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CICLO XXIV

PEDIATRIC KIDNEY TRANSPLANT

EFFECT OF BRAIN-DEAD DONOR RESUSCITATION ON DELAYED GRAFT FUNCTION

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SOMMARIO

ABSTRACT

Introduction and Aim of the Study. Studies devoted to brain dead donor parameters are all based on adult populations. The aim of this study was to analyze the correlation of delayed graft function (DGF) with brain-dead donor variables in a population of 116 consecutive pediatric recipients and to compare the clinical outcomes of non-DGF versus DGF recipients.

Patients and Methods. We classified the recipients into two groups: group 0 (No. 11) with DGF and group 1 (No. 105) without DGF. Endpoints of the study were: DGF, 6 months graft function and short-term patient and graft survival. Multivariate analysis was performed to determine independent risk factors of DGF.

Results. Monovariate analysis of donor parameters showed that donor age above 15 years, gender combination female donor/male recipients, and vascular cause of donor brain death were risk factors for prolonged DGF. The multivariate logistic regression model confirmed as independent risk factors for DGF donor age > 15 years and gender combination female donor to male recipient. After 6 months follow-up, the DGF group showed worse graft function, as well as a smaller incidence of normal histological pattern at graft biopsies.

Conclusions. About parameters associated with brain-death donor resuscitation, except for non-traumatic cause of death, the others did not demonstrate any relationship with DGF. Importantly we show that donor age > 15 years and gender combination female donor to male recipient are clearly major independent risk factors for prolonged DGF in children. Furthermore in our paediatric series DGF revealed an important predictor of poor short-term graft function.

RIASSUNTO

Introduzione e scopo dello studio. In pazienti adulti, danni legati allo stato di morte cerebrale e alle manovre rianimatorie possono influenzare la "*delayed graft function*" (DGF) e l'outcome dell'organo trapiantato. Scopo dello studio è stato valutare, in trapiantati di rene in età pediatrica, la correlazione tra parametri rianimatori del donatore cadavere e l'outcome dell'organo trapiantato.

Materiali e Metodi. Il campione casistico è consistito in 116 pazienti (età ≤ 16 anni), sottoposti a trapianto di rene da cadavere dal 2004 al 2011. I pazienti sono stati divisi in gruppo 0 (No. 11) con DGF e gruppo 1 (No. 105) senza DGF. Gli "*endpoints*" dello studio sono stati: DGF, funzione dell'organo trapiantato a 6 mesi dal trapianto e sopravvivenza del paziente e del rene trapiantato a 6 mesi.

Risultati. L'analisi monovariata dei parametri del donatore in morte cerebrale ha dimostrato che l'età superiore a 15 anni, la combinazione donatore femmina/ricevente maschio e morte da accidente cerebrovascolare rappresentano fattori di rischio per lo sviluppo di DGF. Il modello di regressione logistica multivariata ha confermato come fattori di rischio indipendente per DGF l'età del donatore e la combinazione donatore femmina/ricevente maschio. A 6 mesi di follow-up, il gruppo con DGF ha dimostrato una funzionalità renale e un quadro istologico bioptico significativamente peggiori rispetto al gruppo senza DGF.

Conclusioni. Ad eccezione della causa di morte non traumatica, nessuna variabile ha influenzato la DGF nei bambini trapiantati. L'età del donatore (>15 anni) e la combinazione donatore femmina/ricevente maschio si sono rivelati importanti fattori di rischio indipendente per lo sviluppo di DGF. Inoltre, la DGF è risultato un fattore predittivo di funzionalità a breve termine dell'organo trapiantato.

ABBREVIATIONS

AR - Acute Rejection

ATN - Acute Tubular Necrosis

BUN - Blood Urea Nitrogen

CAPD Peritoneal Dialysis

CIT - Cold Ischemia Time

CNI - Calcineurin Inhibitor

CrCl - Creatinine Clearance

D - Donor

DGF - Delayed Graft Function

ESRD - End-Stage Renal Disease

FSGS - Focal Segmental Glomeruloscrlerosis

GFR - Glomerular Filtration Rate

Hemo - Hemodialysis

HES - Hydroxyethyl Starch

ICU - Intensive Care Unit

NAPRTCS - North American Pediatric Renal Trials and Collaborative Studies

NITp - Nord Italia Transplant Program

R - Recipient

RCP - Cardiopulmonary Reanimation

UNOS - United Network for Organ Sharing

US - United States

USRDS - United States Renal Data System

INTRODUCTION

Over the past forty years, the outcomes of renal transplantation in children have improved markedly due to improvements in surgical techniques, donor selection and organ allocation procedures, prevention, identification and treatment of acute rejection episodes, management of posttransplant complications and better knowledge of immunosuppressive drug doses and metabolism. As a result, transplantation has become the preferred treatment for children with end-stage renal disease (ESRD), now providing better patient survival than prolonged dialysis therapy. The progressive loss of renal function remains, however, the most important cause of graft failure, both in pediatric and adult renal allograft recipients.

Kidney graft outcome is influenced by multiple parameters, among which the host-versus-graft immune response represents a major component. Nevertheless, nonimmune factors such as delayed graft function (DGF) [Giral-Classe M et al, 1998; Ojo AO et al, 1997], which is the most common complication affecting kidney allografts in the immediate posttransplant period, have also been shown to be deleterious for graft outcome [Feldman HI, et al, 1996; Troppmann C et al, 1995]. Although experimental studies have shown the crucial role of ischemia reperfusion injury in the physiopathology of DGF [Perico N. et al, 2004], the relative contribution of donor or recipient-related factors to the development of DGF are still debated.

There is mounting evidence from experimental and clinical studies that the level of injury to organs from cadaver donors may be influenced by events occurring in

the intensive care unit (ICU) [Marshall R et al, 1996; Suri D et al, 1999; Pessione F et al, 2003; Ojo AO et al. 2000] and around the time of brain death [Pratschke J et al, 2001; Van den Eijnden MM et al, 2003; Van der Hoeven JA et al, 2003], and that these have been shown to influence graft outcome.

Several studies have already shown that some drugs used during donor resuscitation, such as adrenergic agents [Schnuelle P et al, 2001; Giral M et al, 2007], certain types of colloid plasma expanders (i.e., hydroxyethyl starch [HES]) [Cittanova ML et al, 1996, Coronel B et al, 1994], can be associated with poor subsequent graft outcome. Otherwise desmopressin [Guesde R et al,1998; Benck U et al, 2011] seems to improve renal allograft survival.

Studies devoted to brain dead donor parameters are all based on adult populations [Suri D et al, 1999; Quiroga I et al, 2006, Giral M et al, 2007, Jung GO et al, 2010] or with a restricted numbers of parameters [Pessione F et al, 2003; Irish WD et al, 2003; Pape L et al, 2006; Giuliani S et al, 2009; Zeier M et al, 2002]. Based on the hypothesis that, as yet unidentified on adults, some donor parameters are risk factors for DGF, the aim of the present research was to explore which brain dead donor parameters including those related to resuscitation correlate with a DGF in children.

AIM OF THE RESEARCH PROJECT

Kidney transplantation has long been recognized as a life-saving procedure for adults with renal failure and prolongs life much more than what is achieved with dialysis. A recent report from the United Network for Organ Sharing (UNOS) showed that children also benefit substantially from kidney transplants; there are several arguments against long-term dialysis in children, including decreased growth velocity, difficulties in nutritional care, poor school attendance, inadequate family and social activity, need for vascular or peritoneal access, increased risk of osteodystrophy and metabolic disturbances [EBPG Expert Group on Renal Transplantation, 2002]. Children who receive their first kidney transplant have a significant survival advantage compared to those on the waiting list [Gillen DL et al, 2008]. Advantages of transplantation compared to chronic dialysis include also improved growth, health-related quality of life, and school performance [EBPG Expert Group on Renal Transplantation, 2002].

Transplantation then is a desired modality for renal replacement in children. There is a consensus to give priority to children on waiting list. The new UNOS allocation policy, which gives priority to children <18 years for organs procured from deceased donors under 35, as soon as they are listed, has almost doubled transplant rates and halved the wait times in the pediatric population. Really the age is part of a scoring system in the Eurotransplant [EBPG Expert Group on Renal Transplantation, 2002].

However, despite efforts to maximize organ transplantation in children, the numbers of living donors are limited, and the numbers of deceased donors

transplants have reached a plateau, while the wait-list for prospective transplant candidates is growing.

In the current decade, not the surgery but the accompanying management needs to be answered – to decrease the waiting time with the number of the transplantable organs and the use of them; immunosuppressive therapy suitable for all recipients in lower dose and lower side effect rate; prevention and treatment of rejections effectively giving longer graft and patient survival and without losing working nephrons; cheap and easy treatment of minor side effects. Nowadays the main goal for the transplant services is to help as many people as possible.

The progressive loss of renal function remains the most important cause of graft failure, both in pediatric and adult renal allograft recipients [Naesens M et al, 2007]. A good knowledge of the natural evolution and the risk factors for progression of a disease is essential to improve therapeutic strategies and long-outcome.

Aim of the research project was:

1) to build a database for collecting data of patients undergoing kidney transplantation at our center; this database should contain all our data on candidate waiting list, organ donation and matching, transplantation and follow-up;
2) to make a review of literature about DGF and kidney transplant short and long term graft and patients outcome on adults and children;

3) to analyze the prevalence of DGF among a group of pediatric recipients of kidneys from deceased donors, and to assess DGF donor-related-risk factors;
4) to explore whether, in addition to classical donor and recipient variables, brain-dead donor parameters, including those related to resuscitation, correlate with a DGF;
5) to identify the impacts of DGF on graft function and patient/graft survival at 6 months posttransplant;
6) to describe the natural histological evolution of nonimmune injury in pediatric transplantation.

REVIEW OF THE LITERATURE

Pediatric Kidney Transplantation

Approximately 1 in 65,000 children develops ESRD each year [United States Renal Data System (USRDS). Available at http://www.usrds.org/. Accessed December 12, 2008]. Before the 1950s, this condition was essentially untreatable. However, because of advances in surgical techniques and suppression of the immune system, the mortality rate of children with chronic renal failure has dramatically declined. Kidney transplantation has become the primary method of treating ESRD in the pediatric population [EBPG Expert Group on Renal Transplantation, 2002] (Fig. 1).

