Extended criteria for organ acceptance. Strategies for achieving organ safety and for increasing organ pool

There is a growing disparity between the demand for and the supply of organs for transplantation. In the last decade, the annual rate of cadaveric donors has been relatively stagnant in most western countries (Fig. 1), while the number of patients on waiting lists, the median waiting times, and the patients who died while on the waiting list for transplantation has considerably increased, and goes on growing. Moreover, many patients who can benefit from a transplant are not in the waiting list because of organ shortage, for heart transplant is higher than three times the patients on waiting list (1, 2). In 2001 in the United States, there were 6081 cadaveric organ donors; 24 076 solid organ transplants; 84 798 registrations on the waiting list at the end of the year and 6124 people who died while waiting (3). Moreover, about 100 000 potential candidates for transplantation die before they are placed on a waiting list (4).

The main goal in transplantation medicine is to provide a successful transplanted graft to all patients who can benefit from it. In the European Union and the United States, 10–30% of patients on waiting list for a heart or liver transplant die before obtaining the graft, and 40% for lung transplant (1). In USA, patients entering the liver waiting list at the highest medical urgency, status I patients, have more than a 12 times higher risk for death while on the list compared with those entering at the lowest two medical urgency categories (5). And the mortality rate of heart transplant waiting list for status I is about 45% (2). In Scandinavia in 1990–2001, 27% of patients listed for a highly urgent liver transplantation did not get


Abstract: The terms extended donor or expanded donor mean changes in donor acceptability criteria. In almost all cases, the negative connotations of these terms cannot be justified. Factors considered to affect donor or organ acceptability have changed with time, after showing that they did not negatively affect graft or patient survival per se or when the adequate measures had been adopted. There is no age limit to be an organ donor. Kidney and liver transplantation from donors older than 65 years can have excellent graft and patient actuarial survival and graft function. Using these donors can be from an epidemiological point of view the most important factor to establish the final number of cadaveric liver and kidney transplantsations. Organs with broad structural parenchyma lesion with preserved functional reserve and organs with reversible functional impairment can be safely transplanted. Bacterial and fungal donor infection with the adequate antibiotic treatment of donor and/or recipient prevents infection in the latter. The organs, including the liver, from donors with infection by the hepatitis B and C viruses can be safely transplanted to recipients with infection by the same viruses, respectively. Poisoned donors and non-heart-beating donors, grafts from transplant recipients, reuse of grafts, domino transplant and splitting of one liver for two recipients can be an important and safe source of organs for transplantation.

Key words: aging donor – bacterial infection – domino transplant – extended donor – hepatitis B virus – hepatitis C virus

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the graft and 16% died without transplantation (6). The so-called marginal organ donor offers the only possibility for living to many patients with a severe clinical status with urgent need for transplant or those potential recipients who would have never obtained a transplant due to their clinical characteristics in the face of the universal problem of organ shortage. For heart transplantation, alternate list recipients who receive ‘non-ideal’ graft can provide the most important source of the increasing heart transplant rate and alternate elderly recipients can have the same short and medium survival rate as the elderly who are transplanted on the regular list with ‘ideal’ grafts (7, 8). Waiting time on dialysis before transplantation is quantitatively one of the largest risk factors for graft loss after kidney transplantation (9). A functioning kidney graft is substantially more efficient than the best of dialysis. The classically so-called marginal kidney donors have shown a substantial increase in life expectancy for their recipients, a substantial improvement in quality of life and a cheaper cost compared with those who are wait-listed kidney transplant candidates and doing dialysis (10).

The terms extended donor or expanded donor mean changes in donor acceptability criteria. In almost all cases, the negative connotations of these terms cannot be justified. Factors considered to affect donor acceptability have changed with time, after showing that they did not negatively affect graft or patient survival per se or when the adequate measures had been adopted. The term ideal organ should imply an integral concept that involves donor and recipient characteristics and all the procedure performances between both, the organ procurement procedure, allocation scheme and transplant; it should be gauged by how it can adapt and safely maintain adequate function in the recipient. Similar patient and graft survival can be obtained with these so-called marginal organs or donors compared with the classically so-called ideal when the adequate management strategies and allocation scheme are adopted.

**Cadaveric organ procurement process**

The adequate selection and evaluation of cadaveric donors and of organs for transplantation should be performed within a context of the adequate fulfillment of the prior organ procurement phases: early identification of potential donors, early diagnosis of brain death, and early, close and strict physiological maintenance of the donor. The procurement of the greatest number of viable organs requires excellence in each of the phases. The
results of inadequate maintenance are loss of donors, loss of organs for transplantation, functional and structural alteration of organs transplanted, an increase in the morbidity-mortality of the recipient, and a reduction in the actuarial graft and recipient survival (11). Early and aggressive physiologic support in the maintenance of potential donors can reduce organ donor loss due to irreversible asystole or multiorgan failure to absolute zero (and it is almost always possible to maintain a correct organ perfusion pressure in all the donors) (12) and can increase the number of organs retrieved and transplanted per donor without increasing post-transplant morbidity or mortality (13, 14). Using catecholamines or desmopressin does not generally alter function or survival of the graft (15–18), and its combined use is usually the only way to obtain prolonged organ donor maintenance with adequate organ perfusion and good organ function (19). Short and long-term kidney graft survival and function are not negatively affected by prolonged organ donor maintenance. The main concept is obtaining a correct hemodynamic and hydro-electrolitic donor status (20).

