© Med Sci Monit, 2011; 17(12): RA282-291
PMID: 22129915

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Review Article

Received: 2011.11.22
Accepted: 2011.11.22
Published: 2011.12.01

Progress in abdominal organ transplantation

Maciej Kosieradzki[1], Wojciech Lisik[1], Wojciech Rowiński[2,3], Piotr Małkowski[4]

[1] Department of General Surgery and Transplantology, Medical University of Warsaw, Warsaw, Poland
[2] Department of Surgery, Faculty of Medical Sciences, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland
[3] Department of Immunology, Transplantology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland
[4] Department of Surgical and Transplantation Nursing, Medical University of Warsaw, Warsaw, Poland

Source of support: Self financing

Summary

The excellent results of vascularized organ transplantation have resulted in an increasing number of end-stage organ failure patients seeking such treatment. The results of organ transplantation depend on a number of factors – the quality of the donor (and an organ), living *vs.* deceased donation, magnitude of ischemic injury (and its prevention), and recipient-dependent factors. Ischemia/reperfusion injury in organ transplantation is a multifactorial process, which may lead to delayed graft function. In addition, surgical and preservation techniques, type of immunosuppressive regimens, complications after transplantation and post-transplant management may also have a significant impact on short- and long-term results of transplantation. In this paper we describe advances in transplantation in recent years, with particular emphasis on kidney, liver, intestines, whole pancreas and pancreatic islets.

key words: **kidney transplantation • liver transplantation • intestines transplantation • pancreas transplantation • pancreatic islets transplantation**

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=882119
Word count: 6778
Tables: –
Figures: –
References: 95

Author's address: Wojciech Lisik, Department of General Surgery and Transplantology, Medical University of Warsaw, Nowogrodzka 59 St., 02-006 Warsaw, Poland, e-mail: wojciech.lisik@wum.edu.pl

ORGAN DONATION AND KIDNEY TRANSPLANTATION

Excellent results of kidney and other organ transplantation resulted in an increasing number of end-stage organ failure patients seeking such treatment. The number of available organs is insufficient; hence, as someone had said, the waiting lists are becoming the waiting to die lists. Deceased organ donors are widely used in the western hemisphere; living donors are used all over the world.

The results of organ transplantation depend on a number of factors – the quality of donor (and an organ), living *vs.* deceased donation, magnitude of ischemic injury (and its prevention), and recipient-dependent factors. The quality of the donor kidney has a direct effect on important clinical outcomes such as acute rejection, delayed graft function, and patient and allograft survival. The term "expanded criteria donor" (ECD) was introduced by Kauffman et al. in 1997 to describe deceased donor organs that do not meet the standard criteria for organ donation (SCD) and is preferred over other terms in use, such as „marginal", „suboptimal", „compromised", „inferior" or „nonstandard". In 2002 UNOS established an ECD definition of deceased donors that can be summarized as follows: a standard-criteria (ideal) donor (SCD) is considered a young patient without hypertension or diabetes who died due to a motor vehicle crash. An expanded criteria donor (ECD) is one who, at the time of death, is age equal to or more than 60 years, or is age 50–59 but has any 2 the following 3 criteria – cerebrovascular accident as a cause of death, history of systemic hypertension, and terminal serum creatinine over 1.5 mg/dL. Kidney transplantation from ECDs increases the risk of a graft failure by 70% (relative hazard ratio 1.70). In addition, the term ECD includes donors with more than 20% globally sclerosed glomeruli on the preimplantation biopsy, HBV- or HCV-infected, with malignant neoplasm, sepsis, or significant anatomic abnormalities.

Donor age is considered as one of the most important risk factors affecting renal transplant outcomes, as demonstrated in several multicenter studies. However, the number of patients waiting for a kidney transplant and aged 65 years and above is steadily increasing as well. Within the Eurotransplant region, there has been a significant increase in renal transplants in recipients older than 65 years – from 3.6% in 1991 to 19.7% in 2007.

Due to the organ shortage, within recent years organs were also recovered from donation after circulatory death (DCD). The donation after circulatory determination of death (DCDD) refers to the situation when the patient does or does not meet the criteria for brain death and in whom cardiac standstill (or failure of circulatory function) occurs before the organs are procured. The cessation of cardiac function could have occurred spontaneously (uncontrolled DCD) or been allowed for deliberately (controlled DCD). Such donors also can be classified as "standard" or "expanded" DCD.

Numerous reports have been published on the outcome of renal transplants from ECDs. ECD kidneys have worse long-term survival than standard criteria donor kidneys. A common conclusion of these studies is that patients younger than 40 years or scheduled for kidney retransplantation should not receive an ECD kidney, and that patients 40 years or older, especially with diabetic nephropathy, show better survival when receiving an ECD kidney than remaining on dialysis therapy. The results of kidney (and sometimes liver) transplantation from DCD donors are generally favorable, but worse in elderly transplant patients. Although ECD kidney transplantation is increasing, the substantial discard rates for ECD kidneys in the USA have not changed, with 20–30% of all ECD-recovered kidneys discarded in 2005, despite implementation of an ECD allocation algorithm designed to facilitate placement.

The number of living donor kidney transplantation has also increased all over the world. The Amsterdam Forum established a consensus on the use of living donors. However, the shortage of organs has led to a more extensive use of live donors in kidney transplantation, and, most unfortunately, a new category of extended (sometimes called "marginal") living donors have also appeared. Good results of kidney transplantation from such extended living donors are reported [1, 2] but, unfortunately, no long-term follow-up data are available.

Due to the organ shortage, many transplant centers broadened their criteria for organ acceptance, including history of a variety of co-morbidities in donors. The use of organs from donors with a medical history of malignancy, in order to reduce the waiting list mortalities, remains a dilemma. Nickkholg recently published a review (with a case report) on the need for vigilance in extended criteria donors with a history of malignancy [3]. The author concluded that in order to minimize the risk of tumor transmission, especially in the donors with a history of cancer, extensive evaluation including surgical exploration of all body cavities is a must. Any suspicious lesion should prompt a frozen section biopsy.