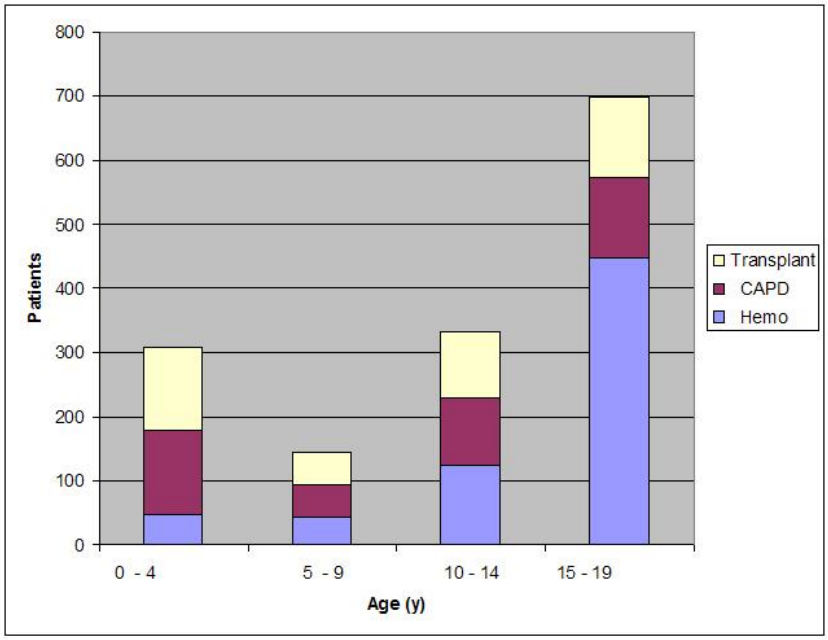


Figure 1

Management of end-stage renal disease in United States (US) children aged 0-19 years by age group. Data from USRDS, 2008.

Kidney transplant history

The first reference to the concept of organ transplantation and replacement for therapeutic purposes was reported in c. 200 AD, as Hua-To in China replaced diseased organs with healthy ones. The miracle by Saints Cosmas and Damian, in which the leg of a deceased Moor was grafted onto a person whose leg was diseased, was reported from the years c.300 AD. Job Van Meeneren documented in 1668 the first successful bone graft from a dog's skull used to repair defect in human cranium. While in 1880 the first reported cornea transplants were done 10 years later Locke invented a preservation solution. Kidney transplantation started in 1902 when the Hungarian Emerich Ullmann performed the first successful experimental kidney transplant (in neck of a dog). Four years later Jaboulay did the unsuccessful first human kidney transplant, using animal kidney (xenograft) and in 1908 Carrell performed the first autologous renal transplantation with survival of several years. The surgical technique of transplantation advanced in 1906, as Carrell and Guthrie performed artery replacement with segment of vein and as Jaboulay transplanted en bloc pig kidney into human after perfused with Locke's solution. 1913 Schonstadt repeats experiment of transplanting a kidney from a Japanese monkey into a young girl with nephritis caused by mercury poisoning. After producing small amounts of urine, the patient died 60 hours after transplant. The first human kidney transplant (allograft) was done but unsuccessful in 1936. The reality of organ transplantation began with advances in chemical anesthesia and aseptic surgery. Early transplantation attempts in humans. It began with transplantation of renal allografts in 1936 but it did not succeed until the discovery of immunogenetics and the implementation of immunosuppressive drugs. Experimental intra-abdominal renal grafts were being

performed in animals in the 1930s and 1940s. Autografts generally survived, although homografts were rejected. On December 25, 1952, Hamburger performed a renal transplantation in a 15-year-old roofer who injured his solitary kidney. The donor of the graft was the patient's mother. The graft functioned immediately following surgery, but it unfortunately ceased to function on the 22nd postoperative day. The patient died 10 days later due to the unavailability of immunosuppression and haemodialysis. Joseph E. Murray and Hartwell Harrison performed the first successful kidney transplant at Peter Brent Brigham Hospital on 23 December 1954. The donor was the living identical twin brother of the recipient, and the kidney functioned for 8 years. This success was followed by subsequent attempts by Murray and Merrill that led to 7 successful transplantations between identical twins in Boston. Most of the recipients of identical twin kidney grafts performed by Joseph Murray did well; some still have functioning kidneys more than 30 years after transplantation. Several transplants between twins followed. However, the possibility of kidney transplantation for patients with renal failure who did not have a twin donor remained unrealized. The attempts at cadaveric renal transplantation universally resulted in graft failure due to rejection. The same hospital gave place for the first successful cadaveric kidney transplant. The kidney functioned for 21 months in 1962. In the early 1960s, cadaveric donations were thought to be impractical and impossible. Living donors were the only available source of organs for transplantation. At Massachusetts General Hospital, a liver was harvested from a police officer whose heart was beating but whose brain was deemed dead. This seminal event led to the development of the concept of brain death as death, rather than the cessation of circulation, which previously defined death. The concept of brain death greatly

increased the number of organs available for donation and improved the preservation of harvested organs. Once the concept of brain death was established, a system for organ procurement was founded to ensure the quality and availability of organs as efficiently as possible. The promising steps of kidney transplantation accelerated other parenchymal organs transplantation as in 1963, Thomas Starzl made the first successful human liver transplant at the University of Colorado or James D. Hardy at the University of Mississippi performed the first lung transplant. In l966 Richard C. Lillehei at the University of Minnesota, performed the first successful pancreas transplant. In l967, Christian Bernard in Cape Town, South Africa, performed the first successful heart transplantation, and in 1968 the first heart transplant in the United States was performed at Stanford University Hospital. The first attempts to control the immune system used total body irradiation. In 1958, a Boston-area woman who was accidentally irradiated with 6 Gy received a functional renal graft, although the patient died from bone marrow aplasia. In 1959, Hamburger and Merrill irradiated 2 transplant recipients with a total dose of 4.5-4.8 Gy; the donors were nonidentical twins. Both of these recipients had successful outcomes. The patients survived 20 and 26 years, respectively. In June 1960, Kuss and colleagues were faced with rejection in a kidney transplant recipient who received the graft from an unselected donor. The use of 6-mercaptopurine in this patient, an immunosuppressive agent previously studied in animals (by Zukowski and Calne), reversed the rejection process and ushered in the era of medications for the prevention and treatment of rejection. In 1964, Crosnier performed another cadaveric transplantation with long-term successful function. Discovery of the fungus - Beauveria nivea, by Jean Borel in samples of soil from Wisconsin and the Hardanger Vidda (fjord) in Norway, leads

to cyclosporine. 1983 cyclosporine, an anti-rejection drug, was approved by the Food and Drug Administration (US Government). In the early 1960s, the pioneering work of Thomas Starzl led to further advancements. His contributions were systematic studies using azathioprine and prednisone therapy to prolong graft survival. Following the demonstration of antilymphocyte serum efficacy by Waksman, Starzl conducted the first clinical trial of antilymphocyte globulin as an adjunct to azathioprine and prednisone in human kidney transplantation [Kuss R et al, 1996].

Frequency of ESRD and Kidney Transplant

The incidence rate of ERDS is very low, about 1-2 children per million general population or about 4-6 children per million childhood population. The proportion for different age groups was 13% under 2 years of age, 20% between 2 and 5 years, 25% between 6 and 9 years, and 42% between 10 and 15 years. A significant increase in the youngest age group was observed in the last decade.

Etiology of ESRD and Kidney transplant

Primary renal diseases in children starting renal failure differ greatly from those in adults. The most common cause of renal failure in children (< 19 y) is glomerulonephritis (Fig.2).

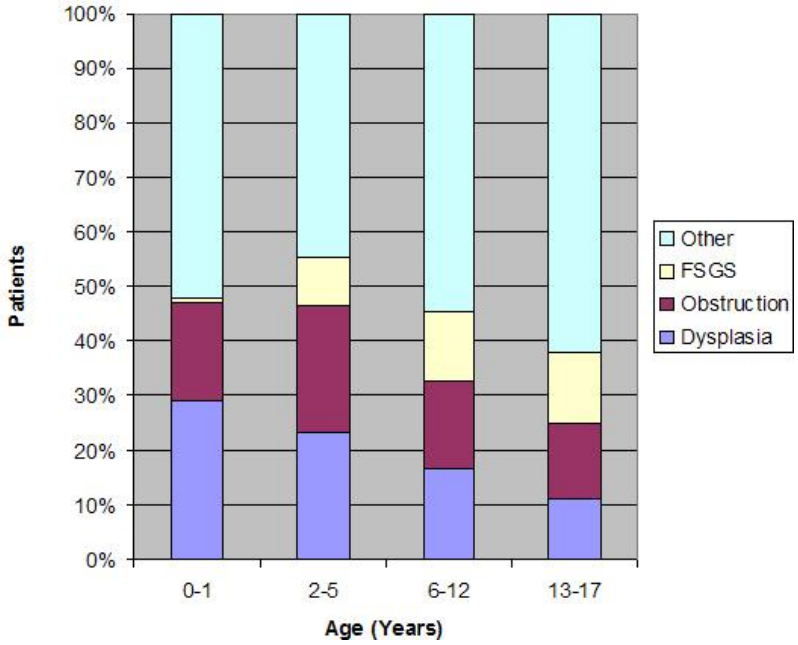


Figure 2

Etiology of end-stage renal disease in children aged 0-18 years by age group. Data from North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Annual Report, 2007.

Other etiologies are demonstrated in all children in the first image below (Fig. 3).

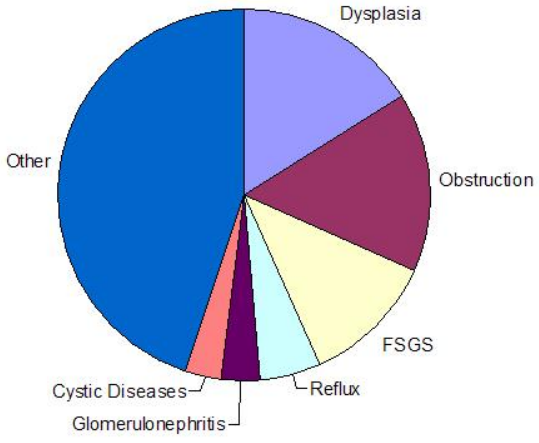


Figure 3

Etiology of end-stage renal disease in North American children. Data from NAPRTCS Annual Report, 2007.

Primary renal disease in children and adults starting renal failure are as follows.

- Congenital (38% children vs 0.2% adults)
  - Aplasia/hypoplasia/dysplasia
  - Obstructive uropathy
  - Congenital nephritic syndrome
- Glomerulonephritis (24.3% children vs 15% adults)
  - Focal segmental glomerulosclerosis
  - Systemic disease
- Metabolic kidney disease (3.3% children vs 0.5% adults)
- Haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura (2.7% children vs 0.2% adults)
- Diabetes mellitus (0.1% children vs 20-25% adults)
- Arterial Hypertension (0.0% children vs 10-15% adults)
- Other (25.7% children vs 15% adults)

Treatment options include hemodialysis, peritoneal dialysis, and renal transplantation. In the late 1990s, about two thirds of children with ESRD received a kidney transplant. Although kidney transplantation is considered to be the management option of choice in children with ESRD, a shortage of available organs has led to a decline in the proportion of patients who receive a kidney transplant (Fig. 4).