Absolute contraindications for being an organ donor

There are a few absolute medical contraindications for being an organ donor: those whose donor-recipient transmissible agents can provoke the death of the recipient or a severe disease. Extracranial cancer with the capacity to metastasize and which is not considered to have been cured (21, 22). Creutzfeldt-Jakob disease and diseases caused by other prions such as kuru, Gerstmann-Straussler-Scheinker syndrome and fatal familial insomnia syndrome, or patients treated with human pituitary-derived hormones (23, 24). And infections: human immunodeficiency virus (HIV); active, disseminated and invasive infection by virus, microbacteria or fungi; and systemic infection by methicillin-resistant staphylococci (25–29).

The presence of an active malignancy is an absolute contraindication to organ donation. Nevertheless, low-grade skin cancers, such as basal cell carcinoma and many squamous carcinomas; carcinoma in situ, uterine and cervix; and primary brain tumors without extracranial metastases, do not preclude organ donation (30–34). Additionally, patients with previously treated malignancies after 5-yr disease-free interval can be considered as cured. UNOS’ report on 257 donors with a past history of cancer resulted in 650 organ transplants and indicated that there were no instances of donor tumor transmission after a mean follow-up time of 45 months (32), and an update of that data included 488 donors with a past history of cancer that resulted in 1276 organ transplants with the result of no cancer transmission donor-recipient (34).

Thoracic and abdominal cavities and all the organs not used for transplant from all the organ donors, without exception, should be meticulously revised for solitary masses or lymphadenopathy during and after retrieval to discard malignancies. Donors with a prior history of malignancies or with primary brain tumors or with an intracranial mass or hemorrhage of unclear etiology should have a complete autopsy performed on conclusion of the organ procurement process (30, 31, 35).

Absolute contraindications for using an organ for transplantation

The criteria which exclude a specific organ from use in transplantation are broad structural lesion or permanent and severe functional deficit or the active infection of organ parenchyma in which the organ is unlikely to function or which can provoke by itself a high risk for the life of the recipient. Every organ should be evaluated independently, and the discarding of an organ does not invalidate the use of other organs from the same donor, whether anatomically distant or adjacent, when these are free of lesions; for example, unilateral pneumonia or trauma does not preclude donation of the contralateral lung (36).

The percentage of discarded brain-dead heartbeating cadavers for organ donation due to absolute medical contraindications can be < 7.5% (Table 1).

Donor age

There is no age limit to be an organ donor. The key concept for organ acceptance is defined by the functional and structural state of the organ subject to removal and transplantation. The lowest number of retrieved and implanted organs per donor is directly related to highest donor age with brain anoxia due to cardiac arrest (37) (Table 2). Older donors have a higher incidence of generalized chronic severe arterial lesion, hepatic and lung arteries not usually being affected due to the fact that these vascular systems are low-pressure systems, and a higher incidence of lesions of parenchyma such as fatty liver and multiple simple cysts of kidneys. Moreover, they have a significant incidence of unknown cancer, usually kidney and prostate cancer, which can be evidenced during organ retrieval (Table 3). Older donors have a higher prevalence of hypertension and diabetes mellitus, frequently of long-standing course.
Primary hypertension and diabetes mellitus affect 25 and 6% of the US adult population, respectively (38). In the USA from 1995 to 2000, 18.5 and 2.9% of cadaveric kidney donors were hypertensive and diabetic, respectively (39), and in 2000–2001 the figures were over 23 and 5%, respectively (14); in Spain during 2000, 20 and 6% of the cadaveric organ donors were hypertensive and diabetic, respectively (40). The target lesion for both diseases is the arterial vascular system and the vascular system inside organ parenchyma, specially of kidneys and heart. Well-treated while alive hypertensive and diabetic donors can have minimal arterial and parenchyma lesions, and can donate any of their organs with good transplant results. Pre-existing donor hypertension and diabetes mellitus can exert only a modest negative effect on several transplant outcomes (38). Longstanding donor hypertension can exert a strong negative impact on kidney post-transplant outcome, delayed graft function and graft function at least up to 1 yr, in cases of important histologic lesions (41). For diabetes mellitus, other authors with a more precise analysis did not find any short and long-term graft and patient survival differences with kidneys from diabetic donors compared with kidneys from non-diabetic donors (42).

Kidney transplantation from cadaveric older donors can have excellent graft and patient actuarial survival and graft function (43, 44). There is correlation between donor age, glomerulosclerosis and fibrosis, but the proportion of glomerulosclerosis in the biopsy does not correlate with either short- or long-term graft function or graft survival (45), and severe glomerular sclerosis of kidney grafts can have similar rates of delayed graft function and 2-yr graft survival to kidney grafts without glomerular sclerosis (46). Our results with single grafts from donors aged 60–87 yr with calculated creatinine clearance above 55 mL/min

Extended criteria for organ acceptance

Table 1. Brain deaths non-potential organ donors. Hospital de la Santa Creu i Sant Pau (HSCSP) 1994-2001 (471 total brain deaths)

