Living donation for a paediatric liver transplantation: an opportunity to be used in accordance with ethical principles

La donazione di organi da vivente per un trapianto di fegato in pediatria: la possibilità di utilizzo nel rispetto dei principi etici

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As a price for its success, liver transplantation nowadays faces the challenge of a limited organ availability. Living liver donation is an alternative to a cadaveric donation and is now a recognised and valid procedure from a technical point of view; it rises however a series of specific ethical questions or issues.

The very ethics of a living donor transplantation may be more about the “how” to do it, not to regulate it, or to negate the opportunity. On the “how” to do side, the process has been specifically and precisely paved by the Legislator to ensure the absence of a possible effect of a conflict of interest from the hospital. That is not to say that teams that are providing this type of service, must have a high level of care, and an obsession for the search of quality: their setting-up of a living donor programme is rich in complex procedure descriptions and protocols of care, and they must work through multidisciplinary and multi-professional networks.

This paper focuses on paediatric transplantation and the content is solely dedicated to the living donation of a left liver lobe, by an adult of the family, for the transplantation of the graft into his or her directly related child.

Key words: Liver transplantation, children, ethics, left liver lobe, justice principle

Come prezzo del suo successo, il trapianto di fegato si trova oggi ad affrontare la grave criticità dell’insufficienza di organi disponibili. In questo scenario, il trapianto di fegato da donatore vivente rappresenta un’alternativa al trapianto tradizionale, alternativa di cui è riconosciuto il valore dal punto di vista tecnico, ma che solleva una serie di quesiti di natura etica.

L’etica vera e propria del trapianto di fegato potrebbe essere più focalizzata sul “come” effettuare l’intervento, piuttosto che su come regolamentarlo o negarne l’opportunità. Per quanto riguarda il “come”, la procedura chirurgica è stata regolamentata in maniera specifica e precisa dal Legislatore per garantire l’assenza di un possibile conflitto di interesse per l’ospedale. Ciò non significa che le equipe che effettuano questo tipo di intervento non debbano poter garantire un alto livello di assistenza ed una ossessiva ricerca della qualità. Istituire un programma di trapianto da donatore vivente implica una serie di procedure complesse e di protocolli di cura che coinvolgono gruppi e network multidisciplinari e multi-professionali.

Il presente articolo riguarda specificatamente il trapianto di fegato pediatrico ed è esclusivamente dedicato alla donazione da vivente del lobo destro epatico da parte di un adulto familiare per il trapianto al proprio bambinolombambina.

Parole chiave: Trapianto di fegato, bambini, etica, lobo destro epatico, principio di giustizia
Background and Introduction

Organ transplantation, and in particular, liver transplantation, has experienced an extraordinary development in the last 30 years. Recognised in the early eighties as a clinically valid option, it has evolved into a major first line therapeutic option and has radically changed the prognosis of many conditions that were previously considered incurable. Today, in fact, a liver transplant offers a new and an effective chance to many patients, enabling them to recover in the majority of cases and to experience a satisfactory quality of life.

As a price for its success, liver transplantation nowadays faces the challenge of a limited organ availability. The latter shortage, being secondary to the decreasing number of patients developing brain death conditions, is in fact a positive result in itself for the overall progress of medicine, and the implementation of risk prevention programmes. On this evolving background, the organ shortage has obliged medical teams to search all possible alternatives, by both developing non-transplant strategies wherever possible, and by using at best, all usable organ sources and each individual donor (multi-organ retrieval, split liver transplantation (one liver for two recipients), domino liver transplantation, and more recently the procurement from non-heart beating donors) (Darwish et al., 2006; Otte et al., 1998; Reding et al., 1999; Gurevich et al., 2015). But an effective and complete solution has not yet been found: the number of donors has remained stable overall, and despite recruiting more organ sources, it is still by far insufficient to meet the growing actual needs. One worse collateral effect of the unceasingly growing number of patients on a waiting list (observed in all developed countries), is the increase in waiting time, and in turn, as consequences, the clinical deterioration of the patients, the increase of peri-transplant morbidity, and of deaths while waiting for an organ.

Increasingly, calls to consider a living donation as a real alternative for a liver transplantation in infants and small children are being made by expert teams that see an alternative to the organ shortage on the one side, and a possible safe and efficient cure on the other side – thus acting to save more children (Otte et al., 1998; Gurevich et al., 2015; Rodriguez-Davalos et al., 2014; Tessier et al., 2014; Lobritto et al., 2012).

