, and made the decision to donate an easy choice that did not require a prolonged evaluation of all considerations [52]. In situations where the child did not survive despite LDLT, the donors derived great comfort from the knowledge that they did their best by directly participating in the attempt to heal the child. At the same time, however, many donors acknowledged that they had not fully appreciated the recipient's future need for chronic medical care and life-long follow up. Even so, none of the donors in this study regretted their decision to donate [52]. The findings of this study further substantiate the argument that a lengthy cooling-off period is needed.

2.7.6 Significance of the Donor's Relationship to the Child

In a study of 20 adults who came forward to be potential liver donors for friends, children, parents or siblings, in-depth interviews revealed important insights into

the donation decision-making process and need for psycho-emotional support surrounding the decision [59]. The study authors classified the subjects into either the "openly ambivalent" or the "openly motivated" type. The motivated donors idealized their relationship with the recipient: they linked their desire to donate with their wishes and expectations for the relationship after the surgery. On the other hand, the ambivalent donors were more likely to view their personal relationships critically, seeing little potential for improvement of the relationships in the future [59]. Moreover, the authors found that "openly motivated" donors idealized both the recipient and the relationship as a subconscious means of protecting the self. Potential donors face a complex medical, ethical and social situation, marked by high levels of familial, institutional and normative pressures. As a result, they might deny the significance of the harmful effects of donation to their own physical integrity. Based on these findings, and findings of other studies on donor ambivalence, we conclude that the emotional bond, the perception of the relationship that the donor has toward the recipient, and the high level of perceived expectations are important factors clinicians should not ignore [54].

The importance of repetitive interviews and conversations with donors prior to consent is that these opportunities to exchange ideas allow for shared decision-making, in an environment that is non-judgemental, and supports either of the two alternative decisions (to donate or not to donate). These interviews should allow for the potential donors to voice their concerns about treatment and complications. Additionally, the clinicians, social workers, nurses and psychologists involved with these interviews should have special training in communication skills in the preoperative interview. It is important that they provide empathy when needed, but also note when help with decision-making is needed, as the level of anxiety and psychological pressure is very high [59].

2.7.7 LDLT from Anonymous or Non-related Donors

Other sources of living donor organs for LDLT are non-related donors (NRDs), who are defined as those donors with neither a genetic nor emotional relationship with the recipient [66]. NRDs can donate in either a non-directed or directed manner. In non-directed donation, a person donates his or her organ unconditionally to the general pool of recipients on the waiting list. In non-related directed donation, a person designates the particular recipient or group of recipients to whom his or her organ is to be given [67]. The published experience with NRD for LDLT is limited [67, 68]. The few centres that do perform NRD transplants have yet to reporting using this option for PALF.

An extensive discussion of NRD in the context of pediatric liver transplantation is beyond the scope of this chapter. However, as it pertains to PALF, there are some unique ethical issues that arise, mainly related to the fairness of subjecting these donors to the increased stress of a rapid work-up and the reduced opportunity for beneficence given the absence of a direct emotional bond with the recipient.

Thus, we conclude that the use of NRD organs for children with PALF and other acute situations should be used with caution, if at all, until more studies and evidence is obtained on the long-term quality of life and decisional regret in this unique and small donor population.

2.8 Key Concepts

- It is important to determine the cause of PALF as quickly as possible to determine the best treatment and avoid the need for a transplant if possible.
- LDLT is driven by respect for donor autonomy and the opportunity for beneficence. The donor program has a fiduciary responsibility to ensure that conflicts of interest are avoided, informed consent is obtained, and potential harm to the donor is minimized (non-maleficence).
- The risk of coercion can be minimized by experienced multidisciplinary assessment, the use of well-developed protocols and safety checklist, and an extensive donor education process.
- Most live liver donors recover fully and have no regrets about donation. LDLT reduces the risks of death on the waiting list and provides long-term graft outcomes that are comparable to DDLT.