<table>
<thead>
<tr>
<th>Cause</th>
<th>n (%)</th>
<th>% total brain deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracranial cancer</td>
<td>19 (54.2)</td>
<td>4</td>
</tr>
<tr>
<td>Severe structural damage of retrievable organ</td>
<td>12 (34.3)</td>
<td>2.5</td>
</tr>
<tr>
<td>Chronic hepatobiliary diseases</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Acute multiorgan failure (post-extracorporeal circulation)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>4 (11.4)</td>
<td>0.85</td>
</tr>
<tr>
<td>HIV(+) or sexual promiscuity and homosexuality</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>HCV(+) and parenteral drug abuser</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Endocarditis with multiple septic metastasis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Table 2. Cause of brain death and organs generated/implanted from the 363 actual organ donors aged 0–90 yr old. Hospital de la Santa Creu i Sant Pau 1994–2001

<table>
<thead>
<tr>
<th>Cause of brain death</th>
<th>&lt;15 yr OG-d/OI-d (n)</th>
<th>15–50 yr OG-d/OI-d (n)</th>
<th>50–65 yr OG-d/OI-d (n)</th>
<th>&gt;65 yr OG-d/OI-d (n)</th>
<th>Total OG-d/OI-d (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT</td>
<td>4/3.6 (17)</td>
<td>4.5/3.9 (59)</td>
<td>3.3/2.8 (12)</td>
<td>3.1/2.2 (17)</td>
<td>4/3.5 (105)</td>
</tr>
<tr>
<td>SAH</td>
<td>4/8.4 (4)</td>
<td>3.6/3.1 (11)</td>
<td>3.1/3 (9)</td>
<td>4/3.3 (37)</td>
<td>3.2/2.3 (25)</td>
</tr>
<tr>
<td>BI</td>
<td>4/3 (3)</td>
<td>3.7/3.3 (7)</td>
<td>3.2/2.2 (6)</td>
<td>3/1.7 (12)</td>
<td>4/3.1 (20)</td>
</tr>
<tr>
<td>ICH</td>
<td>4/8.4 (4)</td>
<td>3.6/3.1 (11)</td>
<td>3.1/3 (9)</td>
<td>4/3.3 (37)</td>
<td>3.2/2.3 (25)</td>
</tr>
<tr>
<td>Bi/Bt</td>
<td>2/1 (1)</td>
<td>2/0.5 (2)</td>
<td>2/0.5 (2)</td>
<td>2/0.5 (2)</td>
<td>2/0.5 (2)</td>
</tr>
<tr>
<td>BA</td>
<td>3.2/2.2 (4)</td>
<td>2.8/1.7 (15)</td>
<td>2.6/1.6 (12)</td>
<td>2.9/1.9 (37)</td>
<td>3.4/2.7 (29)</td>
</tr>
<tr>
<td>BE</td>
<td>4.5/4.5 (2)</td>
<td>2/0 (1)</td>
<td>–/0 (0)</td>
<td>3.6/3 (3)</td>
<td>3.6/3 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>3.8/3.4 (25)</td>
<td>4.2/3.7 (126)</td>
<td>3.2/2.5 (91)</td>
<td>2.8/1.6 (121)</td>
<td>3.5/2.7 (29)</td>
</tr>
</tbody>
</table>

OG = organs generated; OI = organs implanted; d = donor; BT = brain trauma; SAH = subarachnoid hemorrhage; BI = brain infarction; ICH = spontaneous intracerebral hemorrhage; Bi = brain infection; Bt = brain tumor; BA = brain anoxia; BE = brain edema.

Table 3. Non-effective actual organ donors in the HSCSP 1994-2001 (363 Total actual donors; average age: 51.7 yr ± 24.9, range:0.2–90 yr)

<table>
<thead>
<tr>
<th>Cause [Donor age: Average ± SD (range), years]</th>
<th>n (%)</th>
<th>% total actual donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe structural lesions [70.7 ± 9.2 (51–86)]</td>
<td>23 (49%)</td>
<td>6.3%</td>
</tr>
<tr>
<td>Arterial lesions [72.2 ± 7.4 (51–77)]</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Parenchyma lesions [69.2 ± 11(53–86)]</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Extracranial cancer [67.5 ± 12.9(35–82)]</td>
<td>12 (25.5%)</td>
<td>3.3%</td>
</tr>
<tr>
<td>Hypoperfusion or venous thrombosis [56 ± 12.7 (40–72)]</td>
<td>6 (12.7%)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Non-recipients from HCV(+) donors [76 ± 6.9(69–85)]</td>
<td>6 (12.7%)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

HSCSP = Hospital de la Santa Creu i Sant Pau.
(performed using their best creatinemia), including donors with hypertension and/or diabetes and without performing prior renal biopsy, to older recipients, were an actuarial graft survival of 87 and 81%, at 1 and 5 yr, respectively; and none of them was a never-functioning graft [43]. More recently, results with single grafts from donors aged 60–88 yr to recipients younger than 60 were 95 and 83%, respectively (44). Using double renal grafts from aged donors to one aged recipient does not improve actuarial graft survival (47) (Table 4). Similarly, older livers can be used safely (16, 48–52). The analysis from the Spanish Registry for Liver Transplantation for the period 1994–2000 (51) evidences that liver transplantation from cadaveric older donors aged 60–90 yr only had a slightly lower actuarial survival at 1 yr than livers from 15 to 60-yr-old donors, of 80% vs. 76–72% (60–69 and 80–89-yr old, respectively). At 5 yr, the differences in the actuarial graft survival between both groups were higher, 66% vs. 56–51%, respectively, but it is important to stress that recipients from older donors had more severe relapsing diseases, hepatocarcinoma and hepatitis C virus, than the recipients from younger donors (51).

