Donor Recruitment and Selection for Adult-to-Adult Living Donor Liver Transplantation in Urgent and Elective Circumstances

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Abstract

Background: Adult-to-adult living donor liver transplantation is becoming an alternative to cadaveric transplantation in urgent and elective settings. Donor selection crucially affects donor safety and recipient outcome.

Objective: To present our algorithm of urgent and elective donor selection.

Methods: Urgent selection is expeditious and protocol-based. Elective selection permits a comprehensive process. Both include medical, psychosocial and surgical-anatomic evaluations. Liver volumes and vascular anatomy are evaluated with computerized tomographic angiography. Informed consent is obtained after painstaking explanations. Independent institutional committees review and approve all cases.

Results: Between July 2003 and June 2004 we evaluated 43 potential live donors for 12 potential recipients (fulminant hepatic failure, n = 5; chronic end-stage liver disease, n = 6; primary graft non-function, n = 1). Thirty-three candidates (76%) were excluded due to blood type incompatibility (n = 14, 42%), incompatible anatomy (n = 8, 24%) – including problematic volume distribution (n = 2) or vascular anatomy (n = 6) – psychosocial issues (n = 4, 12%), or medical co-morbidity (n = 7, 22%). Five recipients (FHF, n = 4; chronic ESLD, n = 1) were successfully transplanted from living donors. In the acute setting, two patients (FHF, PGNF) died in the absence of an appropriate donor (cadaveric or living donor). In the elective group, one patient died of unexpected variceal bleeding and one received a cadaveric graft just before the planned living donor transplantation was performed. One candidate was transplanted overseas and two cases are scheduled. The ratio of compatibility for donation was 34% (10/29) for blood type-compatible candidates.

Conclusions: Donor selection for living donor liver transplantation is a complex, labor-intensive multidisciplinary process. Most exclusions are due to blood type incompatibility or anatomic details. Psychosocial aspects of these donations warrant special attention.

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Appropriate donor selection for adult-to-adult living donor liver transplantation is the pivotal factor of the procedure, with an impact on both donor safety and recipient outcome [1–4]. The accumulating experience since the recent "mass production" application of this procedure has served well in defining precise selection criteria and a structured process of evaluation. Donor safety is by far the single most important issue related to A-ALDLT and should include attention to all outcome aspects (surgical, medical, psychosocial, occupational and financial). It is not surprising, therefore, that donor evaluation is a complex, multidisciplinary mission and includes numerous steps, starting from the first approach to donate, through the processes of evaluation, selection and preparation, and ending with the receipt of final consent. Due to the nature of the act, there are fundamental serious moral and ethical considerations associated with the procedure and its justification. Like every other medical activity, it should also adhere to principles of cost-effectiveness and be feasible in an era of escalating costs and dwindling resources [5–7].

The time frame of preparation for an elective liver transplantation for most patients with chronic end-stage liver disease allows for a comprehensive donor selection process. The situation for patients with fulminant hepatic failure or following failure of a recent transplantation (primary graft non-function or hepatic artery thrombosis) is an entirely different matter. The procedure has been applied in the urgent scenario [8–13], but the necessarily expeditious and limited evaluation and preparation raised controversy regarding its justifiability [14]. Nevertheless, the severity of the cadaveric organ shortage in Israel and the unpredictability of donor availability have made A-ALDLT a viable alternative for patients awaiting cadaveric transplantation and, occasionally, the only alternative for urgent lifesaving transplantation in FHF [13].

We offered A-ALDLT to a number of patients and families and describe our donor selection process and the lessons we learned from our initial experience.

Patients and Methods

A-ALDLT was suggested to a number of patients and families. These included every case of FHF and selected patients with chronic ESLD in whom segmental grafts were considered adequate, i.e., stable CPT (Child, Pugh, Turcot) B or early C patients, including those with hepatocellular carcinoma who fulfill the Milan criteria, following

FHF = fulminant hepatic failure
ESLD = end-stage liver disease
PGNF = primary graft non-function

A-ALDLT = adult-to-adult living donor liver transplantation

failure of local ablative therapy. This report includes only cases in which potential donors were presented.