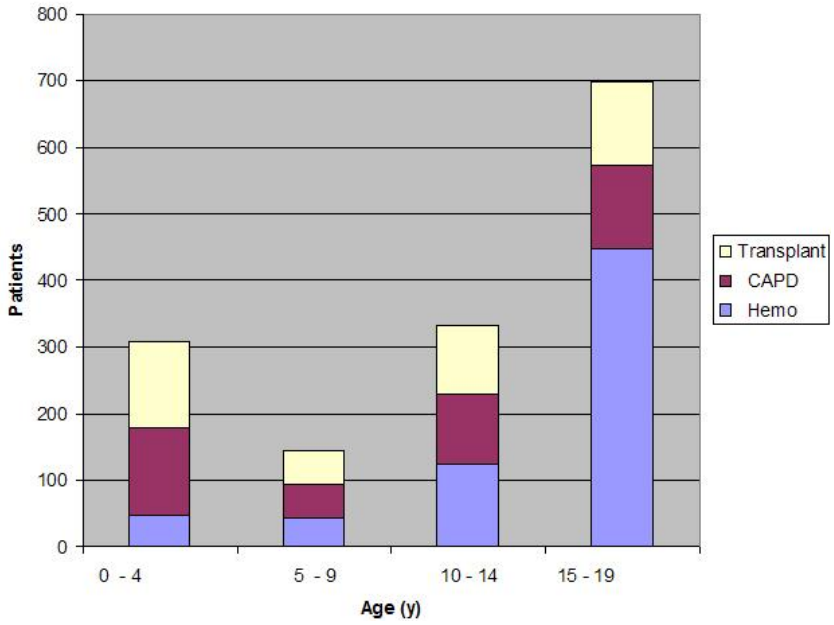


Figure 4

Management of end-stage renal disease in US children aged 0-19 years by age group. Data from USRDS, 2008.

Delayed Graft Function

Most cadaver and some live-donor organ transplants manifest a degree of early dysfunction leading to the clinical syndrome of delayed graft function (DGF). DGF is a form of acute renal failure that results in post-transplantation oliguria. Improvements in donor and recipient management, as well as in diagnostic and therapeutic modalities, seem neither to have reduced overall rates of this disorder nor to have mitigated its short-term and long-term effects. This failure might partly be explained by expansion in adults of criteria for acceptable donors, including marginal and older donors, as well as recipients who could be more predisposed to develop DGF. The reported frequency of delayed function of cadaveric kidney transplants greatly varies worldwide, from 2% to 50%. Such variability mainly results from differences in the rates reported by different

national and international transplantation registries, whether heart-beating or non-heart-beating donors were included, as well as the ambiguity in definition of the event [Perico N et al, 2004].

In most studies, DGF is defined as the need of dialysis treatment in the first week after renal transplantation. This is a criterion that is easy to register and to obtain from large databases. However, dialysis during the first week after transplantation is also performed for other reasons than DGF, like hyperkalemia and/or fluid overload. Another flaw in this definition is the inability to exclude acute rejection and calcineurin toxicity as an additional cause of impaired graft function. For that reason, others have defined DGF as a functional parameter distinct from the need of dialysis and used the time needed to achieve an arbitrarily defined creatinine clearance as a marker for DGF [Gjertson DW et al, 1996; El Maghraby TA et al, 2002].

Pathogenesis of DGF

In the pathogenesis of DGF and acute ischemic failure, 3 stages can be recognized. The first stage is the ischemic phase in which ischemic and reperfusion injury takes place and in which renal epithelial and endothelial cells are subjected to lethal insults leading to apoptosis and/or necrosis. The maintenance phase represents a phase of stabilization of injury by intrinsic or up-regulated defense mechanisms. During this phase, events leading to cellular repair, proliferation and redifferentiation lead to the recovery phase in which epithelial and endothelial function improve, leading to the recovery of renal function (Fig.5).

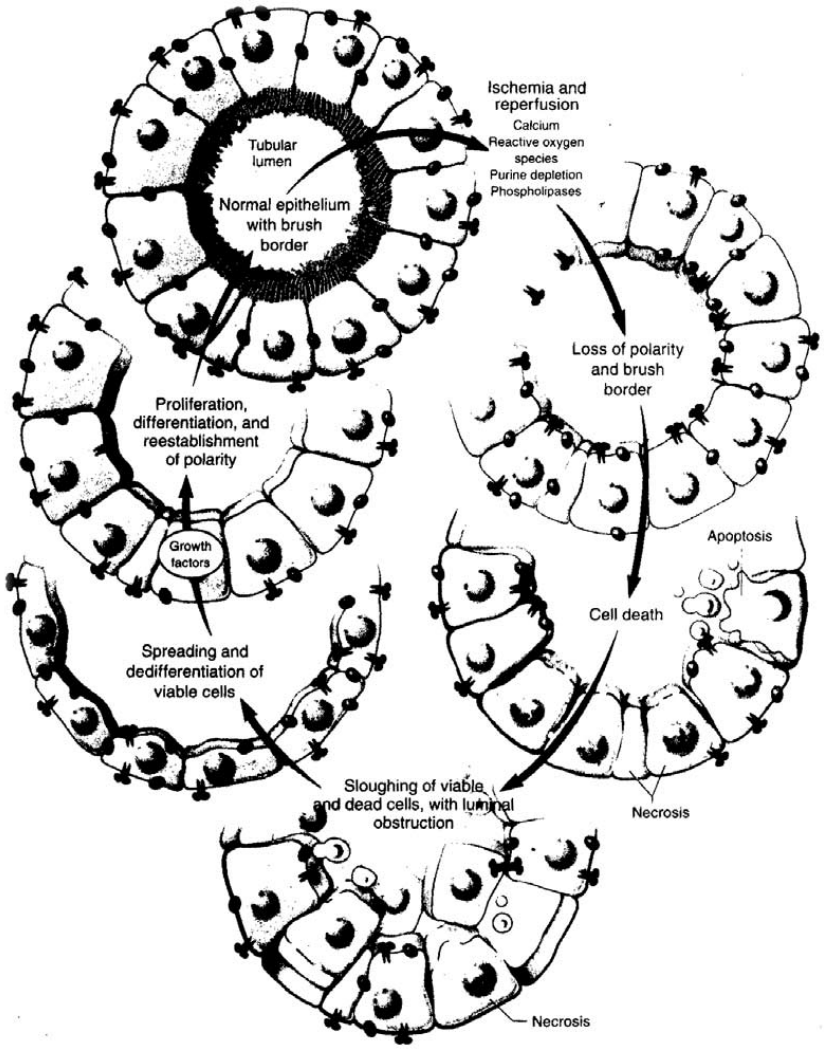


Figure 5

Cell biological characteristics of the acute tubular necrosis.

Pathology and Pathophysiology DGF

Solez et al [Solez K et al, 1991] reviewed the pathology of DGF. The usual findings are of acute tubular necrosis (ATN), similar to ATN in native kidneys. Transplant ATN differs from native kidney ATN in having fewer tubular casts, occasional necrosis of complete tubular cross sections, less tubular dedifferentiation and regeneration, more calcium oxalate crystals, and more

microcalcification and isometric vacuolization (possibly due to calcineurin inhibitor [CNI] toxicity).

Other entities presenting as DGF are antibody-mediated rejection, cortical necrosis/infarction, endothelial damage, acute CNI toxicity, thrombotic microangiopathy, drug-induced interstitial nephritis, and fulminant disease recurrence.

Injury is proinfiammatory in rodent models and also in humans, since infiammation can promote immune recognition, and may contribute to the increased rejection observed in kidneys with DGF. However, caution must be exercised before extrapolating from rodent studies to humans. Experience in human native kidney ATN has shown that the animal models do not predict the behaviour of human kidneys with acute injury (e.g. trials of atrial natriuretic factor and insulin- like growth factor-1).

Possible Etiology of DGF

The risk factors for DGF give an indication of causes. Five categories of risk factors predict DGF:

1) donor tissue quality;
2) brain death and other components of cadaver donation;
3) preservation variables, particularly cold ischemia time (CIT);
4) immune variables (transfusions, HLA mismatch, previous transplants);
5) recipient variables, such as medical status and race/ethnicity.

In human adults well-known donor-related risk factors for DGF are donors of over 50 years of age and an elevated serum creatinine or suboptimal renal function of the donor. Not only factors intrinsically related to the donor but also events preceding brain death and harvest of the kidney contribute to the

occurrence of DGF. Before the establishment of brain death of the potential donor, the kidney may be damaged by the underlying disease process (eg, hypotension or shock) or by the therapeutic maneuvers instituted in an attempt to revive the patient or to maintain circulation after brain death, like the use of dopaminergic medication and resuscitation procedures. Decreasing platelet count and disseminated intravascular coagulation are frequently found and at least suggest that endothelial injury or dysfunction may already be present before the organs are harvested. During episodes of cardiac arrest or prolonged hypotension, the kidney will suffer from warm ischemia and reperfusion injury. Catecholamine release and pharmacological inotropes may contribute to intrarenal vasospasms leading to areas in the kidney subjected to relative hypoperfusion. Because the donor generally is in a catabolic state, recovery from ischemic damage is more difficult. After brain death but before explantation, the potential donor may not be considered a high priority for surgery in the setting of a busy intensive care unit and resuscitation may be delegated to those with limited experience in appropriate care.

The time taken to complete the vascular anastamoses predicts DGF and graft survival in some studies [Halloran PF et al, 2001] but is often not accurately recorded. The impact of the intraoperative variables is difficult to estimate because of poor standardized measurements.

Immune parameters increase the risk of DGF. One mechanism for this association may be that antibody-mediated rejection produces a state of DGF. Thus pre-formed alloantibody that escapes detection in cross-matching, or appears rapidly posttransplant, can cause antibody-mediated rejection. This is difficult to recognize clinically and probably goes unrecognized in many centres. This could

contribute to the increased rate of DGF in sensitized recipients. However, alloantibody alone may not explain all of the association between sensitization and DGF [Halloran PF et al, 2001].

The Consequences of DGF

DGF is a common complication of renal transplantation. The short-term consequences of DGF are well known. DGF generally leads to a more complex post-operative course for the patient. Furthermore DGF is associated with prolonged hospitalization, higher transplantation costs and adverse effects on the rehabilitation of transplant recipients [Almond PS et al, 1991; Rosenthal JT et al, 1991]. Long-term relationship between DGF and patient and graft survival is controversial in the published literature. Otherwise the results of a recent meta-analysis [Yarlagadda SG et al, 2009] emphasize and quantify the long-term detrimental association between DGF and important graft outcomes like graft survival, acute rejection and renal function (Tab.1-4).