References

1. D'Agostino D, Diaz S, Sanchez MC, Boldrini G. Management and prognosis of acute liver failure in children. Curr Gastroenterol Rep. 2012;14(3):262–9.
2. Squires RH Jr. Acute liver failure in children. Semin Liver Dis. 2008;28(2):153–66.
3. Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr. 2006;148(5):652–8.
4. Devictor D, Desplanques L, Debray D, Ozier Y, Dubousset AM, Valayer J, et al. Emergency liver transplantation for fulminant liver failure in infants and children. Hepatology. 1992; 16(5):1156–62.
5. Mohamed El Moghazy W, Ogura Y, Mutsuko M, Harada K, Koizumi A, Uemoto S. Pediatric living-donor liver transplantation for acute liver failure: analysis of 57 cases. Transpl Int. 2010;23(8):823–30.
6. Bucuvalas JC, Campbell KM, Cole CR, Guthery SL. Outcomes after liver transplantation: keep the end in mind. J Pediatr Gastroenterol Nutr. 2006;43(Suppl 1):S41–8.
7. Yamashiki N, Sugawara Y, Tamura S, Nakayama N, Oketani M, Umeshita K, et al. Outcomes after living donor liver transplantation for acute liver failure in Japan: results of a nationwide survey. Liver Transpl. 2012;18(9):1069–77.
8. Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137(12):947–54.
9. Devictor D, Tissieres P, Durand P, Chevret L, Debray D. Acute liver failure in neonates, infants and children. Expert Rev Gastroenterol Hepatol. 2011;5(6):717–29.

10. Uribe M, Gonzalez G, Alba A, Godoy J, Ferrario M, Hunter B, et al. Living donor liver transplantation in pediatric patients with acute liver failure: safe and effective alternative. Transpl Proc. 2008;40(9):3253–5.
11. Shouval DS, Mor E, Avitzur Y, Shamir R, Bar-Nathan N, Steinberg R, et al. Living-related donor liver transplantation for children with fulminant hepatic failure in Israel. J Pediatr Gastroenterol Nutr. 2009;48(4):451–5.
12. Hong JC, Yersiz H, Farmer DG, Duffy JP, Ghobrial RM, Nonthasoot B, et al. Longterm outcomes for whole and segmental liver grafts in adult and pediatric liver transplant recipients: a 10-year comparative analysis of 2988 cases. J Am Coll Surg. 2009;208(5):682–9 (discusion 9–91).
13. Kim WR, Smith JM, Skeans MA, Schladt DP, Schnitzler MA, Edwards EB, et al. OPTN/SRTR 2012 Annual Data Report: Liver.
14. Raia S, Nery JR, Mies S. Liver transplantation from live donors. Lancet. 1989;2(8661):497.
15. Bourdeaux C, Tri TT, Gras J, Sokal E, Otte JB, de Ville de Goyet J, et al. PELD score and posttransplant outcome in pediatric liver transplantation: a retrospective study of 100 recipients. Transplantation. 2005;79(9):1273–6.
16. Tanaka K, Uemoto S, Tokunaga Y, Fujita S, Sano K, Nishizawa T, et al. Surgical techniques and innovations in living related liver transplantation. Ann Surg. 1993;217(1):82–91.
17. Reding R, de Goyet Jde V, Delbeke I, Sokal E, Jamart J, Janssen M, et al. Pediatric liver transplantation with cadaveric or living related donors: comparative results in 90 elective recipients of primary grafts. J Pediatr. 1999;134(3):280–6.
18. Devlin J, Wendon J, Heaton N, Tan KC, Williams R. Pretransplantation clinical status and outcome of emergency transplantation for acute liver failure. Hepatology. 1995;21(4):1018–24.
19. Baliga P, Alvarez S, Lindblad A, Zeng L. Posttransplant survival in pediatric fulminant hepatic failure: the SPLIT experience. Liver Transpl. 2004;10(11):1364–71.
20. Uribe M, Buckel E, Ferrario M, Godoy J, Blanco A, Hunter B, et al. Epidemiology and results of liver transplantation for acute liver failure in Chile. Transplant Proc. 2003;35(7):2511–2.
21. Baliga P, Alvarez S, Lindblad A, Zeng L. Studies of pediatric liver transplantation research G. Posttransplant survival in pediatric fulminant hepatic failure: the SPLIT experience. Liver Transpl. 2004;10(11):1364–71.
22. Bucuvalas JC, Zeng L, Anand R. Studies of pediatric liver transplantation research G. Predictors of length of stay for pediatric liver transplant recipients. Liver Transpl. 2004;10 (8):1011–7.
23. Narkewicz MR, Dell Olio D, Karpen SJ, Murray KF, Schwarz K, Yazigi N, et al. Pattern of diagnostic evaluation for the causes of pediatric acute liver failure: an opportunity for quality improvement. J Pediatr. 2009;155(6):801–6 e1.
24. Liu CL, Fan ST, Lo CM, Tam PK, Saing H, Wei WI, et al. Live donor liver transplantation for fulminant hepatic failure in children. Liver Transpl. 2003;9(11):1185–90.
25. Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the study of liver diseases, American Society of transplantation and the North American Society for pediatric gastroenterology, hepatology and nutrition. Hepatology. 2014;60(1):362–98.
26. Sundaram SS, Alonso EM, Narkewicz MR, Zhang S, Squires RH. Pediatric acute liver failure study G. Characterization and outcomes of young infants with acute liver failure. J Pediatr. 2011;159(5):813–8 e1.
27. Saidi RF, Jabbour N, Li Y, Shah SA, Bozorgzadeh A. Outcomes in partial liver transplantation: deceased donor split-liver vs. live donor liver transplantation. HPB. 2011;13(11):797–801.
28. Bourdeaux C, Darwish A, Jamart J, Tri TT, Janssen M, Lerut J, et al. Living-related versus deceased donor pediatric liver transplantation: a multivariate analysis of technical and immunological complications in 235 recipients. Am J Transpl. 2007;7(2):440–7.
29. Liu CL, Fan ST, Lo CM, Yong BH, Fung ASM, Wong J. Right-lobe live donor liver transplantation improves survival of patients with acute liver failure. Br J Surg. 2002;89 (3):317–22.