A multidisciplinary, structured and staged process of evaluation was carried out in both the urgent and elective settings [Table 1]. Inclusion and exclusion criteria and phases of evaluation followed recently published recommendations [15–17].

Phase 1: Presentation

The introductory meeting between the transplant team, the recipient candidate (if conscious) and family members included a detailed discussion about the patient's condition and prognosis, the indication for liver transplantation, the alternative sources (cadaveric vs. living donor) and the advantage and disadvantage of each option. Special attention was given to donor characteristics, potential morbidity and expected course, based on the most updated available data. The medical team included a transplant surgeon, hepatologist, social worker, transplant coordinator, and an intensive care physician in the case of FHF. Age limitations (>18, <50 years) and basic medical requirements were explained.

Phase 2: Initial screening

Following the presentation, suggested potential donors were screened for significant relations with the recipient, absence of serious medical and surgical problems, blood type compatibility, and normal liver function tests, complete blood count, serum electrolyte levels, as well as negative hepatitis B and C serology.

Phase 3: Detailed evaluation

Based on the most common reasons for exclusion, the third phase included a complete medical and surgical evaluation, history and physical examination, detailed psychosocial assessment and computerized tomographic angiography for volume and vascular anatomic analysis.

Phase 4: Complementary tests

Phase 4 included additional comprehensive laboratory tests [Table 1], a chest radiograph, an electrocardiogram, and other tests or consultations to clarify specific potential problems (echocardiogram, stress tests or scans, etc.). We did not perform a routine hepatic angiogram, liver biopsy, magnetic resonance cholangiopancreatography or preoperative endoscopic retrograde cholangiopancreatography, but rather adopted a selective approach. A liver biopsy was done only if the imaging or laboratory tests were indicative of steatosis or other liver disease.

Phase 5: Decision making

Based on the accumulated data and after exclusion of clearly incompatible candidates, the medical team selected the best donor or approved the candidacy in the case of a single potential suitable donor. As mentioned previously, special attention was paid to psychosocial aspects, i.e., capability of decision, ambivalence, vulnerability to psychological pressure, emotional and financial supportive system, and potential economic or occupational risks associated with the donation [18].

Table 1. Phases of living donor recruitment and evaluation

Phase	Procedures
1	Presentation of the procedure:
Presentation	☐ The patient's condition and prognosis
	☐ The indication for liver transplantation
	☐ The alternatives (cadaveric vs. living donor)
	☐ Advantages and disadvantages of each option
	☐ Donor aspects, potential morbidity and expected course
	☐ Discussion, Q&A
2	Age (>18, <50 years)
Initial screening	Significant long-term relations with the recipient
	Absence of serious medical and surgical problems
	Initial blood tests:
	☐ Blood type compatibility
	☐ Liver function tests
	☐ Complete blood count
	☐ Serum electrolyte
	☐ Hepatitis B serology (HbsAg, HBsAb, HBcAb)
	☐ Hepatitis C serology (anti-HCV Ab)
3	Medical and surgical evaluation
Detailed evaluation	History and physical examination
	Detailed psychosocial assessment
	CT angiography
4	Laboratory tests:
Complementary tests	☐ Coagulation studies (PT, PTT)
	☐ Chemistry (completion SMA20)
	☐ Serum protein electrophoresis
	☐ Autoimmune profile (AMA, ANA, ASMA)
	☐ Ceruloplasmin
	☐ Serum ferritin, iron, transferrin
	☐ -1 antitrypsin level
	☐ Virology (CMV IgG, EBV IgG, VDRL, HIV Ab)
	☐ Arterial blood gases
	Urinalysis
	B-HCG (female)
	PPD
	Chest radiograph
	Electrocardiogram
	Other tests or consultations to clarify specific potential problems (echocardiogram, stress tests, etc.)
	Hepatic angiogram*
	Liver biopsy*
	Preoperative ERCP or MRCP*
5	Donor selection and approval
Decision making	
6	Independent institutional committee – "donor
Review	advocate"
7	Detailed specific informed consent:
Consent acquisition	☐ Risks
	☐ Expected course
	☐ Verification of commitment