Ischemia/reperfusion injury and delayed graft function

Ischemia/reperfusion injury in organ transplantation is a multifactorial process, which may lead to delayed graft function (DGF), and has a significant impact on short- and long-term graft survival. Occurrence of delayed graft function depends on a number of factors: donor hemodynamic stability, warm and cold ischemia time, and the storage method. Suszka-Świtek et al. [4] studied changes in the pro-inflammatory markers in the initial period after transplantation in kidneys from deceased donors, and concluded that delayed graft function is accompanied by high CRP level in donors and prolonged rise of IL-1β content in blood serum on the 4th day after transplantation. IL-6 content in this period revealed a similar tendency in recipients' pairs that had been given kidneys from the same donor, reflecting the condition of the transplanted organ.

Activation of the renin-angiotensin system may be important in the pathophysiology of DGF. Preservation solutions are thought to minimize ischemic injury, and appropriate choice of the solution should contribute to improved graft function and better prognosis for graft survival. Sulikowski [5] studied the effect of UW and EC preservation solutions on expression of selected genes in rat kidneys. Perfusion with UW and EC caused an increase of renin I, angiotensinogen and angiotensin I-converting enzyme genes expression. This increase was abated in kidneys perfused with UW solution in comparison to EC.

Donor treatment with dopamine (DA) proved to be an effective modality to improve organ quality by reduction of hypothermic, ischemic and reperfusion (I/R) injury. It is unknown by which mechanism DA reduces edema formation and inflammation. Hanusch et al. studied the effect of dopamine on edema formation and inflammation of the lung in a rat model, and indicated that dopamine-mediated protective effects on I/R damage and inflammation in donor lungs most likely occur via adrenergic receptors [6].

Ultrasonography has an important role in diagnosis of the post-transplant graft dysfunction. Grzelak et al. [7] studied disturbances in perfusion of transplanted kidneys (KTx) following an acute occlusion of 1 of the supernumerary renal arteries (SRA). Contrast-enhanced ultrasonography may enable a precise evaluation of graft's ischemic foci due to occlusion of SRA in the early post-transplant period. The introduction of ultrasound contrast enhancement (US-CE) opened-up new directions in ultrasound diagnostics, especially in the assessment of tissue perfusion of parenchymal organs (eg, in the diagnostics of focal liver lesions). The use of ultrasound contrast enhancement is a highly promising diagnostic tool in kidney allograft recipients, but to date experience with its use in this clinical setting is very limited. Grzelak et al. assessed the usefulness of this new technique using sulphur hexafluoride in the early post-transplant assessment of graft perfusion [7,8]. Time-intensity curves (TIC) were compared with hemodynamic flow parameters (resistive index: RI) in patients with good early graft function (EGF) and acute rejection (AR) or acute tubular necrosis (ATN) as a cause of delayed graft function (DGF). Results of the study showed that delay of contrast medium inflow strongly indicates delayed graft function, and may be of use in the differential diagnosis of delayed graft function.

Apoptosis is a form of cell death observed in kidney grafts as a result of ischemia/reperfusion injury. Król et al. analyzed the intensity of apoptosis in renal tubules after cold storage in respect to early and 12-month post-transplant graft function. Their study showed that increased apoptosis of tubular epithelial cells after cold storage does not determine early and later kidney excretory function [9].

Kidney storage and preservation techniques

Acute graft dysfunction can be caused by ischemic damage or immunological injury leading to serious consequences both in the short- and long-term. Cold storage (CS) for less than 24 hours of cadaveric kidneys procured from hemodynamically stable donors is a safe procedure. The quality of the renal allograft and the efficacy of the preservation method are directly related to the rate of recovery of renal allograft function upon reperfusion. Although cold preservation with UW or HTK solution has been the standard for years, graft preservation with machine perfusion (MP) has become a method of choice for many centers, in part due to recent reports of superior efficacy. Kwiatkowski, in a small and non-randomized prospective study, documented that storage of kidneys by machine perfusion may improve graft survival by limiting chronic changes in renal allografts, and reduces the number of patients who return to long-term dialysis treatment post-transplant [10]. Moreover, the same authors compared the histological changes 5 to 10 years after transplantation in kidneys preserved with machine perfusion and with cold storage. In the CS group, histopathological lesions consistent with interstitial fibrosis and tubular atrophy were more frequently encountered than in the MP group (90% *vs.* 64%, $p<0.05$). Chronic rejection was more frequent in the CS group (9% *vs.* 3%, $p<0.05$). The remaining lesions encountered in biopsies did not differ significantly between groups. They concluded that kidneys preserved by cold storage are more frequently affected by chronic rejection and interstitial fibrosis [11].

Over the past decade, the criteria for acceptable donor kidneys have been expanded to accommodate a rising demand for transplantation. High-risk donors include children <5 or adults >60 years of age, donors with significant comorbidities such as hypertension, vascular disease or diabetes mellitus, and those with renal impairment. Donation after cardiac death (DCD) donors pose a particularly high risk, as a combination of warm ischemic time (WIT) and CIT contribute to the level of the ischemia reperfusion injury, resulting in an extreme rate of DGF. The efficacy of the preservation method and the duration of the ischemic time, which are crucial in determining the potential for the recovery of allograft function, are even more critical when using DCD donors [12]. Moers et al. recently published results of an international, multicenter, randomized study of MP versus static CS on reducing the incidence of DGF in recipients of deceased-donor transplants [13]. Their results confirm earlier reports that preservation of deceased donor kidneys with hypothermic MP is associated with reduced incidence of DGF. Watson et al. reported the results of a multi-center trial of MP *vs.* CS for prevention of DGF in recipients of DCD organs [14]. The protocol of the study was similar to that of Moers et al. (one kidney from each donor was randomly assigned to MP and the other to CS to control for donor characteristics). Their findings do not support the general conclusions from the Moers study related to this group of high-risk donors (DCDs). Moreover, the study was stopped early after 80 patients were enrolled and no advantage of either preservation method was observed. Despite the documented positive effect of machine perfusion on a long-term kidney function, its wide use is limited due to higher costs. Wszola [15] analyzed the difference in costs of kidney transplantation in patients who received cold stored *vs.* machine perfused organ. Despite higher costs of machine perfusion in the first month post-transplantation, it is a cost-reducing method of renal preservation, and the costs equaled those of cold storage at the 16th month after transplantation.