Using cadaveric donors older than 65 yr has a spectacular major impact on the rate of organ transplantation. Although the number of discarded organs for transplantation from these donors is higher (37, 39, 40) (Table 2), using these donors can be from an epidemiological point of view the most important factor to establish the final number of cadaveric liver and kidney transplantations (39) (Table 5).

Heart transplantation from donors older than 60 yr does not worsen the medium-term outcome of the recipients (53, 54). The careful selection of older donors could make heart transplant with older hearts a safe option, even in older recipients (54). Lung transplantation from donors older than 55 yr does not worsen the medium-term outcome of the recipients (55). For lung transplantation, guidelines suggest that donor age should be less than 60 yr and with a smoking history of no greater than 20–30 pack-years; nevertheless, age and smoking criteria

Table 4. Renal transplant with graft from elderly cadaveric donor. Actuarial survival of the graft and renal function

<table>
<thead>
<tr>
<th>Cadaveric donors</th>
<th>Actuarial graft survival</th>
<th>Creatinemia recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First year</td>
<td>Third year</td>
</tr>
<tr>
<td>HSCSP-Fundació Puigvert, 1992–1997</td>
<td>Donor &gt;60 yr/CCC &gt;55 mL/min, $\bar{X} = 69$ [60–87]</td>
<td>87%</td>
</tr>
<tr>
<td>Transplantation 1998; 66:1159 (43)</td>
<td>Recipient: Single renal Tx.</td>
<td>n = 84; $\bar{X} = 57.8$ [16–71]</td>
</tr>
<tr>
<td>H. 12 de Octubre, Madrid 1996–1998</td>
<td>Donor &gt;75 yr or 60–74 &amp; GE &gt; 15%, n = 21; $\bar{X} = 75 \pm 7$ [61–89]</td>
<td>95%</td>
</tr>
<tr>
<td>Transplantation 2000; 69:2060 (47)</td>
<td>Recipient: Double renal Tx.</td>
<td>n = 21; $\bar{X} = 60 \pm 5$ [49-69]</td>
</tr>
<tr>
<td>Donor 60–74 yr, no GE &gt; 15%, $\bar{X} = 67.4$ [60–74]</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Recipient: Single renal Tx.</td>
<td>n = 40; $\bar{X} = 63 \pm 5$ [51–72]</td>
<td></td>
</tr>
<tr>
<td>HSCSP- F. Puigvert, 1993–1999</td>
<td>Donor&gt;60 yr/CCC &gt; 55 mL/min, $\bar{X} = 67.1$ [60–88]</td>
<td>95%</td>
</tr>
<tr>
<td>Transplantation 2002; 73:1673 (44)</td>
<td>Recipient&lt;60 yr: Single renal Tx.</td>
<td>n = 63; $\bar{X} = 52.6$</td>
</tr>
</tbody>
</table>

CCC = Calculated creatinine clearance; GE = Glomerulosclerosis; HSCSP = Hospital de la Santa Creu i Sant Pau; Tx = Transplant; $\bar{X}$ = Average age.

<table>
<thead>
<tr>
<th>UK + IR (62.88)</th>
<th>USA (268)</th>
<th>Spain (39.66)</th>
<th>Catalonia (6.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COD pmp</td>
<td>13.4</td>
<td>22.3</td>
<td>33.9</td>
</tr>
<tr>
<td>COD &gt;65-yr-old pmp</td>
<td>1.36 (5.8%)</td>
<td>2.79 (7.9%)</td>
<td>10.5 (31%)</td>
</tr>
<tr>
<td>(% over total cadaveric donors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadaveric kidney Tx pmp</td>
<td>23.0</td>
<td>33.5</td>
<td>47.3</td>
</tr>
<tr>
<td>Cadaveric liver Tx pmp</td>
<td>11.2</td>
<td>18.5</td>
<td>24.0</td>
</tr>
<tr>
<td>Heart transplant pmp</td>
<td>3.7</td>
<td>8.4</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Table 5. Cadaveric organ donors and cadaveric kidney, liver and heart transplantation per million population in United Kingdom and Ireland, USA, Spain and Catalonia. 2000

COD = cadaveric organ donors; pmp = per million population; Tx = transplant.
may be more flexible when a waiting recipient’s survival is precarious. Liberalized smoking criteria have resulted in comparable results (36); any kind of smoking history could be acceptable unless there is chronic obstructive pulmonary disease or pulmonary fibrosis on the chest radiograph (56). For pancreas transplantation, guidelines suggest that donor age should be less than 45 yr; nevertheless, using pancreas with good appearance in inspection after retrieval from donors aged 45–62 yr can achieve the same graft survival as pancreas from donors aged under 45 yr (17).

Chronic alcoholism in donors can mainly affect liver and heart, provoking chronic hepatopathy and/or myocardopathy, specially in heavy and long-standing drinkers. These organs should be adequately evaluated before and after organ retrieval to discard liver or heart pathology; additionally, a biopsy can be useful. After evaluation, livers and hearts from these donors can be valid for transplantation (57, 58).