* We adopted selective application of these tests. In some centers, these tests are part of the routine workup.
PT = prothrombin time, PTT partial PT, AMA = antimyosin antibody, ANA = antinuclear antibody, ASMA = anti-smooth muscle antibody, CMV = cytomegalovirus, IgG = immunoglobulin G, EBV = Epstein-Barr virus, HCG = human chorionic gonadotropin, PPD = purified protein derivative, ERCP = endoscopic retrograde cholangiopancreatography, MRCP = magnetic resonance cholangiopancreatography

Table 2. Clinical characteristics of candidate recipients in the current study

No.	Age (yrs), gender, weight, ethnicity	Disease	Etiology	UNOS status	CPT score	Compatible/ evaluated donors	Outcome
1	18, female, 45 kg, Jewish	FHF	Paracetamol intoxication	1	–	1/3	LDLT, alive
2	37, female, 55 kg, Druze	FHF	Unknown	1	–	0/14	No donor, died
3	21, female, 43 kg, Jewish	FHF	Unknown (AIH?)	1	–	1/3	LDLT, alive
4	22, male, 50 kg, Jewish	FHF	Unknown (AIH?)	1	–	1/2	LDLT, alive
5	20, female, 65 kg, Arab	FHF	Wilson's disease	1	–	1/3	LDLT, alive
6	18, female, 50 kg, Arab	PGNF	Wilson's disease	1	–	0/3	No donor, died
7	25, female, 52 kg, Jewish	Cirrhosis	AIH	2B	11	1/2	LDLT, alive
8	27, male, 50 kg, Jewish	Cirrhosis	2° biliary cirrhosis (EHBA)	2B	12	1/3	CLT, alive
9	58, male, 76 kg, Arab	Cirrhosis	HBV, HCC	2B	12	2/5	Died before LDLT
10	42, female, 67 kg, Jewish	Cirrhosis	HCV	2A	13	0/2	CLT overseas
11	57, male, 100 kg, Jewish	Cirrhosis	NASH	2B	10	1/2	Waiting list for CLT
12	61, male, 80 kg, Jewish	Cirrhosis	NASH	1B	11	1/1	Scheduled for LDLT

FHF = fulminant hepatic failure, PGNF = primary graft non-function (following urgent cadaveric liver transplantation), ESLD = end-stage liver disease, AIH = autoimmune hepatitis, EHBA = extrahepatic biliary atresia, HBV = hepatitis B virus, HCV = hepatitis B virus, HCC = hepatocellular carcinoma, UNOS = United Network of Organ Sharing, CPT = Child, Pugh, Turcot, NASH = non-alcoholic steatohepatitis, LDLT = living donor liver transplantation, CLT = cadaveric liver transplantation.

Phase 6: Review (independent institutional committee – ''donor advocate'')

Every case was presented before an independent committee that discussed and approved the candidacy. The committee members, comprising a psychiatrist, psychologist or social worker, a legal advisor, a senior physician and the deputy or general manager of the institution, acted as "the donor's advocates" and were not involved in the recipient's management. They could draw attention to problematic aspects, ask for further evaluation or reject the candidacy.

Phase 7: Consent acquisition

Following the final selection, the elected donor was again given an explanation of the procedure, the risks and the expected course, and only then was a detailed informed consent obtained.

Timetable

In cases of FHF, the process was intensive, expeditious and finalized within 24–36 hours, although it still progressed throughout all the stages. In the elective scenario, donor assessment was done in the setting of an outpatient clinic and completed within a few weeks.