Since acute graft dysfunction after transplantation may lead to serious adverse consequences, there is a need for an ability to predict kidney function before transplantation. Likewise, biomarkers of immune and non-immune injury at different time-points of the transplantation are needed, beginning from potential kidney donors where acute kidney damage (AKI) can pass unnoticed, during the early post-transplant period to predict acute transplant dysfunction of various etiology, and during long-term follow-up to be aware of the cause of chronic histological changes. The implementation of novel biomarkers could increase the sensitivity of diagnosis and monitoring of kidney injury in transplant recipients. The most promising biomarkers in AKI for clinical use include a plasma panel consisting of neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C, and a

urine panel including NGAL, Il-18 and kidney injury molecule 1 (KIM-1). Most of these biomarkers were developed in a non-transplant AKI, so their role in clinical transplantation needs to be confirmed [16].

Machine perfusion has also been documented to allow forecasting delayed graft function before transplantation. Goldstein et al, in a retrospective study, analyzed the contribution of total cold ischemic time (CIT), cold static preservation time (CST), machine pulsatile preservation time (MPT), and donor and histologic parameters to delayed renal allograft function (DGF) in a cohort of 946 deceased donor kidneys, machine perfused before transplantation. They concluded that donor type, terminal eGFR, and MMRR can be used as pre-transplantation predictors of function [17].

Complications after kidney transplantation

Successful salvage of a renal allograft failing from compromised venous outflow due to acute deep venous thrombus (DVT) has not been reported in the post-operative setting. Fulton published a case report of successful renal decongestion by catheter-directed thrombolysis of the DVT with tPA through the ipsilateral popliteal vein over a 48-hour period [18].

Invasive mucormycosis is a very rare infection after kidney transplantation. In a retrospective study, Einollah reported 25 renal transplant recipients with mucormycosis [19]. The definitive diagnosis of mucormycosis was established by a biopsy specimen of the involved tissue. Overall mortality rate was 52% (n=13), and in recipients with pulmonary infection it was 100%; however, mortality rate in the rhinocerebral form of the disease was lower (30.8%).

Immunosuppression

In general, standard immunosuppressive regimens consist of calcineurin inhibitors (eg, tacrolimus or cyclosporine), anti-proliferative agents (eg, mycophenolate mofetil – MMF) and corticosteroids to prevent graft rejection, along with high-dose corticosteroids, or polyclonal or monoclonal antibodies to treat rejection. Induction regimens to prevent early acute rejection have become increasingly common in recent years.

Antilymphocyte globulin induction therapy has been shown to reduce the incidence of acute rejection episodes following kidney transplantation in high-risk patients as compared to induction or use of interleukin-2 (IL-2) receptor antagonists. These findings are consistent with the recent recommendation from the KDIGO clinical practice guidelines. The positive effect of an ATG bolus administered during surgery has been well documented. Kaden [20] recently published results of long-term follow-up of kidney recipients who received deceased donor kidneys. Long-term (10 years) post-transplantation graft function was better than in patients who did not receive ATG. Schenker [21] recently published the results of single-dose thymoglobulin induction (1.5 mg/kg b.w. i.v.) effects of single-dose Thymoglobulin on graft and patient outcomes, with an emphasis on the differences between living-related donors (LRD) and living-unrelated donors (LURD). Despite the retrospective nature of the study, induction therapy in living donor kidney transplantation was associated with excellent patient and graft survival. Low levels of relevant complications were observed, particularly with regard to malignancy and infection rates over a mean follow-up period of 4.5 years.

Dyslipidemia is an important complication affecting kidney transplant recipients. Statins, the first-line therapy, are often insufficient. Ezetimibe may be effective in combination with statin therapy. Ezetimibe is the first of a novel class of selective cholesterol absorption inhibitors recently approved by the US Food and Drug Administration for treatment in the United States. Ezetimibe inhibits the absorption of biliary and dietary cholesterol from the small intestine without affecting the absorption of fat-soluble vitamins, triglycerides, or bile acids [22]. Rodrigues-Ferrero performed a retrospective study to determine the safety and efficacy of ezetimibe treatment in addition to statin therapy among 27 stable renal transplant patients with uncontrolled hypercholesterolemia [23]. The authors confirmed that, when combined with statin therapy, ezetimibe seemed to be a safe and effective therapy for uncontrolled dyslipidemia among renal transplant patients. Similar results were published by Niemczyk [24].

Generic Immunosuppressants

Since a number innovative immunosuppressive drug patents have expired in 2009 and 2010, generic compounds have recently entered the market. There is considerable debate regarding the efficacy and safety of generic drug substitutions in solid organ transplant recipients. In November 2010, the Council of ESOT has commissioned an Advisory Committee to formulate recommendations on the use of generic drugs in solid organ transplant recipients [25]. As a society, ESOT is not opposed to the use of generic drugs. However, in order to safeguard the substitution process of generic drugs, ESOT proposed to regulate generic substitution of the NTIDs in vulnerable patient populations. This applies to calcineurin inhibitors (ciclosporin and tacrolimus), mTOR inhibitors (sirolimus and everolimus) and mycophenolates (mycophenolate mofetil and mycophenolate sodium). In order to achieve safe and controlled generic substitution, we propose detailed monitoring of the patients (ambulatory visits, drug concentration, and metabolic profile). Momper et al. [26] reported a study on converting liver and kidney transplant recipients from brand-name to generic tacrolimus. Drug concentrations fell on average by 15.9%, or 1.98 ng/mL in liver recipients and 11.9%, or 0.87 ng/mL in kidney recipients. The target level reported in this paper was 6-8 ng/mL for stable liver patients and 5–7 ng/mL for kidney patients. However, one-third (10/30) of the liver patients experienced a decrease of 25% or more, and one-tenth (3/30), as high as 50%. Furthermore, 2 of 30 patients had levels that increased by 50% or more. Of 30 kidney recipients, 12 had their levels fall by at least 25%, with 2 patients experiencing a decline of 50%. Only 1 patient experienced an increase of 25%. In a recent issue of the American Journal of Transplantation [27], Klintmalm stressed that there is an urgent need for the US FDA to become involved in this issue and implement changes in its approval process for generics of critical-dose drugs.