**Organs with structural or functional lesions**

Organ anatomical anomalies are not a contraindication for use for transplantation: liver from donors with situs inversus (59), kidneys with multiple arteries, double ureters, ‘horseshoe’ kidneys, crossed non-fused renal ectopia, etc (60–62). All of these organs have been transplanted with survival rates equal to those with normal anatomy. Congenital short or injured (during retrieval) veins and arteries can be reconstructed (60). The rate of damage to kidneys at retrieval is high; most of the organs can be transplanted with no adverse effect on transplant survival (63). Localized structural arterial lesion, atheroma plaques and stenosis, can be surgically remediable and would let the organ be used for transplantation. Successful coronary artery bypass grafting at the time of heart transplantation has been reported (53, 64). Acquired and localized parenchyma lesion of lung, liver or kidney, such as simple cysts, hematoma around the organ, small laceration or urolithiasis can be adequate organs for transplantation, after the lesion has been inspected on the back-table and resected or repaired and if the organ has sufficient and undamaged parenchyma mass (60, 65–70).

Organs with broad structural parenchyma lesion with preserved functional reserve can be transplanted. Kidneys with chronic lesion (diabetic, focal segmental glomerulosclerosis, lupus or hemosiderosis) (71–76) or with acute lesion (nephropathy related to Hellp or Reye syndrome, rhabdomyolysis, or disseminated intravascular coagulation) (57, 77–82) transplanted in recipients without these respective diseases usually reversed their glomerular or tubular lesions in a few weeks or months, maintaining a good function and graft survival. Glomerular mesangial Immunoglobulin A deposits of renal grafts usually disappear quickly following transplantation (83–85), but some authors pointed out the risk that irreversible acute rejection might be greater in the recipients of such kidneys (83), this not being confirmed by others (84, 85). The prevalence of hepatic steatosis in liver donors is 9–26% (86) – only severe macrosteatotic (>60%) grafts have been associated with primary non-function, while donor livers with any severity of microsteatosis are not associated with primary non-function and do not influence graft or recipient survival – and is reversible (87). Donor livers with moderate macrosteatosis (30–60%) have a low risk of primary non-function (86), but livers with mild to moderate steatosis (<30%) do not have worse immediate function or graft survival rate than non-fat livers (16, 88). Liver or kidney graft from donors with autosomal dominant polycystic kidney disease can reach a good function and graft survival (89–92). Donor hearts with mild or mild to moderate left ventricular hypertrophy by echocardiography can be safely used, and the survival for recipients receiving these hearts from donors without an associated history of hypertension or long ischemia time are comparable to survival of recipients receiving optimal hearts. The left ventricular hypertrophy can potentially regress in the recipient, is more frequent in donor hearts with mild grade, and those donors who did not have hypertension or did not have electrocardiographic criteria of hypertrophy (93).

Reversible functional impairment of donor organs is not a contraindication for organ transplantation. Frequently, it is present before brain death. Elevated terminal creatininemia or a reduced terminal calculated clearance of creatinine in the organ donor is not a good predictor of the immediate and late graft kidney function or graft survival in the recipient (38, 57, 94, 95). Similarly, kidney grafts from donor with hepatorenal syndrome and very elevated terminal creatinine in serum, up to 11.8 mg/100 mL, recover good function after transplantation (96). Systolic myocardial dysfunction is common after brain-injury-related brain death, may be either segmental or global, and there is a poor correlation between the echocardiographic distribution of dysfunction and light microscopic pathologic findings (97). These hearts from young donors with mild to severe wall motion abnormalities and/or with low ejection fractions can recover normal function during organ donor
maintenance or improve shortly after transplantation, and they usually achieve the same function and graft survival rate as heart graft without wall motion dysfunction (98–103). Brain death can cause diffuse ST-T wave abnormalities that can mimic ischemia, and atrioventricular conduction delay: complete heart block or trifascicular block. These abnormalities are spontaneously resolved after transplantation (102).

Pulmonary edema is a frequent complication associated with brain death that can be resolved with the adequate management of the donor. Lung transplants from these donors have the same results as those obtained from ideal donors (104). In the face of a unilateral lung injury of any etiology and a PaO₂ < 300 mm Hg with FiO₂ of 1 and positive end-expiratory pressure of 5 cm of water, after clamping the pulmonary artery to the injured lung the PaO₂ often improves to > 400 mm Hg. The uninjured lung can be used for transplantation (105). Hyperglycemia and hyperamylasemia are frequent events observed in brain death in donors without history of diabetes. These two factors do not affect pancreas graft function or survival (17).

**Strategies for achieving organ safety and for increasing organ pool**

Organ safety for transplantation can be achieved by eliminating potential risk factors with treatment in donor and/or recipient or by selecting recipients who have the same agents as donors or have low prospects of developing an affection that was present in the donor.