Living liver donation emerged two decades ago as an alternative to a cadaveric donation (Darwish et al., 2006; Otte et al., 1998; Reding et al., 1999; Gurevich et al., 2015). It is now a recognised and valid procedure from a technical point of view, but continues to raise a series of specific ethical questions or issues. Among these, the first consideration is the autonomy of the potential donor in taking his or her decision. The second addresses the risk for the donor: in brief, a living donor organ transplantation consists of the retrieval of an organ from a healthy subject (the donor), through a surgical procedure that is associated with a given risk, the only beneficiary of which is the recipient. This dual aspect (being only a risk for donor, only a benefit for recipient) has often been put forward by some who disagree with the concept as a stand-alone justification, to not develop living donor programmes. The former view is, however, very limited, and much blinded to the fact that there are eventual benefits for the donor, and of course, there are risks for the recipient to be considered – not only benefits! An ethical balance can be found, when the risks are minimised for both persons, and their benefits are maximised at the same time. This is particularly true when one of the parents donates the left part of their liver to their child: this particular model of donation corresponds, in fact, to the vast majority of the liver grafts needed in the paediatric age transplantation group, and this conundrum is the very subject of this paper.

The text that follows is solely dedicated to the living donation of a left liver lobe, by an adult of the family, for the transplantation of the graft into his or her directly related child (Fig. 1). The general reasoning, together with the pros and cons as outlined, refer to this specific set of cases, and are not simply transposable to other situations or organs.

The Ethics of a Living Donation

This ethical questioning is structured according to three major and fundamental principles:
• the Hippocratic Principle;
• the Principle of Autonomy;
• the Principle of Justice.

A – The Hippocratic Principle

Hippocrates is well known for his principle «do not harm» (primum non nocere), or the Principle of “Non-Maleficence” (Hippocratic Oath). A careful reading of his work perceives evidence that – in his text and most likely in his mind – there is another principle, the Principle of “Beneficence”– namely, a service to provide for the benefit of patients – and precedes the writing of the Principle of Non-Maleficence.

Interestingly, in the text, not only is “Beneficence” said

Figure 1. The gift of life: a donation of the left part of the liver of an adult, smaller than the right part, allows for the successful transplantation in a small child, while keeping most of the liver mass for the adult donor.
Living donation for a paediatric liver transplantation

first: this is stressed twice in the Hippocratic Oath as follow: “I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice”: “Into whatever houses I enter, I will go into them for the benefit of the sick, and will abstain from every voluntary act of mischief and corruption”.

Thus, not only the well-known principle of “non-maleficence” must guide the discussion concerning the ethics of a living organ donation, but as equally important, is the Principle of “Beneficence”.

A1 – The Principle of Non-Maleficence

This basic principle «do not harm» is expressed several times in the Hippocratic Oath and with different examples throughout the document. It is also a fundamental principle in all religions, philosophies, and social behaviour. It is not only a guiding principle in medicine transmitted from doctor to doctor along with the Hippocratic Oath, but above all, a universal moral obligation, clearly formulated and reinforced in the law of every country, where all forms and kinds of “maleficence” are explicitly prohibited; the latter prohibition (or regulation) by law applies to various aspects of medical practice, and in many countries, the law specifically addresses the sectors of surgery and transplantation. The Oviedo Convention and Italian Law clearly ban or allow specific practices, and they regulate the activities of organ procurement or the use of organs, or parts of organs, including those from living donors (Convention pour la protection des Droits de l’Homme et de la dignité de l’être humain à l’égard des applications de la biologie et de la médecine; Protocole additionnel à la Convention sur les Droits de l’Homme et la Biomédecine, 2002; Statement by the Committee of Ministers on the prohibition of any form of commercialisation of human organs, 2014; Council of Europe 2009).

Even when the law allows it, it may seem that the first Hippocratic principle is transgressed when an organ, or part of an organ, is retrieved from a living donor, as the aim of the surgery is not to the benefit of the donors themselves. At first sight, clearly, there is of course no need for cure, and no direct advantages for the donor to offer himself or herself to undergo that operation; if the only way to justify such procedure is to demonstrate a direct medical benefit, or curing a problem, there would be not even place for debating that issue. This is clearly a much too simple conceptual approach, insufficient for the very debating of a complex argument. But with the discussion proceeding, and upon opening itself to many other aspects, it is clear that under certain circumstances, the inequality in the equation of donation versus reception is counterbalanced, by far. There are indeed benefits for the donor and the family (A2).

However, it is eventually within the clinical process itself (the setting-up and the running of a living donor programme) that respect of the principle of non-maleficence may find a more direct application; by limiting the risks of the donors as much as possible and by all possible means. Even knowing that the risk of zero does not exist, the transplantation team is wholly responsible for the setting out of such programmes, and setting only the best conditions and the best environment, to guarantee optimal outcomes. Previous transplantation experience and exhibiting excellent results with similar procedures (split liver), is a must, even before starting such a programme – a guarantee that the operation will succeed, both for the donor and the recipient, at the highest success rate possible, and thus maximising the benefits for both persons, while minimising the related morbidity. Strictly selecting the eligible donors, and excluding all candidates with a condition or a disease that could increase the surgical risk, meticulously assessing them through a multi-disciplinary pathway, are all steps necessary to accept a candidate for donation. This includes an accurate anatomical evaluation of the organ to be retrieved, to ensure that there will be no functional or anatomical sequelae experienced by the donor.