Several generic cyclosporine (CsA) formulations have been developed over the last decade and are now widely available.

Kahn [28] reported results of conversion of 117 renal transplant patients to generic CsA formulation and the use of that generic preparation in 26 *de novo* patients. They concluded that stable and *de novo* renal transplant patients can be safely converted from Neoral to CicloHexal on a 1:1 dose basis. Durlik et al. [29] reported on the efficacy and safety of generic ciclosporin (Equoral) in renal transplant patients. Patients were administered an immunosuppressive regimen of azathioprine (or mofetil mycophenolate [MMF]), prednisolone and Equoral® (10 mg/kg/day, given 12 hours before the patients' surgical procedure, and a maintenance ciclosporin dose of 4–6 mg/kg/day thereafter). The authors concluded that the generic ciclosporin Equoral® is effective and has the usual safety and tolerability profile of ciclosporin when used as a calcineurin-inhibitor component of an immunosuppressive regimen in *de novo* renal transplant patients. Niemczyk recently reported on a 5-year follow-up of kidney transplant patients who were given *de novo* generic formulation of Cyclosporine A [30]. The patients treated with generic cyclosporine had an excellent 5-year patient and graft survival and it effectively prevented acute rejection episodes. However, most patients needed modification of the initial immunosuppressive regimen. Abdallah [31] reported on a comparison of original mycophenolate mofetil and its generic preparation in 18 patients who underwent kidney transplantation. The follow-up period was 2 years. Use of mycophenolate mofetil 500 provided safe and effective immunosuppressive therapy compared with mycophenolate. However, as the duration of the study was short, these results need to be confirmed in a long-term study. Abdulnour [32] reported retrospectively on the drug level and serum creatinine in 4 pediatric patients inadvertently switched from original tacrolimus or cyclosporine to generic preparation. Creatinine levels were similar pre- and post-switch (eGFR >75 mL/min/1.73 m^2) in the first 3 patients. Patient 4 experienced a biopsy-proven acute rejection immediately after switching. Mean creatinine rose from 1.15±0.05 to 2.168±0.07 after switch ($p<0.001$). Given the mixed results of early data, the authors suggest careful monitoring of pediatric patients who get switched to generic tacrolimus.

The main argument for the use of generic immunosuppressive preparations is that such therapy should be cost-saving. However, taking into consideration the costs of more frequent ambulatory visits with the need of drug level estimation, this may not be true. Hederman recently reported on the healthcare cost in renal transplant recipients treated with generic preparation [33]. Despite initial cost savings associated with generic CsA, *de novo* renal transplant recipients incurred greater total healthcare costs than those treated with brand-name CsA. Patients receiving generic CsA may need higher doses or other immunosuppressants to maintain the transplanted kidney than patients receiving brand-name CsA. Providers and payers need to be aware of potential differences in total healthcare costs between formulations of bioequivalent critical-dose drugs to make the best choice for patient care.

Kidney Transplantation in Sensitized Patients

Despite recent advances in the field, antibody-mediated rejection (ABMR) remains an important issue in clinical transplantation. Treatment options are limited and long-term outcomes are not good. Consequently, the presence of alloantibodies continues to be an important challenge to clinicians for providing sensitized patients or incompatible donor/recipient pairs with a suitable option for transplantation.

Basu et al. reported first (n=68) and re-transplants (n=155) functional outcomes. No difference in graft survival was noted between first and re-transplanted patients [34]. Factors affecting patient survival on univariate analysis were age >55 years (p=0.015), deceased donor transplant (p=0.009), first transplant patient (p=0.004) and diabetes mellitus (DM) as the cause of end-stage renal disease (ESRD) (p=0.005). On multivariable analysis, factors affecting patient survival were re-transplant *vs.* first transplant (relative risk [RR]=0.54, p=0.009) and cause of ESRD (DM *vs.* no DM, RR=1.91, p=0.012). Diabetes as a cause of ESRD was the only factor affecting graft survival on univariate (p=0.015) and multivariate analysis (DM *vs.* no DM, RR=1.63, p=0.017). The authors concluded that high PRA recipients of first transplants had poorer patient survival than did high PRA re-transplants. On multivariate analysis, diabetes etiology of ESRD and first transplantation were found to be independent risk factors for poorer patient survival.

Results of kidney transplantation in untreated sensitized recipients with a pretransplant positive crossmatch are drastically inferior to patients with a negative crossmatch. A plasmapheresis-free protocol of desensitization of kidney transplant candidates with high Calculated Panel Reactive Antibody (CPRA) was initiated. Kozlowski et al. published the results of kidney transplantation in 5 patients with CPRA of 94±18% awaiting kidney transplant from living or deceased donors, who received rituximab (1 g × 2 doses) and intravenous immunoglobulin (IVIG 2 g/kg × 2 doses) without plasmapheresis. Three out of 5 patients were sensitized only to class II HLA antigens. All of the candidates initially demonstrated reduction of HLA antibodies, but statistical significance was only obtained in 1 patient with class II antibody and in another with only class I. Depletion was transient, with swift antibody rebound. Rituximab effectively depleted CD20 cells in peripheral blood [35]. They concluded that highly allo-sensitized patients with a CPRA above 85% may not benefit from a combination of rituximab-IVIG alone, and that an individualized approach to the treatment of highly sensitized patients is still required.