Table 1 - *Characteristics of the study populations in the 34 studies.*

First author	F-U (months)	DGF definition	DGF incidence (%)	Rejection (%)	Graft survival *%)		Patient survival (%)		Mean creatinine (mg/dL)	Quality
					1 y	> 1 y	1 y	> 1 y		
Arias	12	Dialysis	30	35	74	n/a	[a]	n/a	[a]	Fair
Asderakis	60	Dialysis	23	49	85	76	[a]	[a]	[a]	Good
Barry	12	Dialysis	45	13	82	n/a	[a]	n/a	1.8	Good
Boom	12	Creatinine reduction	25	23	87	n/a	[a]	n/a	[a]	Good
Brier	60	Dialysis	45	[a]	87	[a]	[a]	[a]	[a]	Fair
Carmellini	60	Dialysis	26	[a]	84	73	[a]	[a]	1.72	Good
Cole	60	Dialysis/ Urine output	32	32	84	70	95	87	[a]	Good
DiPaolo	12	Creatinine reduction	48	8	99	n/a	[a]	n/a	1.64	Good
Dominguez	12	Dialysis	34	30	92	n/a	[a]	n/a	1.44	Fair
Gentil	60	Dialysis	43	37	87	75	97	93	1.81	Good
Giral Classe	120	Creatinine clearance	63	[a]	[a]	72	[a]	[a]	[a]	Good
Gonwa	24	Dialysis	32	22	97.6	92.7	100	93	1.5	Good
Howard	24	Dialysis	30.6	44	[a]	77	[a]	[a]	[a]	Good
Humar	60	Dialysis	22.1	37	[a]	65	[a]	82.4	[a]	Good
Ichikawa	60	Dialysis/ Urine output	82	[a]	90	71.5	[a]	[a]	[a]	Good
Koning	48	Dialysis	24	[a]	87	72	[a]	[a]	[a]	Good
Lechevallier	108	Dialysis	28.9	15	82		[a]	91	1.88	Good
Marcen	72	Dialysis	44	44	86	66	96	85.7	1.76	Good
Moresco	60	Dialysis	29.1	32	[a]	72	[a]	[a]	1.9	Good
Nicholson	48	Dialysis	28	47	83	65.8	[a]	[a]	[a]	Good
Nickerson[b]	24	Creatinine reduction	20		100	[a]	100	[a]	1.69	Good
Ojo	60	Dialysis	26.2	24.8	70	61	[a]	[a]	[a]	Good
Oppenheimer	[a]	[a]	31	[a]	[a]	[a]	[a]	[a]	[a]	Good
Parzanese	48	[a]	22	[a]	[a]	[a]	[a]	[a]	1.48	Fair
Perez-Fontan[b]	60	Dialysis	[a]	[a]	[a]	n/a	[a]	[a]	[a]	Good
Rodrigo	36	Dialysis	25	33	[a]	76	[a]	[a]	1.66	Good
Salvadori[b]	60	Dialysis	21	27	[a]	[a]	[a]	[a]	[a]	Good
Sanchez-Fructuoso[b]	72	[a]	29	[a]	97	84	[a]	[a]	[a]	Good
Senel	60	Creatinine reduction	8.8	31	95	77	98	89	[a]	Good
Siddiqui[b]	60	[a]	17	41	[a]	84	[a]	[a]	[a]	Good
Stratta	12	Dialysis	21	15	83	n/a	93	n/a	1.8	Good
Troppman	72	Dialysis	19	33	100	85	100	88	[a]	Good
Mun Woo	84	Dialysis	31	51	84	55	95	65	[a]	Good

n/a, not applicable; DGF, delayed graft function, dialysis, need for dialysis after transplant; creatinine reduction, failure of serum creatinine to decrease after transplant.
[a]Not available; [b]not included in any analysis due to insufficient data.

Table 2 - *Relative risk of graft loss with DGF. The size of each circle is proportional to the variability of the study.*

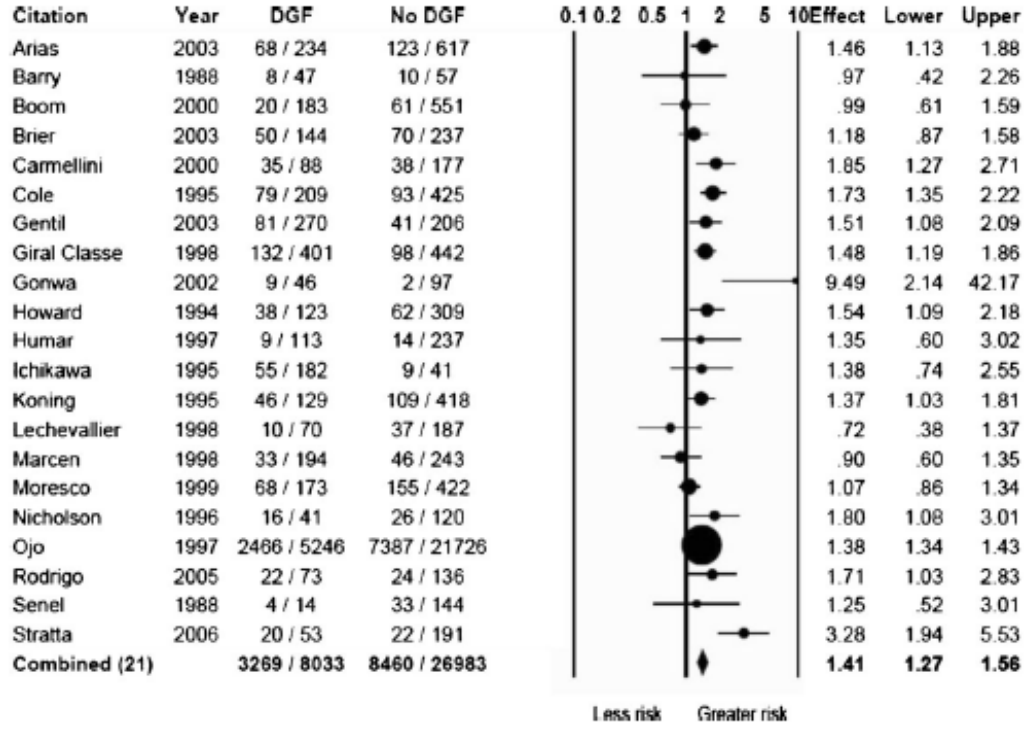


Table 3 - *Relative risk of acute rejection with DGF. The size of each circle is proportional to the variability of the study.*

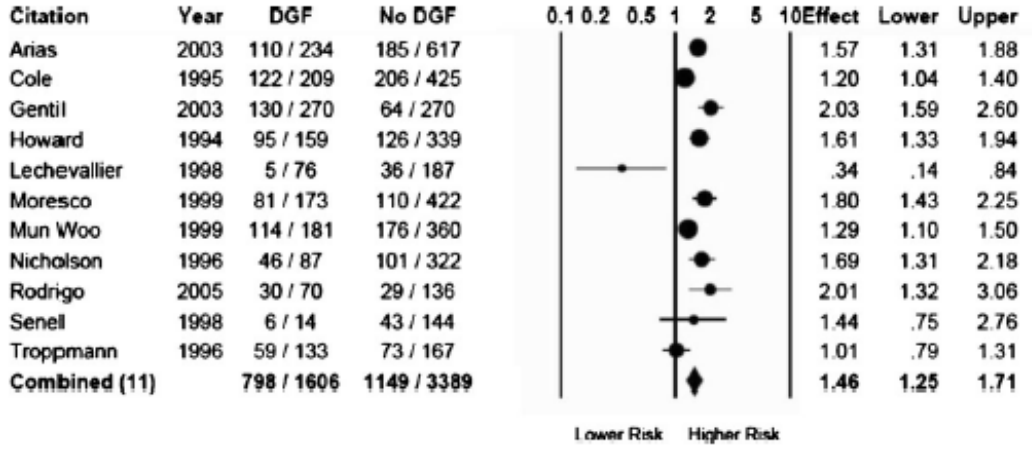
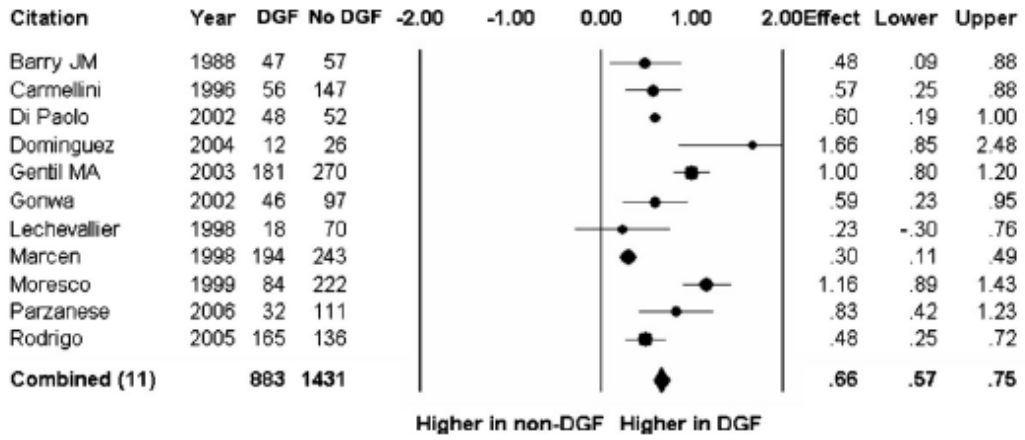


Table 4 - *Effect of DGF on serum creatinine after transplant. The size of each circle is proportional to the variability of the study.*



SUBJECTS AND METHODS

Population characteristics

Between 2004 and 2011, 116 pediatric cadaveric renal transplants were performed at the Pediatric Surgery Division at the University of Padova.

Donors

Data related to donors and the retrieval process were obtained from NITp (Nord Italia Transplant program). Donor-related resuscitation data were extracted from intensive care unit observations from the time of the brain death diagnosis (first flat electroencephalography or cerebral tomodensitometry) to the retrieval procedure. For statistical analysis, resuscitation parameters included: type and volume of gelatin as a volume plasma expander (HES colloid versus gelatins), number of blood transfusions, type of vasopressor employed (dobutamine, dopamine, epinephrine, norepinephrine), occurrence of hypotensive shock due to high variations in blood pressure during the intensive care stay (hypotensive shock criteria were retained as defined by at least one episode of systolic pressure below 80 mm Hg), number of cardiac arrest and cardiopulmonary reanimation episodes, duration in intensive care, creatinemia and uremia at retrieval procedure, and urine production. Other parameters were: donor age and gender, cause of death (vascular or traumatic) and multiple organ retrieval procedure (liver, heart, lung, pancreas and kidney). The retrieval technique and preservation fluid were unchanged during the study period.

Recipients

Recipient data were extracted from our Database (Pediatric Kidney Transplant Database, Access®), in which the biological and clinical data of our transplant patients have been retrospectively recorded by our medical team since 2009. The inclusion criteria were: recipient age <16 years and at least 6 month follow-up. We classified recipients (116) into two groups: group 1 (No. 105; 90.5%) did not experience DGF after kidney transplantation and group 0 (No. 11; 9.5%), showed DGF after kidney transplantation.

All grafts were transplanted into the iliac fossa using extraperitoneal access (Fig. 6-7).