The procurement of the left lobe of the liver from an adult for the transplantation into a child is technically and anatomically speaking, in some way, a relatively simpler and favourable procedure compared to others (i.e. adult to adult liver donation). Firstly, the vast majority of the children who need a transplant are very young and small in weight – and a relatively small volume of the liver parenchyma (only the left liver lobe of an adult) is deemed to be by far enough. Secondly, from an anatomical point of view, 1) the right liver is the preponderant part of the liver and keeping that part in the donor guarantees his safety from a functional point of view; 2) a scissure divides the left liver at some distance from the main hepatic structures, with most of the surgical work being done in, or around, that scissure, which is safe for the donor; 3) the usual mode for the distribution of the hepatic vessels, right and left, is such that it allows the retrieval, in most cases, of the left lobe, with no interference on the vitality of the right liver (Fig. 2). Nature took proper care of everything: the left liver lobe has its own vascular support and a natural cleavage that runs along its surface, guiding the surgeon to retrieve it in utmost safety; the cutting through the liver is limited in size, thus the blood loss is limited (blood transfusions for the donor are exceptionally needed), and the postoperative complication rate is low in most centres (Figs. 3-4). What could be more symbolic than that: the parent, who makes this gift of a new life to their child, is in fact, offering the very part of their liver, where their own umbilical remnant lies. The umbilical remnant is the very trace of his or her old link to the placenta, the vein and link that kept him or her alive for 9 months in the uterus. (Figs. 3-4)! Left liver procurement in living donors for the transplantation in their children is at present the most widespread technique in the world for the liver: it represents the only chance of survival for many children in countries where paediatric organ post-mortem donation programmes do not exist, or
are insufficient, or where split liver transplantation technique is not commonly used. The risk of death for the donors of a left liver lobe – a risk that can never be forgotten, nor entirely eliminated, even in optimum conditions – is estimated to be at around 0.1% (Vancouver Conference – September 2005). Even with those with very low figures, this information is given to the potential donors during their pre-operation interviews; this allows one to clearly outline -at the extreme- that there are some serious risks, and that they will be exposed to them in some way.

A2 – The Principle of Beneficence

From the point of view of the sick child, candidate for transplantation, the risks are known and important. For the child too, the direct benefits of having a parent willing to donate the left lobe of his liver are obvious. All that facilitates his or her access to the operation (in terms of the availability of a liver and an early timing of the transplantation – not to speak of the allocation of an excellent quality graft) is a direct benefit.

When they are asked about their experience, retrospectively, donors too consider that they benefit directly from this operation taking place. This “benefit” is usually not highlighted in ethical discussions; sometimes even surprisingly negated, or presented as self-justification strategy... Who would take the risk of an unnecessary intervention, deliberately and consciently, without gaining any benefit? Parents consider a donation as a natural act in their position, while some discussants consider that they act under the “coercion of being the parent”. The latter is a strong statement and opens up another major question about the right or not, for some people, of being able to decide, in the very place of others, of a matter of death or life (the latter concept is out of this subject and will not be discussed further in this paper).
Very possibly, a series of facts, concepts, and values, that have a significant importance within the family of a sick child, should be considered. When children get seriously sick, or worse, when they face a risk of dying, the whole family who is directly involved, become deeply troubled, and relatives get “sick” themselves. Generational and social changes have transformed the “family” in the last few decades; it is not anymore a large group that is socially organised to help each other, but nowadays, and in a growing number of countries, there is a small “nucleus” with only few elements orbiting very close to each other, and the balance is easy to disturb. Nuclear or family units are made up of only the closest relatives, whose attention is concentrated on a minimum number of children. With this evolution towards nuclear families, children have earned progressively a place and a very role within the family, and that un-comparable to that in the past, and much important for the balance, and the “health”, of the family. In such a family, the severe illness of a child completely disrupts the family balance – and disturb each of its members at a personal level. The disease and its manifestations, the communication of the diagnosis with a severe prognosis, the repeated hospitalisations and medical visits, and the clinical tests, ensure that all of these aspects cancel the projects of the family and create a deep anxiety and uncertainty. Parents may develop guilty feelings with regard to the onset of the disease (more frequently in mothers), or even with regard to the sick child. Unintentional negative feelings towards the disease (thus towards the child) may emerge, as the disease is seen as the disturbing element to the previous family harmony, their projects, and their long-term programmes. In other words, the whole family is unexpectedly forced to confront grief and death, as a whole and at every personal level.