30. Ueda M, Oike F, Ogura Y, Uryuhara K, Fujimoto Y, Kasahara M, et al. Long-term outcomes of 600 living donor liver transplants for pediatric patients at a single center. Liver Transpl. 2006;12(9):1326–36.
31. Northup PG, Abecassis MM, Englesbe MJ, Emond JC, Lee VD, Stukenborg GJ, et al. Addition of adult-to-adult living donation to liver transplant programs improves survival but at an increased cost. Liver Transpl. 2009;15(2):148–62.
32. Hippocrates. The hippocratic oath (updated 2002; cited 2014 Oct 3 2014). Available from: http://www.nlm.nih.gov/hmd/greek/greek_oath.html.
33. Kousoulas L, Emmanouilidis N, Klempnauer J, Lehner F. Living-donor liver transplantation: impact on donor's health-related quality of life. Transplant Proc. 2011;43(10):3584–7.
34. Gruttadauria S, Marsh JW, Vizzini GB, di Francesco F, Luca A, Volpes R, et al. Analysis of surgical and perioperative complications in seventy-five right hepatectomies for living donor liver transplantation. World J Gastroenterol. 2008;14(20):3159–64.
35. Kousoulas L, Becker T, Richter N, Emmanouilidis N, Schrem H, Barg-Hock H, et al. Living donor liver transplantation: effect of the type of liver graft donation on donor mortality and morbidity. Transplant Int. 24(3):251–8.
36. Middleton PF, Duffield M, Lynch SV, Padbury RT, House T, Stanton P, et al. Living donor liver transplantation-adult donor outcomes: a systematic review. Liver Transpl. 2006;12 (1):24–30.
37. Hippocrates. The hippocratic oath. Jones WHS, editor. Cambridge: Cambridge University Press; 1868. 258 p (1 Mar 1825).
38. Beauchamp TL, Childress JF. Principles of biomedical ethics. 6th ed. New York: Oxford University Press; 2009 417 p.
39. Ghobrial RM, Freise CE, Trotter JF, Tong L, Ojo AO, Fair JH, *et al*. Donor morbidity after living donation for liver transplantation. Gastroenterology. 2008;135(2):468–76.
40. Muzaale AD, Dagher NN, Montgomery RA, Taranto SE, McBride MA, Segev DL. Estimates of early death, acute liver failure, and long-term mortality among live liver donors. Gastroenterology. 2012;142(2):273–80.
41. Cronin DC 2nd, Millis JM, Siegler M. Transplantation of liver grafts from living donors into adults–too much, too soon. N Engl J Med. 2001;344(21):1633–7.
42. Abecassis M, Adams M, Adams P, Arnold RM, Atkins CR, Barr ML, *et al*. Consensus statement on the live organ donor. JAMA. 2000;284(22):2919–26.
43. Araujo CC, Balbi E, Pacheco-Moreira LF, Enne M, Alves J, Fernandes R, et al. Evaluation of living donor liver transplantation: causes for exclusion. Transpl Proc. 2010;42(2):424–5.
44. Baker A, Dhawan A, Devlin J, Mieli-Vergani G, O'Grady J, Williams R, et al. Assessment of potential donors for living related liver transplantation. Br J Surg. 1999;86(2):200–5.
45. Pascher A, Sauer IM, Walter M, Lopez-Haeninnen E, Theruvath T, Spinelli A, et al. Donor evaluation, donor risks, donor outcome, and donor quality of life in adult-to-adult living donor liver transplantation. Liver Transpl. 2002;8(9):829–37.
46. Sauer P, Schemmer P, Uhl W, Encke J. Living-donor liver transplantation: evaluation of donor and recipient. Nephrol Dial Transpl (official publication of the European Dialysis and Transplant Association—European Renal Association). 2004;19(Suppl 4):iv11–5.
47. Valentin-Gamazo C, Malago M, Karliova M, Lutz JT, Frilling A, Nadalin S, et al. Experience after the evaluation of 700 potential donors for living donor liver transplantation in a single center. Liver Transpl. 2004;10(9):1087–96.
48. Spital A. More on parental living liver donation for children with fulminant hepatic failure: addressing concerns about competing interests, coercion, consent and balancing acts. Am J Transplant. 2005;5(11):2619–22.
49. Squires RH, Alonso EM. Acute liver failure in children. In: Suchy FJ, Balistreri WF, editors. Liver disease in children. 4th ed. New York: Cambridge university Press; 2012.
50. Marcos A. Right lobe living donor liver transplantation: a review. Liver Transpl. 2000;6(1): 3–20.