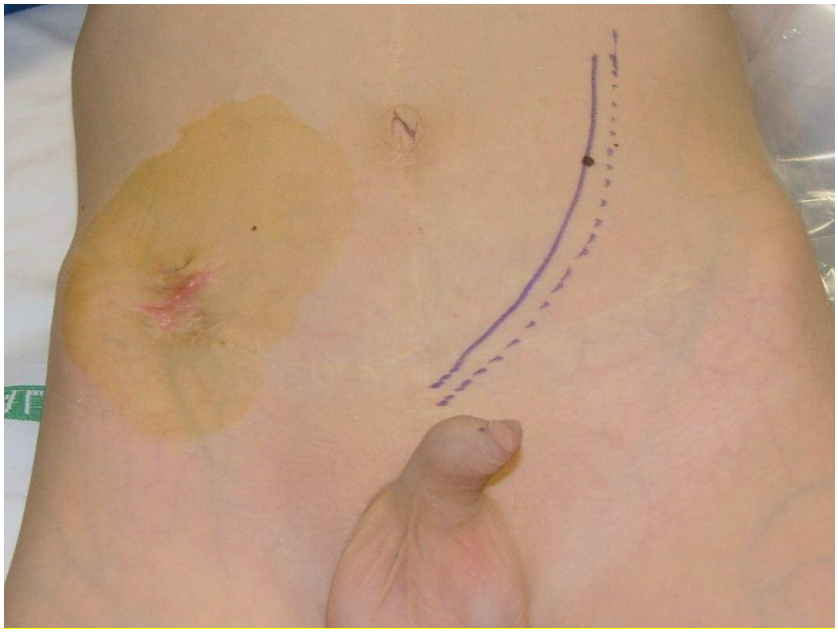


Figure 6

Skin incision "hockey stick" shaped

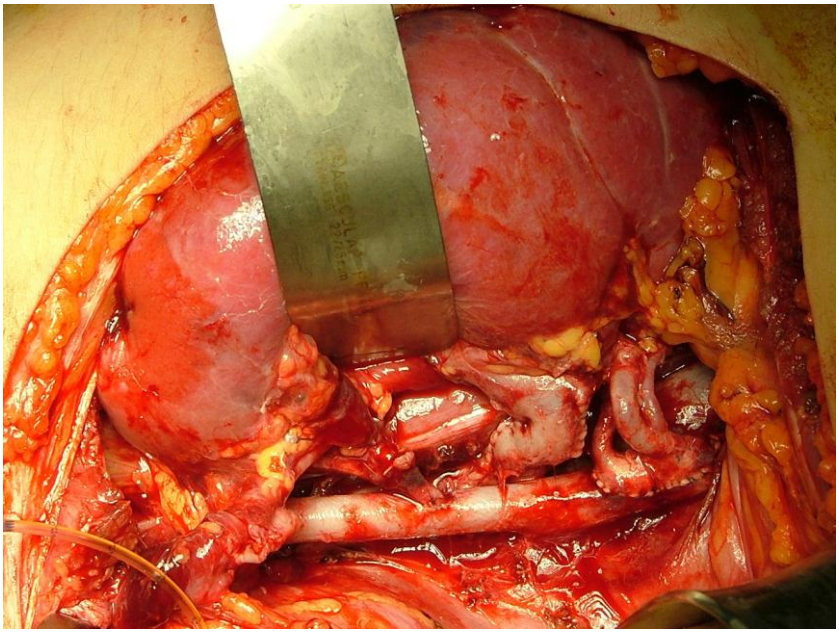


Figure 7

Graft was implanted into the iliac fossa using extraperitoneal access

An end-to-side vascular anastomosis was performed (Fig 9-10), with a Lich–Gregoir ureterovesical implantation. All patients used heparin or low-molecular weight heparin in the early post-operative period, i.e. during the first 10-15 days, and underwent Echo-color Doppler flow monitoring to rule out vascular complications. Immunosuppressive induction was performed using Basiliximab and Methylprednisolone pulses; immunosuppressive manteinance therapy was based on a double or triple drug combinations (CNI [Cyclosporine or Tacrolimus] ± Mycophenolate Mophetil or Everolimus ± Steroids), related to the regimen used at the time of transplantation.

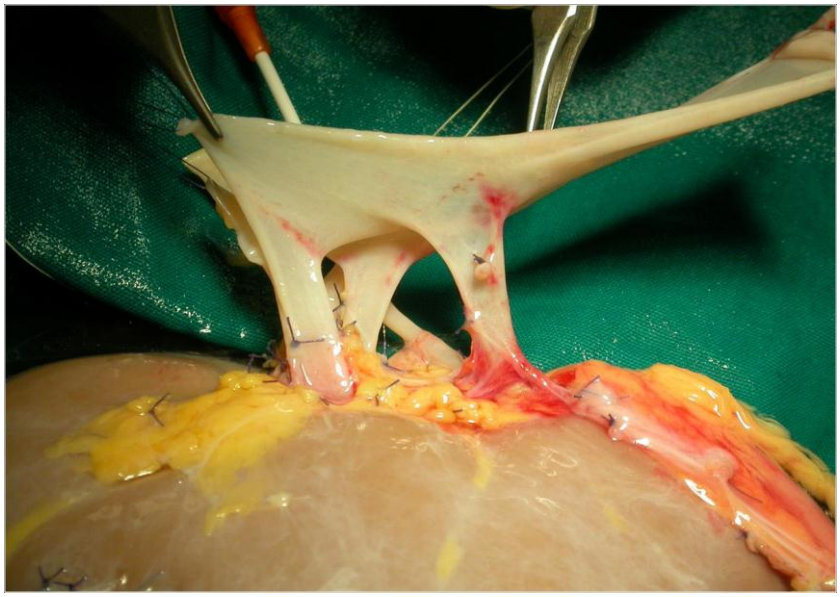


Figure 8

Venous anastomosis

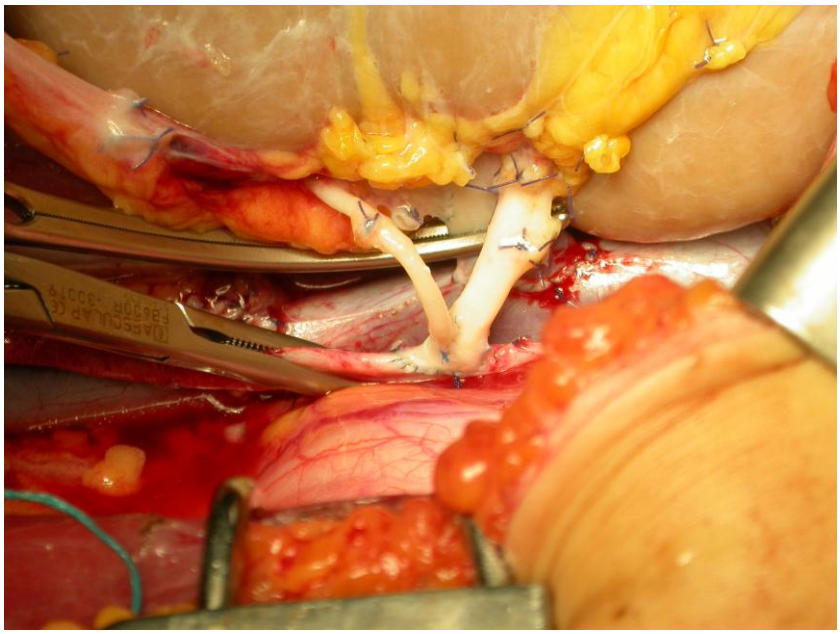


Figure 9

Arterial anastomosis with vascular clamping

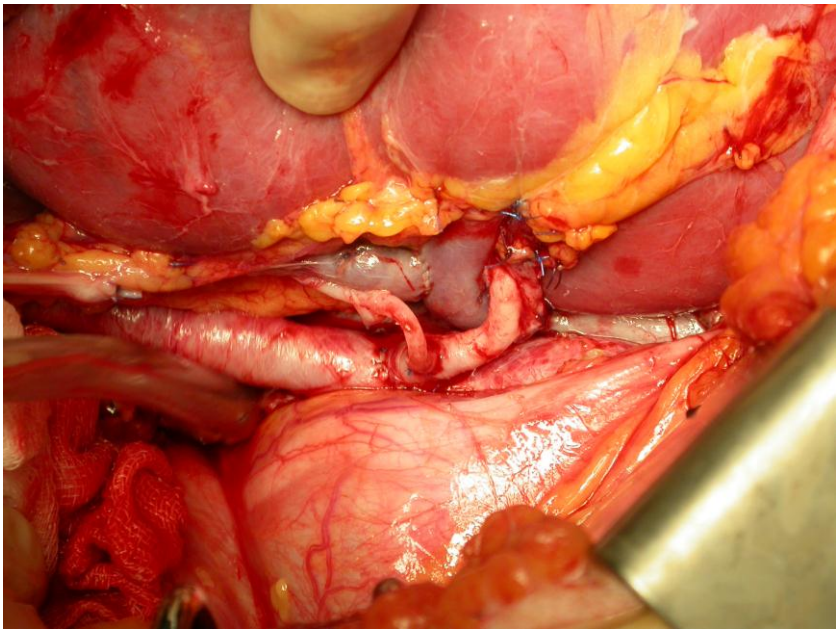


Figure 10

Arterial anastomosis without vascular clamping

Endpoints

The primary end-point of the study was to analyze the prevalence of DGF in a pediatric-kidney-transplant-recipient population, and to assess DGF donor-related-risk factors.

Secondary end-points were: graft function (creatinine clearance and graft histology), patient and graft survival rate at six months posttransplantation.

Primary end-point

Delayed Graft Function

DGF was defined as the requirement for dialysis within the first week after transplantation. Patients transplanted prior to needing dialysis (pre-emptive

transplantation) were considered to have DGF if the creatinine failed to drop in the first week.

Secondary end-points

Graft function

Graft function is an indication of the state of the kidney and its role in renal physiology. Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney. Creatinine clearance rate (CrCl) is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR. Graft function was assessed estimating the CrCl from serum creatinine, and by a graft biopsy at 6 months after transplantation.

– Creatinine clearance rate at 6 months: the Shwartz equation [Schwartz GJ et al, 1976], which takes into account length and age, was used to calculate creatinine clearance (CrCl) for each pediatric patient (Tab. 5)

Table 5 - Schwartz equation

CrCl (ml/min/1.73m^2)=[length(cm) x k] / Serum Cr(umol/L) [Patient population: infants over 1 week old through adolescence (18 years old)]
k = 0.45 for infants 1 to 52 weeks old
k = 0.55 for children 1 to 13 years old
k = 0.55 for adolescent females 13-18 years old
k = 0.7 for adolescent males 13-18 years old

– Graft biopsy at 6 months: all patients in our unit had protocol renal transplant biopsies at 6 months after transplantation, irrespective of renal function. In addition, diagnostic biopsies were performed at any time when clinically indicated. Slides were stained with hematoxylin eosin, Masson

Trichrome, periodic acid-Schiff (PAS), and with polyclonal antiserum to C4d (Biomedica Gruppe, Austria). All adequate protocol biopsies (N = 64 at 6 months) were viewed by our pediatric nephrologist. Inadequate biopsies (with less than 7 glomeruli) were not considered in this analysis. Histological lesions were semi-quantitatively scored according to the revised Banff criteria (Tab. 6) [Solez K. et al.].