In this context, whatever contributes to the child’s recovery, greatly benefits the entire family and each of its members, helping to restore their health and harmony, and reformulate projects and a “future”. Around the child’s healing, the family gradually goes back into normal life. Based upon the above family dynamics and psychology, it is clear that a successful related living donor transplantation brings significant direct and indirect benefits to the whole family, and to the donor, and that the recipient cannot be considered as its sole beneficiary. Not least, proposing oneself to be a donor, can be felt as a way of avoiding fate and paralysis, acting against the uncontrollable, and of initiating a process of contributing to the curing and saving. It is a powerful feeling for a family to know one can actively contribute to the caring and the curing, and save his or her child’s life by being a donor. The donor and the family cease to be paralysed under the “weight” of the disease; they feel they can then directly act against the disease, modelling with their hands, a part of their future. This last feeling is of momentous significance, especially when one is considering on the other hand how families can sometimes painfully experience the conventional process of waiting for a graft, or being transplanted from a post-mortem donor. The feeling of being powerless in the process, and the long-lastingly wait for an organ that could arrive very late – or too late – and at the same time, seeing their child’s clinical conditions progressively deteriorate. Worse, is the experience for some parents of a sense of guilt when at some point one starts wishing that a donor is rapidly found, as this would mean hoping for the death of a stranger.

Overall, in this net of contradictory and complex feelings, the proposal of a living related donor for transplantation may be seen as an actual and reassuring solution. Several follow-up studies on donors have clearly demonstrated the psychological and moral benefit deriving from a living donation. The vast majority of donors declare that they do not regret their decision and that they would be ready to do it again. They also have said that this gesture has given them a sense of serenity and self-accomplishment. Even the parental donors of children, who unfortunately died after the intervention, expressed positive and reassuring feelings, and they have declared that they were glad that they had done all that they could to save their child’s life.
Overall, it is clear that in the dynamics of “parent donor – child recipient”, donors do not solely take risks, but also get some remarkable benefits: a future for their families and a gratification for themselves.

**B – The Principle of Autonomy**

A person’s autonomy, and in this case the autonomy of the donor, demands respect for their right to make a choice with full knowledge of the risks and benefits. Considering that donors are, by definition, in good health, they would not need any surgical intervention, and it is crucial that their decision to undergo surgery is made of their own free will. A respect for the principle of the donor’s autonomy, imposes above all, and to provide them with exhaustive and comprehensive information on the surgery, its effects, and its follow-up – and then to wait for their freely made choice and decision.

Some would argue that – at both a personal level and being a member of the sick child’s family – candidate donors may feel “obliged” (for psychological, moral, and relational reasons) to give a part of their liver to save the life of their child. On a conceptual level, a consent given “under duty” is not ethical, as autonomy consists of being able to choose freely, under no pressure or obligation. On the other hand, also on a conceptual level…, how many of our human choices are really completely “free”? Are they not taken under the influence of emotions or ideas, or are they simply being dictated to by a feeling deep inside that this is “the right thing to do”? Aren’t most important decision in our lifes taken within the context and the feelings of the moment, with an important contribution of our past personal history and our previous experiences? Should we regulate these feelings – that make us human and willing to help others first – and demand on the contrary to have all decisions made only with “cold blood”, logic and rationale calculation?? We all know that if one sees their child sitting in the middle of the street, or on top of the roof, or even within a burning house, nothing in the world would stop us from going to save them in spite of all the danger? It is a natural reaction of all fathers and mothers that when their children are in need, they choose to help them, no matter what. It is not a question of the donor feeling “under pressure” by the threat of the death of the child: there is definitively a huge pressure. But in the very same moment that they understand that living donation may save their child’s life, they make their decision based upon their own free will and by a natural choice (Fournier et al. et al., 2008; Gateau, 2010).

Although very instinctive and immediate, it is actually a free and well aware choice that it is not to rethink all the time. There is no way to change that, even though sometimes donors would say that the decision is for them, both a very clear “no-other-choice” and also much of an inevitable reality at the same time. By the moment the family know about the possibility, it is often clear for them that it is also the way to move forward (Fournier et al. et al., 2008; Gateau, 2010).

In fact not telling about this alternative to parents, or refusing access to it with no valid reason, could be seen on the contrary unethical and inadequate caring. Is it not true that by allowing parents to save their children’s life means at the same time one in fact definitively and fully respects the ethics and the autonomy? The medical team will, in full knowledge, watch over and supervise these emotional re-actions, trying to channel and control the natural impulsiveness of candidate donors, and to tactfully help them to focus on their choices, and to freely and rationally confirm to them, with a clear conscience and no impulsiveness (Fournier et al. et al., 2008; Gateau, 2010). In the past, a living donor transplantation was rarely considered to be an option in cases of great emergency (fulminating hepatitis, oncological problems); this allowed one to avoid situations where the threat of immediate death really did put a major pressure on parents who had to answer within a very short time window (often in less than a day). Voices are currently emerging to consider a living donation, even under these circumstances, as it can be the only life-saving alternative in some cases and in some countries (Reding et al., 2008; Rosen et al., 2015). In Italy, a living donation for emergencies is not authorised by law, as these patients are, in fact, entitled to the highest level of priority for the allocation of a liver graft on a National Level; but a donor is not always available in time even with such a high priority.