Bacterial and fungal infections

A bacterial or mycotic infection or colonization can be present in 60% of cadaver organ donors and mainly affects the respiratory and urinary tracts, 15% with pneumonia and 10% with positive hemoculture. Cadaveric organ donors do not usually have fever; on the contrary, they are usually hypothermic. When they have fever, it begins many hours or days before brain death, then progressively decreases and lasts a few hours, and 24 h after brain death all of them are hypothermics. This fact is associated with the lesion events of the hypothalamic temperature-regulatory center. Similarly, hypotension is the rule in almost all organ donors, this being due to the irreversible and complete functional loss of the medulla oblongata cardiovascular center (106). Therefore, hypothermia, hyperthermia, and hypotension are not valid clinical parameters for evaluating the septic state of donors.

Bacterial and fungal donor-to-host transmission with the allograft with result of loss of the infected graft or death of the recipient has been widely documented (107). Nevertheless, the adequate antibiotic treatment of donor and/or recipient prevents infection in the latter (56, 108–121). In this context, recipients from these donors do not have different complications, and do not have more medical or surgical early or late complications, than recipients transplanted with organs from donors without infection, and both recipients present the same patient and graft actuarial survival rate (115–117).

In 1993, we established in our hospital a prophylaxis or treatment protocol to prevent or treat organ donor bacterial and fungal infections (122). Those potential organ donors with known infections before death went on specific or empiric treatment against causal germs during maintenance, and those without any infection were treated prophylactically with broad-spectrum antibiotics. Immediately after brainstem death, from all potential organ donors we always obtained samples of bronchial secretion, urine, blood and secretions from drainage tubes for culture before starting prophylactic antibiotic treatment. During organ harvesting, we obtained from those with pneumonia a lung sample for culture and a thoracic or abdominal sample from those with free collection in these cavities; after organ retrieval, all the tips of venous central catheter were cultured. Then, a strict surveillance of the different donor cultures was performed. All recipients received prophylactic antibiotic treatment for 3 d. In the face of a donor positive culture from blood, lung sample, catheter, or cerebrospinal fluid all the recipients of any organ were treated with specific antibiotic or fungal anti-causal germ treatment for 7–10 d. In the face of positive culture from bronchial secretion all lung recipients were treated, and with positive urine culture kidney recipients were treated. From 1994 to 1998 we had 199 effective actual organ donors that procured 622 organs for 596 recipients; 60% of donors had at least one positive culture for bacteria or fungus. In none of them was any bacterial or fungal infection transmitted from donor to recipient following the above-mentioned protocol.

**Hepatitis B virus and hepatitis C virus**

The organs, including the liver, from donors with infection by the hepatitis B virus (HBV) and C virus (HCV) can be safely transplanted to recipients with infection by the same viruses, respectively. Their use can also be considered in life-
saving transplantation for recipients not infected by HBV or HCV. In HBV naive recipients, effective vaccination against HBV before transplant can prevent HBV infection; similarly, preemptive treatment with HBIG and lamivudine can be effective.

More than 1% of potential organ donors have an active HBV infection (40, 123) and over 12% in hyper-endemic areas (124), demonstrated by a HBsAg-positive or Immunoglobulin M (IgM) anti-HBc-Ag positive serology, and from 3 to 4% have a past history of HBV infection in countries with a low prevalence like USA (125, 126), and over 10% in some areas of USA (127) or some European countries like Spain (123), and over 50% in HBV-hyperendemic areas like Taiwan (124), demonstrated by a positive Immunoglobulin G (IgG) anti-HBcAg and a negative HBsAg. Organs from HBsAg positive donor do not always transmit HBV infection to non-HBV-vaccinated HBV-negative recipients (109, 128), excluding liver graft. When the HBV infection occurs, the recipient can spontaneously clear the virus and turn to a negative HBsAg status, including liver graft (129). Prior recipient immunization, presence of anti-HBsAg positive antibodies after natural or post-vaccine immunity, or IgG anti-HBcAg-positive recipients are protected from HBsAg positive organs against HBV infection (124, 128, 130–132). Kidney or heart graft from HBsAg-positive donors to HBsAg-negative recipients does not have a higher rate of acute or chronic recipient hepatopathy or severe hepatopathy than kidneys or hearts, respectively, from HBsAg-negative donors to HBsAg-positive recipients, nor does it have a poorer graft and patient survival rate (124, 133). Kidney or heart graft from HBsAg-positive/anti-HBcAg-positive donor to HBsAg-negative/IgG anti-HBcAg-positive recipient does not become newly HBsAg-positive (124, 130, 134). Organs from HBsAg-negative/IgG anti-HBcAg-positive donor can transmit HBV infection to HBV-negative liver recipients at a rate of 22–100% (123, 135–139), and the risk can be dramatically reduced for recipients who have pre-existing antibodies anti-HBsAg or who were IgG anti-HBcAg-positive (123, 127, 131, 136, 138–141). Liver graft from HBsAg-negative/IgG anti-HBc-positive donor to recipients with HBV-related cirrhosis does not affect graft or patient survival, but they are 2.5 times more likely to develop HBV recurrence (142), although those recipients who receive preemptive treatment with HBIG and lamivudine do not develop HBV recurrence (140). In contrast to liver transplantation, with HBsAg-negative/IgG anti-HBcAg-positive donor, HBV infection is excep-tional with extrahepatic recipients who are negative for HBV (124, 126, 131, 132, 137, 143–146), and kidney recipients with a history of prior HBV infection or reported vaccination do not develop HBV clinical infection or seroconversion to HBsAg-positive (147). Moreover, isolated IgG anti-HBcAg positivity can have a false-positive rate of over 20% (137, 148, 149), the simultaneous presence of antibodies anti-HBsAg and histological findings consistent with cirrhosis or hepatitis on liver biopsy would strongly suggest that the result is true positive (1). Prophylactic regimen with HBIG, HBIG plus lamivudine, pre-transplant vaccination plus lamivudine or lamivudine alone can prevent HBV infection in naive recipients transplanted with grafts from donors who are positive for HBV, including liver transplantation (150, 151). HBIG and lamivudine treatment can prevent HBV infection in those naive recipients who are transplanted with grafts from donors who are HBsAg-positive or IgM anti-HBcAg-positive (137) or who are transplanted with a liver graft from donors who are IgG anti-HBcAg-positive (125, 138–141, 150–153).