Histological changes were considered to be due to rejection, acute (A – Fig. 11-12), chronic (B – Fig. 13-14), or not (normal specimens, C).

Table 6 - Banff 97 diagnostic categories for renal allograft biopsies - Banff'07 update (Solez K et al, 2008)

1. **Normal**
2. **Antibody-mediated changes** (may coincide with categories 3, 4 and 5 and 6)
   Due to documentation of circulating antidonor antibody, and C4d[3] or allograft pathology
   C4d deposition without morphologic evidence of active rejection
   C4d+, presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e. g0, cg0, ptc0, no ptc lamination). Cases with simultaneous borderline changes or ATN are considered as indeterminate
   Acute antibody-mediated rejection[4]
   C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):
   I. ATN-like minimal inflammation
   II. Capillary and or glomerular inflammation (ptc/g >0) and/or thromboses
   III. Arterial—v3
   Chronic active antibody-mediated rejection[4]
   C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries
3. **Borderline changes:** 'Suspicious' for acute T-cell-mediated rejection (may coincide with categories 2 and 5 and 6)
   This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis
4. **T-cell-mediated rejection** (TCMR, may coincide with categories 2 and 5 and 6)
   Acute T-cell-mediated rejection (Type/Grade:)
   IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
   IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
   IIA. Cases with mild-to-moderate intimal arteritis (v1)
   IIB. Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
   III. Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
   Chronic active T-cell-mediated rejection
   'chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)
5. **Interstitial fibrosis and tubular atrophy**, no evidence of any specific etiology
   (may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointerstitial features)
   Grade
   I. Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
   II. Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)
   III. Severe interstitial fibrosis and tubular atrophy/ loss (>50% of cortical area)
6. **Other:** Changes not considered to be due to rejection—acute and/or chronic (for diagnoses see Table 14 in (42); may include isolated g, cg or cv lesions and coincide with categories 2, 3, 4 and 5)

[1]The 2007 updates are underlined.
[2]All existing scoring categories (g, t, v, i, cg, ct, ci, cv, ah, mm) remain unchanged (42)
[3]Please refer to Table 2 and Figure 1.
[4]Suspicious for antibody-mediated rejection if C4d (in the presence of antibody) or alloantibody (C4d+) not demonstrated in the presence of morphologic evidence of tissue injury.

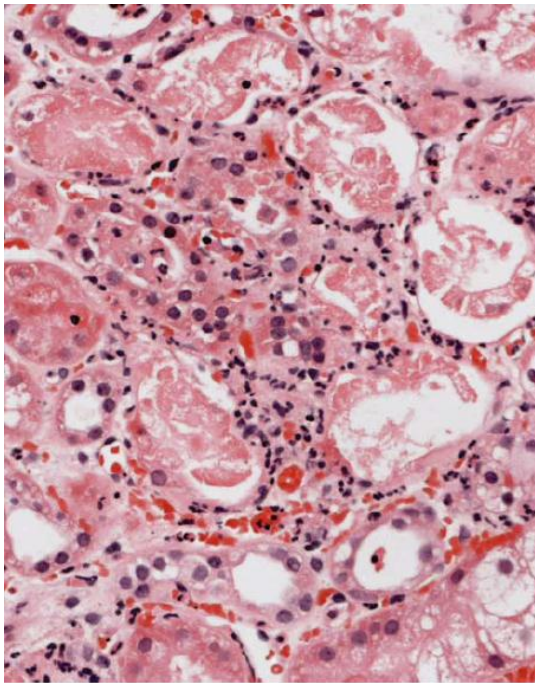


Figure 11

Tubules show severe acute damage, with a heavy infiltrate of neutrophils in intertubular capillaries.

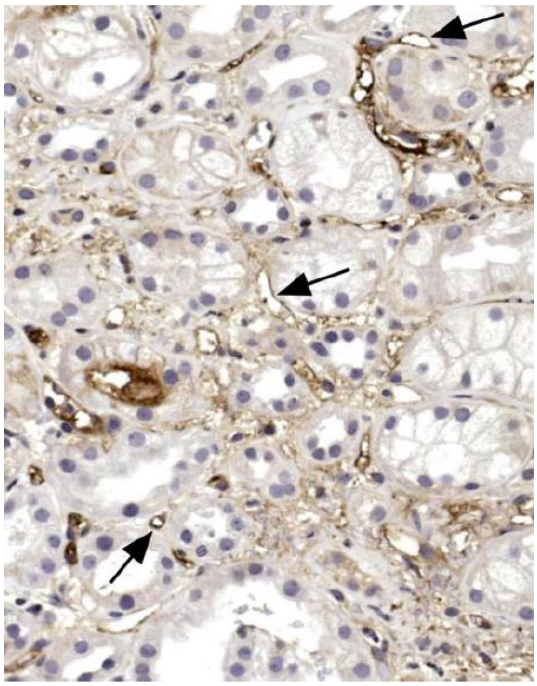


Figure 12

Immunoperoxidase staining for C4d helps to suggest the diagnosis of antibody mediated rejection

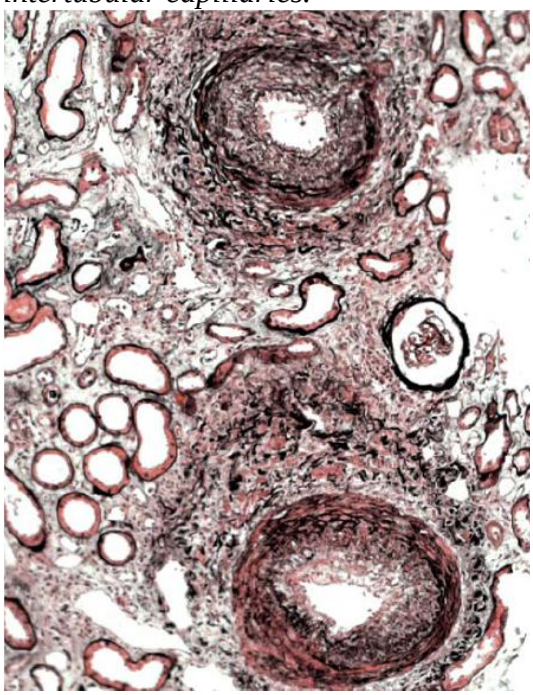


Figure 13

Concentric intimal thickening in arteries with the appearances of chronic vascular rejection

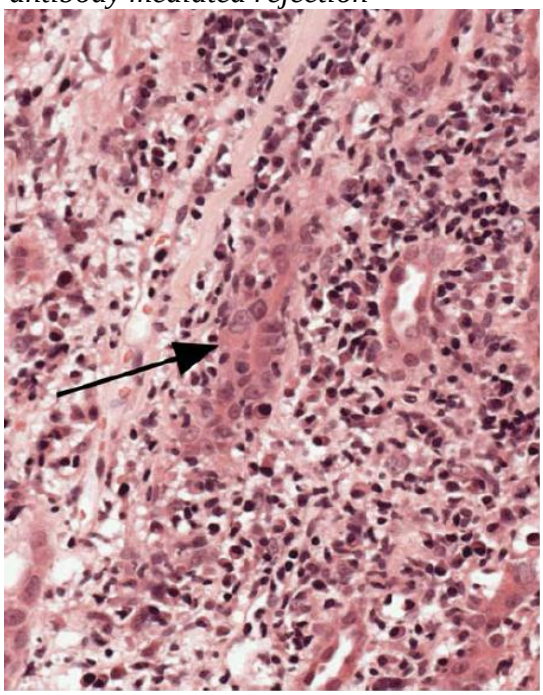


Figure 14

Heavy chronic inflammatory infiltrate with abnormal nuclei in tubules, particularly the one arrowed.

Patient and graft survival rate

Complete failure, or graft loss was coded when the patient required a graft nephrectomy, a return to permanent dialysis, or re-transplantation.

Statistical analysis

Continuous variables with normal distribution (assessed by the Shapiro-Wilk normality test) are presented as mean±standard deviation (S.D.), otherwise as median and interquartile range (25%-75%). Categorical variables are shown as a percentage. Continuous variables with normal distribution were compared using Student's t-test, and those with a non-normal distribution were compared using the Wilcoxon rank sum test. Categorical variables were compared by the $\chi 2$ test or Fisher's exact test as appropriate. Only the variables found to be significant at univariate analysis (at a p-value < 0.1) were considered for the multivariate analysis. Multivariable logistic regression was performed by means of a stepwise algorithm (cut-off for entry: 0.05, for removal: 0.10). All tests were two-tailed with a significance level of 0.05. Statistics was performed using Stata MP 10.0 software (StataCorp).

RESULTS

Population characteristics

Donors

In this cohort, the median donor age was 13 years (interquartile range 6.75-18.25 years). Sex distributions (male/female) donors was 79/37.

Recipients

The median recipient was 14.64 years (interquartile range 8.56-18.24 years) and sex distributions (male/female) was 76/40.

Endpoints

Primary end points

Delayed Graft Function

- DGF prevalence. Primary graft nonfunction did not occur, but 11/116 (9.4%) cases experienced DGF. Comparisons between the two groups are summarized in Table 7.
- DGF risk factors - Univariate Analysis. The univariate analysis showed that some donor parameters correlated with a lower risk for DGF. Male donors (P.10) and a traumatic cause of donor brain death (P.049) were associated with a lower risk of DGF. On the other hand donor age above 15 years (P.02), the gender combination female donor/male recipients (P.02) and vascular cause of donor brain death (P.04), such as spontaneous intracerebral hemorrhage or subarachnoid hemorrhage, represented risk factors for DGF. Cold ischemia time, the only surgical parameter considered, was similar between the two groups. About the analysis of

donor management data and laboratory results just before starting brain-death evaluation and at organ procurement, parameters like type and volume of gelatin as a volume plasma expander, duration in intensive care and urine production at retrieval procedure were excluded because data were available just for few patients. The use and dosage of inotropics (dopamine, dobutamine, epinephrine and norepinephrine) was similar in group 0 compared with group 1. The laboratory results (blood urea nitrogen level, serum creatinine level) between the two groups at retrieval procedure were not different. Even number of blood trasfusions, hypotensive shock episodes and cardiac arrest occurred in intensive care unit did not showed difference among the two groups. Comparisons between the two groups are summarized in Table 7.