The Roche Organ Transplantation Research Foundation (ROTRF) organized a symposium during the XXIII Congress of the Transplantation Society in Vancouver, Canada to discuss current understanding in ABMR and ways to prevent it. Bradley reported the summary of this meeting [36]. As discussed by Dr. Denis Glotz, desensitization is the practice of eliminating pre-existing alloantibodies to reach a negative crossmatch and thus allow transplantation, as well as avoiding their adverse effects. Desensitization protocols are mainly based on the use of IVIg, either high-dose alone or in combination with rituximab, or low-dose in combination with plasma exchange.

Pancreas and Pancreatic Islets Transplantation

Transplantation of the whole pancreas

Insulin-dependent diabetes mellitus is associated with a high incidence of management problems and secondary

complications. Simultaneous kidney and pancreas transplantation (SPKT) has become an effective therapy for a selected group of patients with end stage renal disease due to type 1 diabetes mellitus. The University of Minnesota Minneapolis Transplant Center has the world's largest experience in pancreas and pancreatic islets transplantation. Dr. Sutherland founded the International Transplant Registry, which collects the results of the procedures done all over the world. The results of pancreas transplantation published in 2001 [37] improved over the last decade. Gruessner [38] has recently analyzed the outcome of 25 000 cases followed-up over the course of 24 years at the International Pancreas Transplant Registry. Procedures were divided into 3 categories: simultaneous kidney pancreas transplantations (SPKT), pancreas after kidney transplantations (PAK), and pancreas transplants alone (PTA). The number of transplants was increasing until 2004 and then declined. The decrease was observed not only in PAK (50%), but also to some extent in SPKT. The tighter donor criteria could be observed (younger donors, trauma cause of death, shorter ischemia time). However, this might also have been due to improving results of islets transplantation. During the last decade incidence of serious surgical complications have decreased and immunosuppressive protocols have improved. This has led to significant improvement in patient survival and graft function in all 3 categories of pancreatic transplantation.

Nevertheless, several complications still occur and affect early results of pancreas transplantation. The surgical technique used for organ procurement from deceased donors is of major importance. Different procurement techniques have been depicted for combined pancreas and liver graft retrieval, which ranged from a complete *in situ* dissection of the vascular supply before cold perfusion to rapid en bloc removal of both organs without warm dissection. Despite significant differences between these 2 techniques, duodenal stump closure is always required. Rapid en bloc technique for liver and pancreas recovery has been used by different groups around the world with slight modifications. Fridell [39] described multiorgan procurement technique, which can be used when both liver and pancreas are recovered for transplantation. Recently Ruy Cruiz [40] described a new promising technique of modified multivisceral graft procurement.

Pancreas graft recipients still face a higher postoperative morbidity than in other types of solid organ transplantation [37]. Rejection and graft thrombosis are the main causes of early graft loss. Early diagnosis of pancreas graft rejection is important. There are some clinical non-invasive parameters, which let to recognize complications early, and can help to improve graft survival. Decreasing urinary amylase excretion is no longer in use since the bladder drainage technique of the transplanted pancreas is seldom used. Increasing serum amylase concentrations are not specific, and the rise of blood glucose is a relatively late indicator of pancreas allograft destruction. Complement activation might occur during rejection and thrombosis, leading to elevated complement split products. Suermann [41] investigated the value of serial complement split product C3d measurement in differentiation of acute rejection and graft thrombosis after pancreas transplantation. The authors found that plasma C3d levels increase during pancreas graft rejection, but not during kidney rejection. However, single C3d measurement has no predictive diagnostic value after SPKT, and routine testing cannot be recommended. The finding of decreasing C3d values suggests thrombosis.

Intra-abdominal infections (IAI) are among the most common causes of pancreatic graft loss and recipient death in the early period following simultaneous pancreas-kidney transplantation (SPK). Ziaja et al. [42] recently reported their experience in SPK with 46 transplants; IAI developed in 10 recipients (21.7%). More IAI recipients required transfusion of more than 2 blood units (90% *vs.* 47%, p=0.028) or relaparotomy (80% *vs.* 14%, p<0.001) in comparison with patients without IAI. The authors concluded that perioperative blood loss requiring transfusion and necessity for relaparotomy increase the risk of IAI after SPK. Development of IAI after SPK may result in impaired kidney graft function and increases patient mortality in the early postoperative period.

Pancreatic islets transplantation

Islet transplantation represents a good therapeutic alternative to whole pancreas allotransplantation, especially since the introduction of glucocorticoid-free immunosuppressive regimens. However, while 80% of cases achieve insulin independence at 1 year, islet function decreases steadily to 10% of insulin independence by 5 years after transplantation. Loss of islet function is not only due to immunological reasons (allotransplantation only) but also due to the site of grafting and instant blood-mediated inflammation reaction (IBMIR) and apoptosis [43].

Complications associated with intraportal islet injection and the progressive functional decline of intrahepatic islets encourages the exploration of alternative sites. Tchervenivanov was the first to show in pigs that transplantation of pancreatic islets into the submucosal space of the stomach offers minimally invasive access [44,45]. Transplanted islets functioned well. Caiazzo also documented that autotransplantation of the islets into the gastric submucosa showed promising results and was considered a possible alternative site for islets transplantation [46]. Stomach and the gastric submucosal space are well vascularized, with a poor immunological status and easy access. Echeverri presented an interesting paper at the ATC in 2009 [47], later published in the American Journal of Transplantation, documenting that islets can be transplanted endoscopically. Wszola published similar results [48]. The authors endoscopically transplanted allogeneic islets into the gastric submucosa in diabetic pigs (induced by injection of streptozotocin). Tx-group animals had a significantly lower insulin requirement and significantly lower mean glycemia since the first day post-transplantation.

Liver Transplantation

There has been continuous progress in surgical techniques, immunosuppressive therapy and post-transplant management in the field of liver transplantation. This progress is resulting in improved long-term survival rates, which at 1 and 5 years are now 90% and 85%, respectively, in children [49] and increase in graft half-life in adults to 8.5 years [50]. This success, however, has resulted in more patients seeking liver transplantation than can be served with available grafts. To meet increasing demand, healthcare managers have been forced to look for other sources of transplantable

organs, with growth of living donation programs, split livers, harvesting from donors after cardiac arrest, and intensive research in liver regeneration.