51. Pomfret EA, Pomposelli JJ, Gordon FD, Erbay N, Lyn Price L, Lewis WD, et al. Liver regeneration and surgical outcome in donors of right-lobe liver grafts. Transplantation. 2003;76(1):5–10.
52. Crowley-Matoka M, Siegler M, Cronin DC 2nd. Long-term quality of life issues among adult-to-pediatric living liver donors: a qualitative exploration. Am J Transplant. 2004;4 (5):744–50.
53. Fukuda A, Sakamoto S, Shigeta T, Uchida H, Hamano I, Sasaki K, et al. Clinical outcomes and evaluation of the quality of life of living donors for pediatric liver transplantation: a single-center analysis of 100 donors. Transpl Proc. 2014;46(5):1371–6.
54. Simpson MA, Kendrick J, Verbesey JE, Morin DS, Dew MA, Trabucco A, et al. Ambivalence in living liver donors. Liver Transpl. 2011;17(10):1226–33.
55. Cotler SJ, McNutt R, Patil R, Banaad-Omiotek G, Morrissey M, Abrams R, et al. Adult living donor liver transplantation: Preferences about donation outside the medical community. Liver Transpl. 2001;7(4):335–40.
56. Erim Y, Beckmann M, Kroencke S, Valentin-Gamazo C, Malago M, Broering D, et al. Psychological strain in urgent indications for living donor liver transplantation. Liver Transpl. 2007;13(6):886–95.
57. Durand F, Belghiti J, Troisi R, Boillot O, Gadano A, Francoz C, et al. Living donor liver transplantation in high-risk vs. low-risk patients: optimization using statistical models. Liver Transpl. 2006;12(2):231–9.
58. Levine RJ. Informed consent in research and practice: similarities and differences. Arch Intern Med. 1983;143(6):1229–31.
59. Walter M, Papachristou C, Danzer G, Klapp B, Frommer J. Willingness to donate: an interview study before liver transplantation. J Med Ethics. 2004;30(6):544–50.
60. Hawkins J, Emanuel E. Clarifying confusions about coercion. Hastings Cent Rep. 2005;35 (5):16–9.
61. Gordon EJ. Informed consent for living donation: a review of key empirical studies, ethical challenges and future research. Am J Transpl. 2012;12(9):2273–80.
62. Parekh AM, Gordon EJ, Garg AX, Waterman AD, Kulkarni S, Parikh CR. Living kidney donor informed consent practices vary between US and non-US centers. Nephrol Dial Transpl (official publication of the European Dialysis and Transplant Association—European Renal Association). 2008;23(10):3316–24.
63. Rodrigue JR, Pavlakis M, Danovitch GM, Johnson SR, Karp SJ, Khwaja K, et al. Evaluating living kidney donors: relationship types, psychosocial criteria, and consent processes at US transplant programs. Am J Transplant. 2007;7(10):2326–32.
64. Beavers KL, Sandler RS, Fair JH, Johnson MW, Shrestha R. The living donor experience: donor health assessment and outcomes after living donor liver transplantation. Liver Transpl. 2001;7(11):943–7.
65. Charlie W. Norwood living organ donation act, 121 STAT., 1813 Public Law no: 110-144 (2007).
66. Dew MA, Jacobs CL, Jowsey SG, Hanto R, Miller C, Delmonico FL, et al. Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States. Am J Transpl. 2007;7(5):1047–54.
67. Reichman TW, Fox A, Adcock L, Wright L, Abbey SE, Levy G,et al. Anonymous living liver donation: donor profiles and outcomes. Am J Transpl. 2010;10(9):2099–104.
68. Wright L, Ross K, Abbey S, Levy G, Grant D. Living anonymous liver donation: case report and ethical justification. Am J Transpl. 2007;7(4):1032–5.

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