Laws and regulation by law are different between countries. In France and Italy for example, the process is relatively complex: the time for assessing a candidate donor can take between 3 weeks to 3 months: It may seem relatively long but on the other hand this allows for avoiding too rapid or impulsive decision by the donor. Also the way the process (selection, assessment than the preparation of a candidate donor) is organised by the transplant team must be in a way to prevent impulsive decision. If setup adequately, the process entails repeated contacts, with a series of different interlocutors (including several external experts) and under the supervision of coordinat-ing nurses, as well as repeated contact with different doctors of the group. Last, the processus concludes with a series of external verifications (quality commission and respect of procedures), and interviews with the candidates (third party, judge). Moreover, all of the candidates are requested to confirm their decisions over and over again during the course of the preparation process: a candidate who feels “forced”, would not show the required determination (to undergo all of the tests, and to keep in good health); this with the unwavering will, to get prepared for the intervention (which may mean losing weight and to quit smoking), and to always remain present and close to the child, to be active within the family, and to be calm in the interactions with the team.
C – The Principle of Justice

Within the Ethics of Organ Donation, the concept of “Justice” primarily concerns the protection and the safeguard of the donor’s interests.

The majority of candidates for transplantation, who are waiting for an organ from a cadaveric donor, face the problem of an increasing paucity of organs when compared to the actual demand. In this scenario, the organ from a living donor adds to the usual supply of organs, and thus, in a way, the whole of society takes a benefit from this donation. However, often, donors do not receive anything from society in return, eventhough the operation exposes them to a degree of immediate physical and socio-economic risks (absence from work, or sick leave, and direct and indirect costs related to the hospitalisation and rehabilitation). The latter collateral effects are not present, or not the same magnitude, when the recipient can benefit of an organ from a post-mortem donor. Not to speak about the possible long-term consequences, if any, for the health of the living donor, or the economy of the family.

It is clear that a donation is a free gift and that there is no payment in any way for the graft that is donated (as it is commonly for blood donation), nor is there any remuneration for the organ donation itself. But is it fair that living donors and their families do not get any compensation of any kind, including for socio-economic losses, directly caused by the intervention, or for long-term morbidities, that could be a consequence? Would it not be fair to provide for some sort of compensation covering complications and medical costs related to the organ procurement surgery? Many voices have emerged, for many years already, to make the living donation a “financially neutral” processus for the donor’s family (Fournier et al. et al., 2008; Gateau, 2010; Delmonico et al., 2015; Delmonico et al., 2002; Guide de prise en charge financière des donneurs vivants d’éléments du corps humain). Compensation would represent a just and necessary protection for the donor’s family, covering all medical costs and possible revenue losses sustained by the donor. It could also be extended to cover sequelae or even the risk of death, as was provided for in an old resolution of the European Council (Resolution n. 29 of May 11, 1978), which has still not been executed in most European countries.

Discussion

With the development of living donor programmes in many expert paediatric centres, it has been shown that more than excellent results can be achieved: not only is the risk of the recipient’s death before the transplantation much reduced (coming close to zero), but also, the long-term results are excellent (at least equal, and often superior in some aspects, when compared to conventional transplants).

The very ethics of a living donor transplantation may be the “how” to do it, not to regulate it, or to negate the opportunity. On the “how” to do side, the process has been specifically and precisely paved by the Legislator to ensure the absence of a possible effect of a conflict of interest from the hospital. That is not to say that teams that are providing this type of service, must have a high level of care, and an obsession for the search of quality: their setting-up of a living donor programme is rich in complex procedure descriptions and protocols of care, and they must work through multidisciplinary and multi-professional networks (Fig. 5).

Historical Background

The pilot study performed by the Broelsch team in Chicago in the late eighties (Broelsch et al., 1991) eventually opened the real story of a living donation for paediatric liver transplantations; this trial was set-up after a fully comprehensive analysis and an in-depth ethical discussion and approbation (Singer et al., 1988) – and was realised with an “all-along” dedicated attention to not deviate from the first-line objectives (no-detriment to the donor + a benefit for the recipient). This included a detailed analysis of the technical aspects and of a modification during the trial. In a few words, all of the concepts that founded this trial have definitively established the methodology and are still valid today. It is of a value to re-read the setting and the performance of this trial, which is exceptional within the area of medical development and progressive history. The success of this study led to the acceptance of that procedure and its rapid expansion throughout the world.

Immediately, the first results showed an improved outcome in terms of graft and patient survival: both the quality of the graft and the strategical advantages (earlier planning in the progression of disease, the elective operation, and the patient’s preparation) were pointed out as eventually contributing to this more beneficial immediate outcome. Also, the possibility of a better immunological match, when a parent was the donor, was also considered a potential long-term benefit, in terms of a lower chronic rejection or a late graft loss rate – and that had yet to be demonstrated.