Approximately 5% of all potential organ donors in USA and Europe are positive for antibody to HCV (154–156), and half of these are RNA-HCV positive by PCR (155, 156). Detection of antibody to HCV by serological screening of the donor is not predictive of HCV transmission to the recipient (102, 154–158). The consequence of receiving an organ from a donor who is positive for IgG antibody to HCV is: 50% of the recipients will have detectable antibody to HCV, 74% will have detectable hepatitis C viremia by PCR analysis, and 35% may develop liver disease (155, 156). Short and medium-term patient and graft survival for heart and kidney recipients with de novo HCV infection acquired with transplant has been similar to patient and graft survival with their matched cohort recipients without HCV infection (157, 159). Liver transplantation from an anti-HCV-positive donor to an anti-HCV-positive recipient does not seem to cause an increased morbidity or mortality in the liver recipient and they have the same graft and patient actuarial survival as when the graft was from an anti-HCV-negative donor (160–163). Those liver recipients in whom the donor HCV strain becomes predominant can have significant longer liver disease-free survival than recipients who retain their own HCV strain (161). Similarly, donor HCV status does not adversely affect short or medium-term outcomes in HCV-positive recipients in renal transplantation (164–166). Long-term experience with kidneys from HCV-positive donors that are transplanted to extended criteria for organ acceptance
HCV-positive recipients have shown that liver disease and graft and patient survival are not different than the results obtained transplantsing organs from HCV-negative donors to HCV-positive recipients (167). If HCV-positive kidneys were transplantsed into HCV-RNA-positive recipients, organ loss would be 0%, the transmission rate 2.4%, and the rate of new infection 0% (155, 156). Moreover, if it were possible to test anti-HCV positive donors by PCR and genotype match PCR positive donors and recipients, superinfection with a different strain could also be eliminated (155).

Poisoned donors

Transplantation of organs obtained from patients who die from intoxication with acetaminophen, amanita phalloides, barbiturates, benzodiazepines, butane, carbon monoxide, cocaine, cyanide, ecstasy, ethanol, ethylene glycol, isoniazid, lead, lithium, methanol, organophosphate, rodenticides (brodifacoum), thioridazine, trichloroethylene and tricyclic antidepressants has been performed without transmitting intoxication to recipients and without adding additional complications to the recipients compared with organs from non-intoxicated donors (57, 168–177), and without different short and long-term graft and patient actuarial survival compared with organs from non-intoxicated donors (57, 172, 176, 177). Thoracic and abdominal organs have been successfully transplanting from donors who were chronic consumers of ethanol or inhaled cocaine or marijuana, without affecting immediate and late graft function or short and long-term graft and patient survival (57, 169, 178, 179).

Two main considerations are necessary in all donors who die from poisonings. First, a specific assessment of the structural and functional lesions of the organs caused by the pathologies associated or concomitant with the cause of death. Second, it is mandatory to rule out possible organ structural lesions in progress in addition to the possibility of toxic action subsequent to the transplantation. This last phenomenon may occur when the toxic responsible for the death of the donor accumulates in the organ transplanted. For example, the transmission of intoxication due to tricyclic antidepressant has been described in the recipient of a liver from a donor who died from this intoxication (180). It is recommended to establish an interval between the ingestion of toxic and organ removal related to its specific metabolism to let the toxic be cleared and to assure that an organ such as heart or liver has not been affected (176, 177, 181).

Use of grafts from transplant recipients, reuse of grafts and domino transplant

Transplant recipients can be organ donors of any of their organs structurally and functionally well after death (182–186), even many years after transplantation (184, 186), without differences in the incidence of early or late rejection and with the same graft survival compared to the cohort of recipients whose donor had not been previously transplanted (183). The transplanted graft has been successfully reused a few hours or days after transplantation (185, 187–191), or even more than 2 yr after transplantation (182), or has been successfully transferred to another anatomical position many years after transplantation (192). Moreover, transplant recipients can be organ living-donors of their own therapeutically retrieved organs with successful transplant outcomes and without harmful effect on heart or liver donation; for example, the hearts donated by recipients of heart–lung transplants that are associated with an excellent early and longer-term outcome (193), and in United Kingdom comprise 7% of heart transplants (194); or the liver donated by recipients of liver transplants who were affected by familial amyloidotic polyneuropathy (195–197).