– DGF risk factors - Multivariate Analysis. The multivariate analysis confirmed, trough a multilogistic regression method, as independent risk factors for DGF donor age > 15 years (P.0109, Odds Ratio [OR]: 0.1338) (Fig 15), gender combination female donor to male recipient (P.0203, OR: 0.1806), while traumatic cause of donor brain death seems to be protective for DGF (P 0.01 OR: 7.05) (Table 8).

Table 7 - *Comparison of general characteristics between group 0 and group 1.*

			Group 0 (N=11)	Group 1 (N=105)	P
D Age	**Medium (yr)**		19 (8,75-38,75)	13 (6,75-17)	0.07
	> 15 (%)		72% (8)	35% (37)	0.02*
Sex	**D Male**		45.45% (5)	70.47% (74)	0.10*
	R Male		72,72% (8)	64,76% (68)	0.74
Relation between D and R		♀ → ♂	54,54% (6)	21,90% (23)	0.02*
		♀ → ♀	0%	7,6% (8)	1.00
		♂ → ♂	18,18% (2)	42,8% (45)	0.19
		♂ → ♀	27,27% (3)	27,62& (29)	1.00
Cold ischemic time (min)			13 (12-15) [N=10]	13 (11-15,25) [N=97]	0.67
Weight (Kg)	**D weight**		57 (27,25-73,75)	51 (22-65,5)	0.47
	R weight		40 (15,65-51,8)	39,8 (15,2-51,8)	0.83
R/D weight			0,76 (0,58-0,89)	0,75 (0,55-0,99)	0.86
D cause of death	**Vascular**		45,45% (5)	17,14% (18)	0.04*
	Traumatic		27,27% (3)	61,90% (65)	0.049*
	Other		27,27% (3)	20,95% (22)	0.7
D Hypotensive shock			63,63% (7)	53,08% (43) (N=81)	0.51
Inotropics	**Total**		72,72% (8)	79,04% (83)	0.7
	Dopamine		27,27% (3)	48,57% (51)	0.17
	Epinephrine		9,09% (1)	2,85% (3)	0.33
	Norepinephrine		54,54% (6)	43,81% (46)	0.53
	Dodutamine		18,18% (2)	12,38% (13)	0.63
D No.RCP			45,45% (5)	26,13% (23) (N=88)	0.28
D Creatinine (mg/L)			0.77 (0,6-1,2) [N=10]	0.7 (0,6-1) [N=98]	0.44
D Multiorgan-removal			81,81% (9)	94,28% (99)	0.16
D No. blood transfusions			80% (4) (N=5)	80,32% (49) (N=61)	1
D BUN (mg/L)			25 (12,5-37) [N=8]	25 (15-39) [N=87]	0.87

D donor
R recipient
RCP cardiopulmonary reanimation
BUN blood urea nitrogen
*significant value

Table 8 - *Multivariate analysis for the risk factor of occurrence of DGF after kidney transplantation.*

	P Value	Odds Ratio	Coefficent	SD	95% CI for OR
D Age (yr) > 15	0.0109*	0.1338	- 2.0114	0.7897	0.0285-0.6290
D/R: Female/male	0.0032*	0.1806	-1.7112	0.7376	0.0426-0.7668
Traumatic cause of brain death	0.0141*	7.0501	1.9530	0.7960	1.4812-33.5568

SD Standard Deviation

OR Odds Ratio

CI Confidence Intervals

*significant value

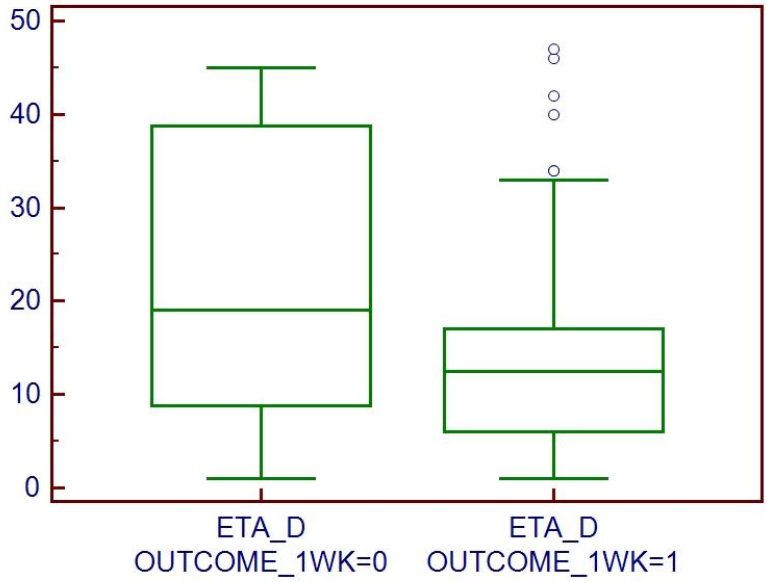


Figure 15

Donor age and risk of DGF: comparison between group 0 and group 1.

Secondary end-points

Graft function

– Glomerular Filtration Rate at 6 months. At 6 months post transplantation glomerular filtration rate, expressed by CrCl using the Shwartz equation, was significantly higher in group 1 versus group 0 (P.002) (Fig. 16).

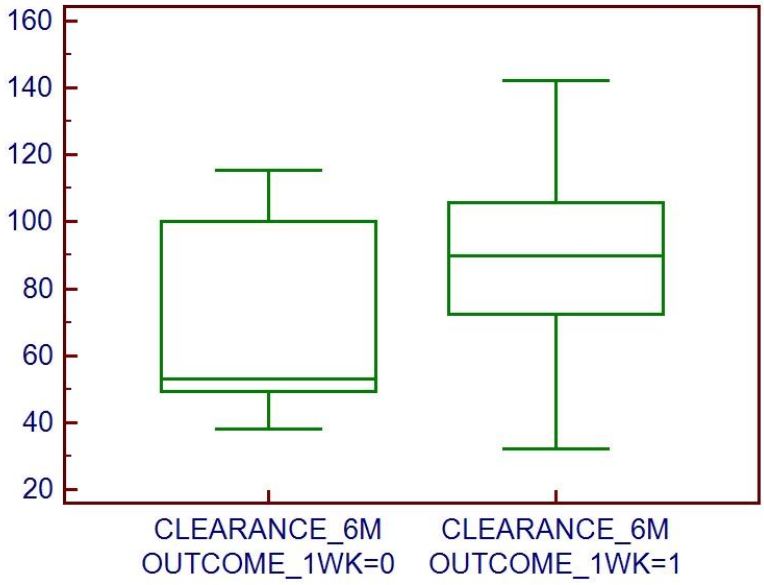


Figure 16

Creatinine Clearance at 6 months: comparison between group 0 and group 1

– Graft biopsy at 6 months. Graft biopsies at 6 months after kidney transplant were available in 64/116 (55.17%) recipients. 3/116 (2.58%) patients were excluded from the analysis, respectively two for recurrence of underlying disease and one for BK-virus nephropathy. In the remaining 49/116 patients (42.34%) fine-needle graft biopsy was contraindicated. For histological lesions semi-quantitatively scored according to the revised Banff criteria,

the univariate analysis showed that group 1 had a significative (P.09) higher rate of normal biopsies than group 0. Otherwise acute and chronic rejection histological patterns did not revealed any differences between the two groups (Table 9).

Table 9 - *Comparison of histological characteristics between group 0 and 1.*

Histology at 6 months	**Group 0 (N=11)**	**Group 1 (N=105)**	**P**
AR	25% (1) [N=4]	6,6% (4) [N=60]	0.28
CR	25% (1) [N=4]	6,6% (4) [N=60]	0.23
Normal	50% (2) [N=4]	88,4% (53) [N=60]	0.09*
Ar Acute Rejection CR Chronic Rejection * significant value.			

Patient and graft survival rate

In this cohort, overall graft and patient survivals at 6 months were respectively 97.15% and 98.1%; 3/11 grafts of group 0 were lost in the immediate post-operative time for vascular trombosis. Acute rejection episodes after transplantation between groups 0 and 1 were 1 (4%) versus 4 (6.6%) (p ns).

DISCUSSION

Kidney transplantation is widely accepted as the optimal treatment modality for children with ERDS. Nowadays pediatric kidney transplantation is so successful that >80% of children will survive to become teenagers and adults. Therefore, it is essential that these children maintain a good quality life, free of significant long-term side effects. Consistent informations are based only on perfect knowledge of the long-term outcome and prognosis of transplanted patient with a whole-life treatment. European Best Practise Guidelines for Renal Transplantation for pediatrics specific problems recommend to provide longitudinal documentation from pediatric nephrology using registries and healthcare networks [EBPG Expert Group on Renal Transplantation, 2002]. The creation of a single register (Access®) including data from pediatric surgery and nephrology of the University-Hospital of Padova answered this project. The input data are readily available for the possible future inclusion in a national or international pediatric register, both for scientific and clinical purposes, especially during the follow-up period. Furthermore understanding the dimensions of the problem DGF, identify risk factors for DGF related to the donor and comprehending the impact of DGF on graft function and graft and patient survival aim to better define the prognosis of these selected patients but also to recognize where closely we have to work to improve long-term out-come.

Despite a decade of advancement in kidney transplantation, non-immune factors remain a major influence on graft outcome, as suggested by a rate of graft loss that has been only weakly influenced by the level of immunosuppressive drug

exposure after one year [Halloran PF et al, 2004; Opelz G et al, 2001; Vincenti F et al, 2004]. Donor parameters represent potentially important risk factors in terms of kidney graft outcome [Ojo AO et al, 2006; Keith DS et al, 2004; Feduska NJ, 1994; Gourishankar S et al, 2003; Zeier M et al, 2002]. Latest studies have suggested that donor factors may account for 35–45% of the variability in graft function [Cosio FG et al, 1996; Cosio FG et al, 1998].

Brain death itself has a serious impact on organ quality and graft outcome [Gasser M et al, 2000] and some risk factors seem to be related to the resuscitation procedure of the brain dead donor, such as the type of fluid expander [Coronel B et al, 1994; Cittanova ML et al, 1996] or vasopressive drugs [Schnuelle P et al, 2001]. The central aim of our research was to explore the clinical and histological consequences of a large number of donor-related parameters in a pediatric monocentric cohort of recipient. Particularly the intend of the study was to determine which donor parameters, especially those stemming from the brain death status and the retrieval procedure, represent risk factors for prolonged DGF.

A single-centre study permits the use of more detailed data in a fairly homogeneous set and provides a useful complement to multi-centre studies. We selected the last five years for this study because in our unit this was a period of very uniform immunosuppression and clinical practice. Similar studies published previously have often come from multi-centre adults registry data, where the level of HLA matching is variable, CITs are often longer and there are large variations in induction and maintenance regimens between centres [Ojo AO at al, 1997;

Hariharan S et al, 2002; Giral-Classe M et al, 1998]. Very few patients were excluded from this study, only then when there was a lack of donor information.