Twenty five years later, results confirm that a living donation is the key for the survival of children with end-stage liver diseases in countries where a post-mortem donation remains absent, or exists at extremely low rates, where the living donor option allow allocating a large number of grafts to small children. Even in countries with relatively high donation rates, children may not have access to all donors in an equal manner as adults, as it happen when the allocation system differentiates the allocations to adults and to children. In such countries, the balance between both allocation routes is not always easy to balance and to maintain in an equal manner.
Figure 5. A schematic view of the clinical, administrative, and legal components of the candidate donor assessment, and of the living donation pathway as used at the Bambino Gesù Children’s Hospital, Rome.
In many countries, the increasing organ shortage combined with the shift towards much older donors and procurement after cardiac death has significantly reduced the number of grafts that can be allocated to children. Hence, in few European systems, the latter imbalance has been re-adjusted by enforcing the priority of liver splitting and giving to paediatric centres the decision of splitting. In these conditions, the alternative of proposing living donation also can contribute positively to offer a chance to all children.

Importantly, the safety procedure for the procurement of the left lobe of the liver (left lateral segment) for the donor has been confirmed in many expert centres (Darwish et al., 2006; Gurevich et al., 2015; Kasahara et al., 2013). This is the result of both a strict selection of optimal donors, a systematic multidisciplinary approach and work, and optimising the procedure, technically speaking. On the donor side, morbidity remains low – no major complication was observed. On the recipient side, excellent outcomes have confirmed the transplant benefits (early and late good outcomes) even compared to conventional transplantations (superior graft and patient survival and lower overall complication rates)(Darwish et al., 2006; Otte et al., 1998; Reding et al., 1999; Gurevich et al., 2015; Rodriguez-Davalos et al., 2014; Tessier et al., 2014; Lobritto et al., 2012; Kasahara et al., 2013).

“Watchdogs” of the Ethics in a Clinical Practice

In a clinical practice, the Law, and a high standard of clinical care, are the “watchdogs” of the respect of Ethics.

1 – Information and Consent

Proposing living donor transplantation as an optimal or a better therapeutic solution would not be not ethical. On the other hand, not mentioning this possibility would not be ethical either: physicians are expected to not omit any available and valuable therapeutic options. In a transplant centre, where living donor transplantation is performed routinely, families are usually informed about the latter option, even before the first information session takes place. This usually goes through their contacts with other families of hospitalised children, who have been either transplanted or are waiting for a transplant. The work of the medical team may thus, consist of providing all of the details about the procedure, and answer the questions of the family, rather than informing parents who do not know anything about it. It is however crucial that the medical team verify that all of the families understood well all issues, checking that the information that they have received from other sources is accurate to their situation, and is complete and precise. According to the previous knowledge of the parents, a complementary or comprehensive information must be given in a «neutral» way. For those who already know much about living donation, it is important also checking that they fully understand that a living donation is only one of the available options that they can be offered – with access to a post mortem donation always being the standard of care. This approach seems to fully respect the autonomy of the potential donor, and be compliant with the ethics that are required.

Respecting the donor’s autonomy, obtaining their consent after clear and exhaustive information about the risks of the procedure, performing a comprehensive medical evaluation, selecting only those donors that are at a minimal risk, and also ensuring the safest and the best possible conditions for the surgery, are all indispensable factors, ethically speaking – but are they enough? Many issues must be discussed with the parents, not only the process of donation, but also, what are the potential benefits. The latter information may have a direct contribution to the family choices, and ultimately, to the decision of a potential donor. It would seem unethical to not deliver such information:

- the actual condition of the recipient, the stage or end-stage of the actual disease, and the predictable prognosis in the short term (including the risk of death while waiting on a waiting list);
- the very results of the caring surgical team in transplanting either split grafts, or living donor liver grafts, in order to give the family a clear perspective of what they can expect from the transplantation itself, independently of the donation;
- the benefits of avoiding a long wait, and thereby limiting the complications before the transplantation, and by anticipating the timing of the surgery date, by allowing for the medical preparation of the recipient, and for the transplantation to be in elective conditions.

The information is provided to patients both through meetings and various informative documents. The potential risks for the donor are clearly outlined, and the outcome— including the risk of failure or complications – are explained in detail. Donors are explicitly informed that a left liver lobe donation entails a risk of death estimated at 0.1% (Vancouver Conference – September 2005).

Time wise, meetings with the parents and the delivering of information starts in the early phase of assessing a candidate for transplantation; first, comes information about the disease and the prognostic of the child; then the therapeutic alternatives and the transplantation as a life-saving option; next, meetings and interviews will be recurrent throughout the process of assessment and the preparation of the recipient, in order to give families all the necessary time to think things over. At some point during this timeline, if the parents are interested, and ask for it, the process of a candidate donor assessment can start in parallel.

Repeated contacts with the different members of the team, and meetings with external interlocutors, and with Control Committees, allow for ensuring that the donor’s decision is free, aware, and autonomous. Another impor-
tant aspect in defence of the donor’s autonomy is that they know explicitly that they can change their mind and give up the project, at any stage of the process, even at the very last moment. Overall, the consent of the donor is a “many-step” pathway during which the donor will repeat and confirm several times, including in front of external auditors and a judge, his free and informed decision making.