Donors and recipients

A limit on deceased donor age was challenged and livers from donors over 70 years old have been used. Inferior survival was reported in univariate tests, but was not confirmed in multivariate analysis. Hepatitis C recurrence, often postulated to be graft age-dependent, in fact was not increased in this group [51]. The Berlin group were not able to find any difference in survival of >50- or >60-year-old donor liver recipients in comparison to younger donors. Moreover, fibrosis, inflammation and steatosis at 5-year follow-up biopsies were also similar [52].

The most experienced centers utilize the living donor pool, with development of adult-to-adult living donation programs, which although higher cost, offer improved survival and quality of life to a larger number of patients [53]. To increase the living donation rate and meet the need in emergency situations, some centers accepted ABO-discordant donors with acceptable results after immunological preparation of the recipient [54] or, in very small children, even without any change in immunosuppression protocol [55].

More and more centers have adopted DCD liver transplantation programs, with uncontrolled donors with circulatory definition of death constituting up to 10% of total donor population shortly after program initiation [56]. The results of these transplants are encouraging, with 88.9% death-censored 1-year graft survival [57]. Satisfactory results led also to broadening of the acceptance criteria of controlled DCD donors. This turned out to be completely safe for the recipients, as 1-year patient and graft survival in the extended criteria DCD group was 90%, and was not inferior to standard criteria DCD liver donors [58]. However, to obtain results equal to those of standard brain-dead donor liver transplantation, it seems advisable to shorten cold ischemia time (CIT) of DCD livers as much as possible, as CIT is a strong predictor of primary nonfunction [59]. A small DCD liver transplantation group of 14 pediatric recipients had outstanding patient and graft survival of 100% after a mean of 42 months follow-up, with short organ ischemia times [60].

The sometimes desperate need for organs forces even further expansion of the limits. A discussion on utilization of extended-criteria livers from anti-HBc-positive donors was ongoing for quite some time; however, the Bolonia group have recently described a small series of transplants from HBsAg-positive donors, with satisfactory postoperative control of virus replication and no symptoms of hepatitis at 42-month follow-up [61]. Such a controversial allocation can be justified by the significant number of HBV-infected wait list candidates with HCC who, when transplanted early while still within Milano criteria, may enjoy excellent long-term results [62].

Progress in understanding liver regeneration has led to development of auxiliary liver transplantation programs for acute liver failure in young patients. Refined surgical technique, scrutiny in monitoring of the regeneration process, and slow weaning of the immunosuppression to allow graft atrophy without further complications have all recently resulted in improvement of survival, which now equals to that of whole liver replacement in acute failure [63]. However, as acute liver failure is always an emergency situation and a transplant may not be available, research on repopulation of damaged liver with healthy hepatocytes, and thus regenerating liver function, is ongoing in animal models [64]. There are strong suggestions that regeneration in acute liver failure may be enhanced pharmacologically with drugs such as plerixafor and G-CSF [65]. Another option for critical care in acute liver insufficiency can be artificial liver support to allow detoxification and time for auto-regeneration. Although MARS® and PROMETHEUS® showed no survival benefit, new devices and technologies such as albumin-leaking membranes are being tested [66].

As hepatorenal syndrome remains an unresolved problem complicating liver failure and potentially leading also to irreversible renal failure, research on its pathophysiology and treatment is ongoing. Vasopressive therapy with terlipressin or norepinephrine has proved effective in short-term reversal of hepatorenal syndrome. Those not responding to vasoconstrictors and requiring prolonged dialysis (8–12 weeks) prior to transplantation can be good candidates for simultaneous renal transplant [67]. Those with a chance of renal function recovery can be managed with intraoperative hemodialysis or hemodiafiltration. Experience with 140 such procedures was summarized by Sedra and Strum [68].

Portopulmonary hypertension is another serious problem, with 100% and 50% mortality in liver transplant recipients with mean pulmonary artery pressure of >50 or 35–50 mmHg, respectively. It has been shown recently that patients with portopulmonary hypertension can benefit from simultaneous liver and lung transplantation, yet very few centers worldwide are capable of performing this complicated operation [69].

Preservation

In 2010–2011 some important progress in liver preservation could also be observed. Columbia University Medical Center completed a phase 1 clinical trial on hepatic machine preservation, with no case of primary nonfunction and 5% early graft dysfunction compared to 25% in the control group, lower serum injury markers and shorter hospital stay [70]. Regarding static preservation, results of a randomized study comparing IGL-1 and UW solution were published, showing similar effectiveness and significantly lower cost of IGL-1 [71]. Non-anastomotic biliary complications are severe complications of liver preservation injury, and their frequency increases with ischemia time. They constitute a major surgical problem, are very difficult to treat, and often lead to retransplant. It's difficulty is illustrated by the experience of the Neuhaus group, who after 25 endoscopic interventions in a single patient were finally forced to perform a left hemihepatectomy of the transplant [72]. Some patients may be genetically more prone to non-anastomotic strictures, and CCR5, MMP2 and MMP9 polymorphisms were known to be involved [73].

Surgical technique

Outstanding progress in surgical equipment in liver transplantation has improved technical devices, biological

hemostatics, prevention and early diagnosis of coagulopathy, which all reduce the risk of intraoperative hemorrhage [74, 75] and make the procedure feasible even in extreme risk Jehovah's Witnesses.

In a recent review on full split liver transplantation for 2 adults, the Busuttil group showed that in selected, experienced centers this technique can be safely applied with excellent results and yields more liver grafts available for transplant, especially in emergency situations [76].