DGF is a well known immediate post-operative complication after deceased donor kidney transplantation. Several definition has been applied in the current literature. Many studies have defined DGF as the need for dialysis during the first week posttransplantation. To obtain comparable data, in the present study we applied this definition. We observed a DGF prevalence of 9.4% in our series, which was relatively lower than other studies on adults recipients [Quiroga I et al, 2006; Giral M et al, 2007]. DGF generally leads to a more complex post-operative clinical course fot recipents, with higher costs, prolonged hospitalization, and averse effects on recipents rehabilitation [Jung GO et al, 2010]. Known risk factors for DGF on adults include prolonged CIT, older donor or recipients, donor female gender (female donor kidney into male recipient), and elevated donor terminal creatinine level and non-traumatic cause of death [Iglesias-Marquez RA at al, 2002; Jung GO et al, 2010; Ojo AO, 2000; Boom H et al, 2000; Shoskes DA et al, 1998; Pfaff WW et al, 1998; Rodrigo E et al, 2004; Humar A et al, 2002]. Among the large numbers of donor resuscitation parameters studied in the model, our results on a pediatric selected series demonstrated independent predictive factors for DGF to be just donor of age more than 15 years, gender combination female donor/male recipients and brain-dead death due to non-traumatic vascular cause.

Many studies have shown an association of DGF with donor and recipient age. We found donor age to be risk factor for DGF in the univariate model and the

marginal model then confirmed donor age > 15 years as independent risk factor for DGF. Contrasting with our results, in 2007 Giral et all [Giral M et al, 2007] found on an adults series recipient and donor age to be risk factors for prolonged DGF in the univariate model, but the marginal model identified recipient but not donor age as the independent risk factor for DGF. One explanation given by the colleagues was that it could be the advanced vascular disease in older recipients, which increases the risk of hypoxia and ischemic damage of the usually aged-matched in suboptimal kidney from old donors. To the other hand in the same year Naesens and colleagues [Naesens M, 2007] demonstrated in a pediatric population the independent role of higher donor age in the development of medial arteriolar hyalinosis and herewith associated glomerular changes. They demonstrated that progressive, irreversible, functionally relevant, nonimmune injury was detected early after adult-sized kidney transplantation in pediatric recipients. Adult kidneys transplanted into the smallest recipients showed more interstitial fibrosis, tubular atrophy and tubular microcalcification in the earliest phase after transplantation. Early tubular microcalcifications, associated with a worse long-term graft survival, were almost exclusively present in our smallest recipient group and more prevalent in female recipients. In addition, small children receiving an adult kidney had an absolute GFR early after transplantation that was similar to the normal GFR that would be expected if they had 2 native kidneys, but importantly, the adult kidneys transplanted into small recipients lack the increase in absolute GFR that would be expected with growth of the child, as is seen in older children. These histological and clinical findings are suggestive of

chronic ischemia and support the hypothesis that “aging” leads to defective autoregulation, possible condition in older grafts. Even Doubourg and colleagues [Dubourg L et al, 2001] documented that adult grafts may adapt to pediatric recipients during the first months post-transplantation, but graft function cannot improve thereafter along with the increase in body size of the recipient. Moreover they promoted the use of young cadaveric donors in pediatric kidney transplant, as graft function adapts to the body size increase of the child over time.

Surprising donor/recipient size mismatch, proven to be decisive in many pediatric studies [Pape L et al, 2006; Giuliani S et al, 2011], was poorly represented in our series and therefore it did not increase the risk of DGF. In children donor/recipient size divergence is a common matter dealt with in kidney transplantation, and can lead to technical difficulties. In 2009 Giuliani S. et al [Giuliani S et al, 2011] have shown that in a pediatric population during the developmental period a bigger for weight pediatric donor kidney (> 5 yr and > 15 kg) is associated with better early and long-term graft outcome in the majority of patients. Furthermore, believing that in children an inadequate nephron dose is a critical point in graft outcome, they have demonstrated that a small donor kidney for a relatively larger recipient is a major risk factor for early and late allograft failure. In adults series size discrepancies seem to be not so decisive. In fact several authors have focused attention on the impact of nephron mass in adult renal transplantation outcomes and the results have been conflicting [Pourmand G et al, 2001; Lee LS et al, 1997; Feldman HI, Fozio I et al, 1996; Pelletier SJ et al, 2006]. In our pediatric series we did not find discrepancy between donor and recipient weights to be a risk

factor for DGF. We postulate that this similarity between the weights in our series is due to the timing of transplant, which was performed when the donor/recipient ratio was <4/1.

About donor and recipient gender, we found in an univariate model male gender to be associated with a lower risk of DGF (P.10) and gender combination female donor to male recipient (P.0203) was confirmed in a multivariate analysis as independent risk factors for DGF. The detrimental influence of female donor gender on the outcome of cadaver kidney transplants was first described in 1985 and later confirmed by several authors from single-center studies [Neugarten J et al, 1996; Vereerstraeten P et al, 1999] and in larger series [Zeier M et al, 2002]. Nowadays it had been known that short-term and long-term graft survival was worse when kidneys from female donors were transplanted to male recipients. Our results about gender confirmed those from previous studies but the significance has not yet been found. A proposal to explain earlier observations of a worse outcome of kidneys graft coming from female donors was the idea of nephron underdosins [Taal MW et al, 1998; Remuzzi G et al, 1999; Gridelli B et al, 2000]. Although anatomic studies have documented larger kidney weight in men, the results were inconsistent when the kidney size was corrected for body surface area [Latimer J K et al, 1942]. Even information on the number of glomeruli in the two genders is also conflicting [Nyengaard JR et al, 1992]. In the search for alternative mechanisms involved in the donor gender effect, immunologic factors have been considered. In fact some authors have documented higher incidence of acute rejection episodes (but also more technical problems) in male recipients of

kidney grafts from female donors [Vereerstraeten P et al, 1999; Zeier M et al, 2002]. Our data confirmed this trend but the real meaning of this tendency is not clear. Further possibilities to consider would be an influence of chromosomal sex or sex hormones on vascular endothelial cells, one potential interface relevant for allograft recognition [Briscoe DM et al, 2002], or gender differences in the susceptibility to ischemia reperfusion injury. Anyway even if kidneys of female donors are more susceptible to ischemia/ reperfusion injury is still controversial [Zeier M et al, 2002].

The importance of prolonged cold ischemic time as a risk factor for DGF has been described in many studies, we did not observe its significance in the present study. Quiroga et al reported that CIT [Quiroga I et al, 2006] is the most significant risk factor for the development of DGF in an adults cohort and its effect appears to be continuous. It means that each hour even at short CIT adds additional risk. This observation is supported by some investigators on adults kidney transplant [Kyllonen LE et al, 2000] but confuted from others, who suggested that there are significant time points after which the risk of DGF accelerates. Su et al. [Su X et al, 2004] show that the effect is significant for times over 37 h compared with baseline. The Collaborative Transplant Study [Collaborative Transplant Study. Newsletter 2, 2004: www.ctstransplant.org] suggests that there is 'little effect below 25 h', but their proofs do not seem to be statistically strong. The probable causes of short cold ischemic time in our experience are: (1) the small geographical characteristic of Italy, as compared with other countries

transplantation centers, and (2) our deceased donor kidneys were not implanted if CIT exceeded 24 hours.

About parameters associated with donor brain-death donor resuscitation, except for non-traumatic cause of death, the others did not show an relationship with DGF. Cerebrovascular accidents as the cause of donor death negatively affected graft function in the immediate post-opertaive time and this was consistent with other recent published studies on adults [Giral M et al, 2007; Shaheen MF yet al, 2010]. Epinephrine has been demonstrated to be as independent predictive factor for DGF in many reports. Giral et al [Giral M et al, 2007] reported that this drug, used in cases of severe hemodynamic and cardiogenic instability in the donor, could increase the risk by 4.3 in an adults population. However, we did not observe a significance of any inotropics utilize. However indirectly, being the resuscitation covariates traumatic cause of death associated with a significantly shorter DGF, this could be related to an efficient resuscitation of the donor without massive use of inotropics to control of the hemodynamics.

The short and long term effects of DGF are controversial. Several studies have reported negative influences on long-term graft survival [giral.Classe et al, 1998; Marcen R el al, 1998; Boom H et al, 2000], while other authors have not claimed such an association [McLaren AJ et al, 199; Chatziantoniou C et al, 2008]. In present study, 6 month graft function between the two groups showed significant differences, but the survival was similar. When evaluating kidney function in the child recipient at 6 months after transplant, GFR, expressed by the CrCl, was significantly lower in the group that experienced DGF in the immediate post-

operative time. Furthermore the graft biopsy made at the same time showed in an univariate analysis that group 1 had a significative (P.09) higher rate of normal biopsies than group 0. Acute and chronic rejection histological patterns did not revealed any differences between the two groups. Just 3/11 grafts of group 0 were lost in the immediate post-operative time for vascular thrombosis, thanks to the use of heparin or low-molecular weight heparin in the early post-operative period, i.e. during the first 10-15 days. Our overall graft survival at 6 months of 97.15% was comparable with current actuarial graft survival at 1 year in unselected renal transplant children that exceed 90% [Offner G et al, 1999; Tejani AH, 2000]. Patient deaths at 6 months showed no significant difference between the two groups. Although DGF influenced short-term graft function, this study did not demonstrated a reduction in patient or graft survival at 6 months after transplantation.

CONCLUSIONS

Kidney transplantation is considered the optimal treatment for children with chronic kidney failure. The approach to very long-term prognosis is a major issue in pediatric nephrology. The reduction of donor and recipient risk factors is essential to improve the long-term graft outcomes, especially in the pediatric population, due to their life expectancy. Taken together, based on a larger number of brain dead donors than in previous studies and based on a unique pediatric recipient population, we show that some donor parameters have even in children a significant impact on DGF and that they are dependent on a good management of the donor in the intensive care unit. We also understand that donor age is critical. We have had the confirmation that paediatric donor kidneys should be given preferentially to paediatric recipients, due to better long-term graft function, as it adapts to the body size increase of the child over time. Donor/recipient gender combination revealed important to be considered but its meaning have to be ruled out. The limitations of the study, that we want to overcome in the future, include the low number of patients explored and short follow-up considered.

In conclusion careful management of brain dead donor resuscitation, particularly in case of vascular cause of donor death, combined with the usual attempts to maintain CIT above 24 hr and to avoid donor/recipient age and weight discrepancies, should further decrease DGF and increase graft survival. Although CIT has not been clearly identified as in adults series as an important risk factor, efforts should be made to reduce it as much as possible. It is unwise to place emphasis on ‘cut-off values’ that have not been rigorously demonstrated.

Furthermore we have learnt that renal transplantation in the pediatric group is an interdisciplinary task involving transplant surgeons, nephrologists, and intensive care physicians. The influence of a specialized pediatric transplant and nephrological environment has a direct effect on the results (e.g. intensive care, nurse training, nutrition, pharmacology and psychology).

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