2 – The Procedure Provided by Law and the Control Committees

A living donor liver procurement is subject to strict legal provisions, defining precise rules, obligations, and administrative steps, in the selection and the evaluation of candidates. Organ retrieval for transplantation purposes represents an exception to other laws providing for the inviolability of the human body, and in doing so, prohibiting the performance of surgical procedures, which are not directly related to the care of clinical conditions or diseases. The Declaration of Istanbul, the European Council, and the Oviedo Convention, calls on governments to ensure the protection and safety of living donors (Convention pour la protection des Droits de l’Homme et de la dignité de l’être humain; Protocole additionnel à la Convention sur les Droits de l’Homme et la Biomédecine, 2002; Statement by the Committee of Ministers on the prohibition of any form of commercialisation of human organs, 2014; Council of Europe, 2009).

In Italy, the candidate selection process is strict and precisely regulated and entails a series of control filters, external to both the medical and the transplantation teams (Figure 5): firstly, a donor’s meetings with several external experts (physicians, psychologists); interventions of the Third Committee (Multi-Disciplinary Meeting, Medical Committee, Third Party); and the donor’s interview by a Judge in the Court. Furthermore, the surgical procedure needs to be formally authorised by the competent regional authorities (healthcare and transplantation), which demonstrates how the legislator’s priority is deemed to protect the interests of the donors, respect their autonomy, and assess their freedom of choice. A similar approach has been set up in France (Agence de la Biomedecin, 2009).

There is no other way to run a living transplant programme than by respecting the letter and the pathway as defined by law (Fig. 5). In addition, the National Transplant Centre is in charge, as deemed by law as well, keeping track of all living donor transplant activity, through a National Registry, collecting the relevant information and the outcomes.

3 – Good Medical Practice in Real Time

It goes without saying that the medical team represents, in many aspects, a major self-screening and filter throughout the whole process, as well as being the main guarantee for the overall quality.

Proposing living donor liver transplantation in small children obviously requires that first of all, the centre is able to offer a high success rate both for donors and for the recipients. Such a project should be considered and proposed only after having acquired a wide experience in hepatectomy and paediatric liver transplantation, with optimal outcomes.

The surgical team being able to present excellent clinical outcomes in the classical transplantation techniques of a left lobe split liver transplantation (from cadaveric donors), and a graft survival rate of > 90% at a one year follow-up, seems to be a necessity and an adequate guarantee for starting a living donor programme.

A candidates screening must be strict, neutral, and accurate: the fact that parents wish a living donation at any price, and insist that they make themselves available as candidates, although they may have health issues, needs attention: pressure placed on the team would also be unethical. Candidate donors need to be in excellent health and present themselves with no particular surgical risks – this, with no exception. Obesity and heavy smoking, a congenital disease, or an active clinical condition, are an exclusion criteria. An accurate anatomic evaluation should also be performed, in order to detect any peculiar cases of complex anatomy, which may compromise the quality of the surgery, and cause sequelae for the donor. Frequently, when both parents propose themselves as donors, in this case, the selection is made based upon the most favourable anatomy.

On a technical level, a left liver procurement in an adult is associated with a low risk of severe complications or sequelae, if the surgery is performed by an expert surgeon (Darwish et al., 2006; Otte et al., 1998; Reding et al., 1999; Gurevich et al., 2015; Rodriguez-Davalos et al., 2014; Tessier et al., 2014; Lobritto et al., 2012; Kasahara et al., 2013). However, it is a complex and delicate procedure, and is different from a simple resection, as the retrieved liver lobe needs to be vital associated with a low risk of severe complications or sequelae, upon the most favourable anatomy.

On the technical level, a left liver procurement in an adult is associated with a low risk of severe complications or sequelae, if the surgery is performed by an expert surgeon (Darwish et al., 2006; Otte et al., 1998; Reding et al., 1999; Gurevich et al., 2015; Rodriguez-Davalos et al., 2014; Tessier et al., 2014; Lobritto et al., 2012; Kasahara et al., 2013). However, it is a complex and delicate procedure, and is different from a simple resection, as the retrieved liver lobe needs to be vital for the subsequent transplantation. When performed properly, the liver function is not compromised and quickly gets back to normal.

On the recipient’s side, these grafts are small in volume and mass, which is precisely what they need (most are infants or small children); more importantly, the function of the graft is excellent as a result of short ischemic time and of the perfect health of the donor. Functional resumption and technical results of the procedure are excellent, with a very low technical complication rate in the hands of an expert, as well as in the long-term outcomes (comparing favourably, in expert centres, to those of conventional transplantation).

4 - Audit and Revision of Practice: A Permanent Need

Regularly and continuously re-assessing results and practice is crucial: short-term and long-term follow-up registers of living donors and recipients are in place in Italy (CNT – Centro NazionaleTrapianti), and in Europe (Euro-
pean Liver Transplantation Register – ELTR). This data represents a scientific basis for the analyses of living donor transplantation outcomes, as well as being a reliable quality control system.