Studies on hepatocellular carcinoma (HCC) treatment with liver transplantation remain the focus of various surgical teams. A new consensus for HCC treatment with liver transplantation after an experts meeting in Zurich was issued early November 2011 [77]. Among other issues, the guidelines address the problem of prioritizing HCC patients on the waiting lists over other etiologies against inferior long-term results of transplantation. Also, the role of bridge therapies – although the level of recommendations remained low – in prevention of waiting list dropout was emphasized.

Post-operative management

Improvement of the results in liver transplantation was in major part achieved with ameliorated post-operative medical treatment of the recipient. Emphasis shifted from treatment of rejection towards long-term survival and avoidance of immunosuppression-related complications. It is known that only a minority of long-term (>12 months) liver transplant protocol biopsies present with normal histology, with 33% found to show features of mild but progressive idiopathic chronic hepatitis regardless of liver failure etiology, and 65% having fibrosis at 5 years. These patients are suggested to benefit from increased steroids [78], yet few of them will benefit from standard anti-rejection therapies. On the other hand, many trials focus on tolerance induction and minimization protocols to reduce the rate of immunosuppression-related complications. Steroid sparing or withdrawal showed no difference in acute rejection rate, graft or patient survival [79]. Markers of operational tolerance are extensively sought, and protocols of weaning therapy in patients with stable long-term function and no signs of rejection have been tested, with 20% successful withdrawal rate [80]. In terms of immunosuppression, a systematic Cochrane review performed in 2009 showed only minimal advantage of tacrolimus over cyclosporine for treatment of liver transplant recipients [81]. Since it can be safely converted to a once-daily regimen, tacrolimus may become a drug of choice [82].

Infections remain a serious post-operative problem in liver transplant recipients, with an increasing trend in multi-resistant bacteria. Colonization with MRSA in some centers is as high as 80% and up to 55% of VRE and infections with linezolid-resistant VRE were noted [83]. CMV disease with aggressive forms of gastrointestinal tract infection, including gastritis, colitis and hepatitis with cholestatic pattern, are also a problem on the rise. CMV immunomodulation was lately found to occur via the interleukin 10 pathway and is responsible for higher rates of bacteriemia, and fungal and viral infections [84]. More than half of invasive fungal infections are due to *Candida* spp. [85], with a growing proportion of non-albicans species, inherently resistant to fluconazole. The most severe risk factors for Aspergillus infection are retransplantation and renal failure requiring dialysis, increasing the risk 30- and 25-fold, respectively. Mortality from invasive fungal infection remains high (25–77%), and some studies claim it to be higher than after any other organ transplantation [83].

Intestinal Transplantation

The most important progress in recent years in intestinal transplantation was the significant improvement of survival, with unadjusted patient and graft 3-year survival close to 70% and 60%, and 1 year survival of 78.4% and 74%, respectively. In parallel, within the last 10 years survival on the waiting list has improved from 495 deaths/1000 patient-years at risk to less than 130 [86]. There are more than 70 centers running or developing bowel transplant programs, with over 200 procedures performed each year worldwide. In 2008, recommendations to reduce mortality from intestinal failure, including intestinal rehabilitation, transplantation and interaction among these 2, were issued [87]. Lack of standard criteria for a deceased donor of intestinal graft remains a major obstacle to development of bowel transplantation programs, although the German Transplantation Society has issued their recommendations [88].

In the beginning of intestinal transplantation, only the small bowel was used, to minimize the risk of complications. Lately, the majority of experienced centers consider inclusion of the colon in the transplant. Studies have shown the superiority of such a procedure in terms of quality of life, fecal continence and weaning off of parenteral nutrition [89]. A percentage of multi-visceral transplants (which include liver and intestine and at least 1 other visceral organ: pancreas, colon or stomach) lately has risen substantially to over 25%, although they are more likely to develop GVHD, which occurs in 9% of recipients and is a potentially lethal complication [90].

More than 70% of the recipients are on tacrolimus, and induction with antibodies (antilymphocyte globulins, daclizumab, alemtuzumab) was used in more than 80% [91]. Rejection continues to occur in approximately 50% of patients, and is an important cause of graft loss [92]. It can be facilitated by infection, even a minor one – in a group of 23 patients after intestinal transplant, who developed rotavirus diarrhea long-term after transplantation, acute rejection was diagnosed in 70% during or shortly after infection [93]. Noninvasive methods of testing for rejection are being sought, including bile acid analysis, laser Doppler flowmetry, serum gentamycin levels, granzyme B and perforin, plasma citrulline and stool calprotectin [94].

Prognosis was better in recipients with negative donor-specific antibodies, those who did not have splenectomy, and those who had a liver-inclusive transplant [95].

References:

1. El-Agroudy AE, Wafa EW, Sabry AA et al: The health of elderly living kidney donors after donation. Ann Transplant, 2009; 14(2): 13–19
2. Shrestha A, Basarab-Horwath C, McKane W et al: Quality of life following live donor renal transplantation: a single centre experience. Ann Transplant, 2010; 15(2): 5–10