Table 3. Exclusions: phase of evaluation, diagnostic tools and specific reasons

Phase of evaluation	Modality	Reason for exclusions	N
Phase 2	Blood tests	Blood type incompatibility	14
		Positive hepatitis B serology	2
	Total		16
Phase 3	Medical evaluation	Co-morbidity: COPD, DM	2
	Psychosocial evaluation	Familial responsibilities and condition	2
		Lack of support	1
		Suspected external pressure	1
	CT angiography	Problematic volume distribution	2
		Arterial anatomy	4
		Venous anatomy	2
		Steatosis	2
	Total		16
Phase 4	Stress test, Thallium scan	Active IHD	1
Total			33

COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, IHD = ischemic heart disease.

Results

Between July 2003 and June 2004 we evaluated 43 potential living donors for 12 potential recipients. There were five cases of fulminant hepatic failure and one case of primary graft non-function following transplantation and, therefore, urgent transplantation was indicated for them. Another six cases were chronic end-stage liver disease and the planned transplantation was elective [Table 2].

There were no ethnic specific characteristics or differences between the recipient candidates (eight Jews of different origins, three Arabs, one Druze).

Of the 43 evaluated donor candidates, 10 were compatible for donation. Thirty-three exclusions were due to blood type incompatibility (n=14), problematic volume distribution (n=2), vascular anatomy (n=6), major psychosocial issues (n=4), or medical co-morbidity (n=7) including steatosis (n=2). The reasons for exclusion are summarized in Table 3.

Five recipients were transplanted successfully. Four patients who suffered from FHF and were comatose before transplantation recovered without any neurologic damage [13]. Two patients (FHF and PGNF following urgent transplantation for Wilson's disease) died in the absence of an appropriate donor (cadaveric or living). Of the six patients with chronic ESLD, one was transplanted successfully, one patient died of unexpected variceal bleeding, and one received a cadaveric graft just before the planned elective living donor transplantation was performed. One candidate whose condition deteriorated while waiting for a donor (UNOS status 2A) was transplanted overseas. One case is under reevaluation and one is scheduled.

The distribution of the 33 exclusions spread along the stages in the process of evaluation was as follows: 16 (49%) in phase 2, 16 (49%) in phase 3, and 1 in phase 4 (due to a positive stress test, followed by a positive thallium scan).

Invasive studies (phase 4) were done twice. In the first case, we added an arterial angiogram to identify the origin of segment 4 hepatic artery. Later, we were able to acquire a detailed arterial anatomy with CT angiography and computerized reconstruction, and the use of the arterial angiogram was abandoned. We performed a liver biopsy in a single case due to suspected steatosis because of the candidate's body shape and findings on the CT scan. The fraction of fat infiltration was acceptable (5–10%), but the candidate was finally excluded due to a positive thallium scan.

The ratio of compatibility for donation was 34% (10/29) for blood type-compatible candidates. CT angiography was the single most definitive tool in the process of evaluation (10/19 exclusions) for blood type-compatible candidates who fulfilled the initial prerequisites (i.e., "passed" phase 2).

On two occasions the process of donor evaluation revealed serious medical problems in asymptomatic candidates. In one case, positive stress test and thallium scan mandated coronary angioplasty and in the second, CT revealed a kidney obstruction with a stone, which was removed via ureteroscopy.