It is, however, necessary to regularly reassess the outcomes and the practice at the level of each centre itself, in order to confirm the quality level and to the continuation of the project. In a permanent search of excellence, and of the need for improving pathways, the process of prospectively assessing clinical practice and the updating of protocols, approaches, and strategies, on a regular basis, allow to keep patients on the safe side, and therefore, anticipate any problems.

5 – Analysing Clinical Results: A Necessity to Confirm the Eligibility of the Centre

With the recent development of a living donation liver transplantation programme at the Bambino Gesù Children’s Hospital in Rome, a strategy combining both approaches for donation (post-mortem and living) was set-up with the intention of offering a better cure option to children. The results and the advantages of such a strategy are now confirmed. Starting September 2011 until now, a total of 123 candidates for a living donation were assessed: only 32 were considered adequate for a living donation, which confirms the strict process of selection, with only ¼ of the candidates being selected for the procedure. Information to the families is given through a general information leaflet, although many families know about that possibility before they receive information from the centre (either from Internet reading, or from contact with other families in the hospital, or others). The set-up of the assessment process is divided into successive steps, starting with a very simple and straightforward initial assessment, through which the essential contraindications are pointed out (compatibility contraindication, pre-existing disease, major extrahepatic problems, abnormal liver tests, or serology, obesity, pregnancy, and a major anatomical change). Further steps include more of an invasive assessment as well, as are external specialist opinions. The last steps consist of obtaining the acceptance or the authorisation from several multidisciplinary groups, or local and/or regional committees, and a legal (judgement) approval (Fig. 5). The whole process is run through a period that is never less than 2 weeks and can culminate in a few months time, giving each family enough time to rethink their options a few times.

These 32 positive selections of candidates allowed for 32 liver transplantations performed during the last 40 months; none of the candidate donors changed their opinions during the process. These 32 transplants represent 26% of all liver transplants performed at the centre, but represent, in fact, 45% of the transplantations done contemporaneously. With a 100% survival for both grafts and patients, the living transplantation programme compares well with the conventional graft programme – where graft and patient actual survival rates are both 96% for comparable conditions (first isolated liver transplants).

All of the recipients that were prepared and listed for a living donor transplant had reached the time of the operation, even though some had complex and advanced clinical conditions, and severe health problems to deal with, while the donors were assessed and prepared. In comparison, of the 90 patients who have been listed by our centre until now, on the national waiting list for an elective transplant (code status on list “2” or “3”), from a post-mortem donor, 4 died from the progressive worsening of their condition, or from an acute complication occurring while waiting. The overall figure of 4 pre-transplant deaths out of a total of 122 candidates for transplant (3%) is a satisfactorily low rate – even one aims at zero. In fact, we believe that it shows that running both programs (living and conventional), in parallel, in recent years, has been successful in terms of giving the best equal access to transplantation, and an optimal outcome for all patients. It is clear that, for those who could not benefit from a familial donation (because of parental choices or contraindications), the fact that close to 50% of the candidates went (in the same period of time) through the living donor programme had the effect of decreasing the waiting time being allocated a conventional graft for the other patients, and of lowering the risk of clinical deterioration before the transplantation.

Overall, both on a theoretical and observational basis, the results of a strategy consisting of a double program running in parallel –offering both a living and a conventional graft allocation- seems to be beneficial to all recipients. Furthermore, it has the major advantage of offering an alternative to parents, and thus, freely allowing them to have a choice between a conventional program and the living donor option. This is an overall win-win situation; not only does it consolidate the ethical need for a free alternative, with no pressure on the families, but offers to the whole cohort of candidates for transplantation, a benefit in term of access to the transplant procedure (even for those who are already listed for a conventional allocation). This is not to speak about the added benefits of gaining technical expertise, by all specialist teams involved in such a complex process, and by specialising in the living donor liver procurement and the management of the recipients. The experience gained with such procedures also contributes to a better performance for conventional transplants.

Conclusion

With a persisting organ shortage, and a progressive change in donation patterns, the imbalance between the offer and the demand for a liver graft to care for children, is rapidly worsening. A donation of the left part of the liver from
a living donor is an alternative; it represents a potentially important source of a liver grafts, much adapted to the needs of those candidates of a paediatric age, as these are mostly very young and small in weight. The latter characteristics allows one to propose to the donor candidate, a procedure that is moderately “aggressive” anatomically and medically speaking. Additionally, this procedure has already been in use for a very long time, and thus helping to show that the risks are limited, and that the results for the child are excellent. Important benefit has been shown to be available for the recipient, and also the donor and the family (Fig. 6).

The teams choosing to propose this alternative to families for the transplantation in a child should be very aware that such programmes need a particular and a specific set-up and demand for constant attention, in order to maintain the right balance between the information and the pressure, knowing that any coercion would be strictly unethical. In order to maintain the right balance, a large component of the pathway, for the selection of the candidate donor, must be external to the transplant team directly – and in particular – the many steps that are important in the final decision making (Fig. 5).

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