Splitting of one cadaveric liver for two recipients

Splitting the liver for transplantation into two adults is a further step toward the more efficient use of cadaveric organs. It should almost always be possible to identify two adult recipients, of different sizes, who can benefit from one donated liver (198). The split-liver technique can eliminate the need for obtaining a graft from a living related donor when a child requires liver transplantation, and the results obtained can be excellent (199, 200). In adults, when both the cadaveric organ donor and the transplant recipients are chosen carefully, split-liver transplantation can be safely performed without a delay in allograft function, increase in technical complications, or compromise in graft or patient survival (201).

In March 2001, the American Society of Transplant Surgeons and the American Society of Transplantation (202) jointly sponsored a conference to explore mechanisms for maximizing the cadaver-organ donor pool. These committee members concluded that there is adequate experience with adult/child splitting for an adult to argue that a split liver should be the first option for donors meeting the appropriate criteria for the split procedure. A national policy for splitting appropriate
donors into left lateral and extended right grafts whenever possible was recommended.

Small en bloc kidneys in one recipient

Single kidney transplants with kidneys from donors under 12-yr old have a poorer graft survival than kidneys from donors above 12 yr or from adults. The poorest results are obtained with kidneys from donors under 5-yr old (203). Kidney transplantation with en bloc grafts from donors aged 0–5-yr old to adult recipients has much better survival rates than single grafts. These small en bloc kidneys transplanted in one adult recipient allow similar results to be obtained to adult-to-adult single kidney transplantation (203, 204).

Non-heart-beating donors

Kidneys, livers, pancreas and lungs from non-heart-beating donors have been successfully transplanted with good results (205–212). This can be a substantial additional source of cadaveric organs for transplantation. The procedure with these donors is much more complex and the transplant results are worse than with heart-beating organ donors: higher rate of discarded donors or organs after retrieval (209), never-functioning graft (207, 210), delayed graft function (207–209, 212) and lower long-term liver graft survival rate (210). The most interesting types of non-heart-beating donors from a point of view of increasing donor pool and obtaining better transplant results are those who are dead on hospital arrival (209), and those hospital patients with sudden cardiac arrest and without prior cardiovascular agonizing phase (211).

Living donors

Living donors can alleviate cadaveric organ shortage. This could be the best option in selected cases. However, the concentration of all the efforts to promote living organ donation in western countries is not justified unless adequate measures are first adopted to increase cadaveric organ donor rate, and maximize the number and quality of organs procured from a cadaveric donor (11, 12, 213). In USA during 2001, for the first time, the number of living donors surpassed the number of cadaveric donors, 6445 of 12 522 total donors, an increase of 12.5% over 2000, while cadaveric donors increased by just 1.7%. Current peroperatory mortality rate among liver and kidney living donor is 0.3 and 0.03%, respectively. This includes liver donors who donated the left lateral segment or the right lobe and kidney donors who underwent laparoscopic nephrectomy (214–217). More than 14% of living liver donors can have one or more serious complications and more than 0.2% can require a liver transplant a few days after their partial-liver living donation (217). The incidence of potentially life-threatening or permanent debilitating complications of kidney living-donation is 0.23% (215), and the rate of kidney living-donors with advanced renal disease after donation can be between 0.04 and 0.15% (215, 218). Short-term graft survival

Table 6. Actuarial renal graft survival from cadaveric and living donors

<table>
<thead>
<tr>
<th></th>
<th>Living donor and cadaveric donor</th>
<th>Actuarial renal graft survival</th>
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<tbody>
<tr>
<td></td>
<td>Cadaveric donors</td>
<td>First year (%) Third year (%) Fifth year (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;60 yr, X = 69 [60–87], Recipients: n = 84, X = 57.8 [16–71] 87 81 81</td>
</tr>
<tr>
<td>UNOS, USA</td>
<td>Cadaveric donors (n = 43341)</td>
<td>82 70</td>
</tr>
<tr>
<td>NEJM 1995; 333:333 (219)</td>
<td>Living donors</td>
<td>Unrelated (n = 129) 91 81</td>
</tr>
<tr>
<td></td>
<td>Parents (n = 3348)</td>
<td>90 82</td>
</tr>
<tr>
<td></td>
<td>Spouses (n = 368)</td>
<td>90 85</td>
</tr>
<tr>
<td>UK Transplant</td>
<td>Living donor</td>
<td>92 85 78</td>
</tr>
<tr>
<td>BMJ 2002; 324:530 (221)</td>
<td>Cadaveric donor</td>
<td>83 78 73</td>
</tr>
<tr>
<td>Massachusetts General Hospital 1984–2000</td>
<td>Living donor (n = 422)</td>
<td>92 84 78</td>
</tr>
<tr>
<td>NEJM 2002; 346:580 (220)</td>
<td>Cadaveric donor (n = 645)</td>
<td>86 76 64</td>
</tr>
<tr>
<td>HSCSP-Fundacio´n Puigvert 1999–1999</td>
<td>Cadaveric donor (n = 298)</td>
<td>Donor &gt; 60 yr, Recipients: n = 63; X = 67.5 95 88 83</td>
</tr>
<tr>
<td>Transplantation 2002; 73:1673 (44)</td>
<td></td>
<td>Donor &lt; 60 yr, Recipients: n = 235; X = 40.6 94 90 81</td>
</tr>
</tbody>
</table>

HSCSP = Hospital de la Santa Creu i Sant Pau; X = Average age.
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Extended criteria for organ acceptance


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Extended criteria for organ acceptance