Discussion

A-ALDLT is becoming a feasible alternative to cadaveric liver transplantation. Inherent to the procedure, however, is a conflict of interest between the recipient's needs (early transplantation with maximal liver volume and optimal inflow and outflow) and the donor's safety (comprehensive preparations, minimal liver volume and no vascular and biliary compromises). There are nine reported cases of donor's death in nearly 3,500 recorded living donor liver transplants (0.25%), but the rate may be higher following donation of the right lobe as needed in most A-ALDLTs (estimated rate 0.3–0.4%) [19]. The incidence of complications is also not negligible, and, indeed, some should be considered as major, such as portal vein thrombosis, liver failure, biliary stricture or bile leak, or incisional hernia that may mandate re-operation [19–21]. Moreover, given the recent introduction of the procedure, long-term follow-up is limited. Another important and problematic issue, which has not been addressed in depth, is the influence of liver donation on quality of life [22,23]. Nonetheless, the severity of organ shortage, the waiting list mortality and the urgency of transplantation in the FHF setting essentially forced the transplanting community to expand the implementation of this method. In Israel, the concept of organ donation after brain death is still less developed than in Western Europe and North America, and the low numbers also affect the predictability of donor availability. The option of transferring patients for transplantation overseas is limited, uncertain and replete with ethical controversy. This makes the establishment of LDLT competence all that more crucial. Towards this end, we recently initiated an LDLT program. The process of donor recruitment and evaluation was based on a rigid protocol with defined phases of interaction with the recipient, his or her family, and the potential donors [Table 1]. The guiding principles of the algorithm were directed towards using the most definitive diagnostic tools first and avoiding invasive studies whenever possible. Several issues emerged as particularly important in this milieu:

Preoperative anatomic studies

In all cases we found CT angiography sufficient both for volume assessment and for vascular details (arterial, portal and venous), which are critical for donor selection or exclusion and for preoperative planning of the donor's and recipient's operations. We had initially performed arterial angiography to verify the CT findings, but later were able to avoid this invasive study. It became clear that CT radiologists need to be familiar with the technical details of the operation so that CT reconstructions could be done accordingly, and that their interpretation of the data should be done together with the surgeons. Since the biliary anatomy, although highly variable, rarely prevents donation, we did not use preoperative MCRP or ERCP, but studied the donor's biliary system with intraoperative cholangiography.

Preoperative liver biopsy

Some centers recommend routine liver biopsy to exclude liver disease and steatosis [15]. We applied a more selective approach in which a preoperative biopsy would be done only if liver function tests were abnormal, if the CT was indicative of a fatty liver, or in obese patients (body mass index >30 kg/m^2).

Detailed psychosocial assessment

The basic initial requirement for donation was significant long-term relations with the recipient, usually as first- or second-degree familial relatives. In the absence of quantitative measures for all the psychosocial aspects, we used multiple interviews and "common sense" to clarify questions of motivation, capability of decision, ambivalence, or vulnerability to psychological pressure. The evaluating team was experienced with more than 100 living donor evaluations for renal transplantation. We identified external pressure on two occasions and those candidates were excluded. Special attention was also given to the existence of a supportive system and any potential familial, economic or occupational risks associated with the donation; such concerns assisted in the selection and exclusion of donors in one case.

"Donor advocate"

Since its introduction, the procedure of A-ALDLT has been subject to medical and ethical criticism. One of the main concerns of the critics was the fact that the process of donor recruitment and evaluation was conducted by the transplant team, which might be influenced by the recipient's needs. The proposed solution was an independent team that would represent the donor and not be involved in the recipient's care [17,24]. We found the interaction with the "donor advocate" team very helpful. Although they have

MCRP = magnetic resonance cholangiopancreatography
ERCP = endoscopic retrograde cholangiopancreatography

not (yet) used their veto privilege, their questions and requirements assisted us in clarifying several issues.

Justification of A-ALDLT in the elective setting

Donation in the urgent situation of life-saving transplantation as in the FHF scenario, although involving inferior results, is intuitively acceptable in our society. This sense of moral and ethical appropriateness is less direct and evident in the elective environment. However, critical analysis of waiting list mortality and lack of true long-term alternatives should drive the implementation of this approach in carefully and systematically selected cases.

Conclusions

Donor selection for adult-to-adult living donor liver transplantation is a complex and labor-intensive multidisciplinary process. Most candidate exclusions are due to blood type incompatibility or anatomic details, and the evaluation algorithm should be managed accordingly. Special attention should be given to psychosocial aspects of the donation. A donor's advocate has an important responsibility and should be involved in the process of approval independently of the recipient's needs.

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