3. Nickkholgh A, Frey E, Krenzel C et al: The need for vigilance in extended criteria donors with a past history of malignancy: a case report and review of literature. Ann Transplant, 2011; 16(1): 75–79
4. Caban A, Budzinski G, Oczkowicz G et al: Factors determining changes in concentrations of pro-inflammatory markers in blood serum in the initial period after kidney transplantation from dead donor. Ann Transplant, 2009; 14(4): 10–13
5. Sulikowski T, Domanski L, Zietek Z et al: The effect of preservation solutions UW and EC on the expression of renin I, angiotensinogen and angiotensin I-converting enzyme genes in rat kidney. Ann Transplant, 2011; 16(3): 108–13
6. Hanusch C, Hauser C, Geisler A et al: Reduction of oedema formation after preconditioning with dopamine in an isolated rat lung model is mediated by adrenergic receptors. Ann Transplant, 2011; 16(3): 97–107
7. Grzelak P, Kurnatowska I, Sapiecha M et al: Ultrasonographic evaluation of disturbances in the perfusion of renal graft parenchyma as a result of acute occlusion of supernumerary arteries – a new application for contrast-enhanced ultrasonography. Ann Transplant, 2011; 16(3): 23–29
8. Grzelak P, Szymczyk K, Strzelczyk J et al: Perfusion of kidney graft pyramids and cortex in contrast-enhanced ultrasonography in the determination of the cause of delayed graft function. Ann Transplant, 2011; 16(1): 48–53
9. Krol R, Chudek J, Karkoszka H et al: Apoptosis of tubular epithelial cells in preimplantation biopsies of kidney grafts with immediate, slow and delayed function. Ann Transplant, 2011; 16(3): 17–22
10. Kwiatkowski A, Wszola M, Kosieradzki M et al: The early and long term function and survival of kidney allografts stored before transplantation by hypothermic pulsatile perfusion. A prospective randomized study. Ann Transplant, 2009; 14(1): 14–17
11. Kwiatkowski A, Wszola M, Perkowska-Ptasinska A et al: Influence of preservation method on histopathological lesions of kidney allografts. Ann Transplant, 2009; 14(1): 10–13
12. Irish WD, Katz E: Cold machine perfusion or static cold storage of kidneys: why the debate continues. Am J Transplant, 2010; 10(9): 1955–56
13. Moers C, Smits JM, Maathuis MH et al: Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med, 2009; 360(1): 7–19
14. Watson CJ, Wells AC, Roberts RJ et al: Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. Am J Transplant, 2010; 10(9): 1991–99
15. Wszola M, Kwiatkowski A, Latek M et al: Long term medical and economical benefit of machine perfusion (MP) kidney storage in comparison to cold storage (CS). Ann Transplant, 2009; 14(2): 24–29
16. Halawa A: The early diagnosis of acute renal graft dysfunction: a challenge we face. The role of novel biomarkers. Ann Transplant, 2011; 16(1): 90–98
17. Goldstein MJ, Ying A, Dikman S et al: Forecasting Delayed Renal Allograft Function Prior to Transplantation. Am J Transplant, 2011, 11(Suppl. s2): 213
18. Fulton C, McGregor T, Forbes TL et al: Catheter-directed thrombolysis with tPA to restore renal function after iliac venous thrombosis post-renal transplantation. Ann Transplant, 2011; 16(1): 61–65
19. Einollahi B, Lessan-Pezeshki M, Aslani J et al: Two decades of experience in Mucormycosis after kidney transplantation. Ann Transplant, 2011; 16(3): 44–48
20. Kaden J, May G, Volp A, Wesslau C: Improved long-term survival after intra-operative single high-dose ATG-Fresenius induction in renal transplantation: a single centre experience. Ann Transplant, 2009; 14(3): 7–17
21. Schenker P, Ozturk A, Vonend O et al: Single-dose thymoglobulin induction in living-donor renal transplantation. Ann Transplant, 2011; 16(2): 50–58
22. Nutescu EA, Shapiro NL: Ezetimibe: a selective cholesterol absorption inhibitor. Pharmacotherapy, 2003; 23(11): 1463–74
23. Rodriguez-Ferrero ML, Anaya F: Ezetimibe in the treatment of uncontrolled hyperlipidemia in kidney transplant patients. Transplant Proc, 2008; 40(10): 3492–95
24. Niemczyk M, Paczek L: Ezetimibe in sirolimus-associated hyperlipidemia: to add or not to add to statins? Ann Transplant, 2011; 16(3): 132–34
25. van Gelder T: European society for organ transplantation advisory committee recommendations on generic substitution of immunosuppressive drugs. Transpl Int, 2011; 24(12): 1135–41
26. Momper JD, Ridenour TA, Schonder KS et al: The impact of conversion from prograf to generic tacrolimus in liver and kidney transplant recipients with stable graft function. Am J Transplant, 2011; 11(9): 1861–67
27. Klintmalm GB: Immunosuppression, generic drugs and the FDA. Am J Transplant, 2011; 11(9): 1765–66
28. Kahn D, Muller E, Pascoe M: Safe conversion to cicloral, a generic cyclosporine, in both stable and *de novo* renal transplant recipients. Saudi J Kidney Dis Transpl, 2010; 21(3): 426–32
29. Durlik M, Paczek L, Rutkowski B et al: The efficacy and safety of ciclosporin (Equoral(R)) capsules after renal transplantation: A multicentre, open-label, phase IV clinical trial. Ann Transplant, 2010; 15(3): 51–59
30. Niemczyk M, Paczek L: Generic formulation of Cyclosporine A, Equoral(R), in *de novo* kidney transplant recipients: five-year follow-up. Ann Transplant, 2011; 16(2): 59–62
31. Abdallah TB, Ounissi M, Cherif M et al: The role of generics in kidney transplant: mycophenolate mofetil 500 versus mycophenolate: 2-year results. Exp Clin Transplant, 2010; 8(4): 292–96
32. Abdulnour HA, Araya CE, Dharnidharka VR: Comparison of generic tacrolimus and Prograf drug levels in a pediatric kidney transplant program: brief communication. Pediatr Transplant, 2010; 14(8): 1007–11
33. Helderman JH, Kang N, Legorreta AP, Chen JY: Healthcare costs in renal transplant recipients using branded versus generic ciclosporin. Appl Health Econ Health Policy, 2010; 8(1): 61–68
34. Basu A, Falcone J, Dvorchik I et al: Outcomes of renal transplantation in recipients with peak panel reactive antibody >30% under tacrolimus-based immunosuppression. Ann Transplant, 2011; 16(3): 5–1335. Kozlowski T, Andreoni K: Limitations of rituximab/IVIg desensitization protocol in kidney transplantation; is this better than a tincture of time? Ann Transplant, 2011; 16(2): 19–25
36. Bradley JA, Baldwin WM, Bingaman A et al: Antibody-mediated rejection – an ounce of prevention is worth a pound of cure. Am J Transplant, 2011; 11(6): 1131–39
37. Sutherland DE, Gruessner RW, Dunn DL et al: Lessons learned from more than 1,000 pancreas transplants at a single institution. Ann Surg, 2001; 233(4): 463–501
38. Gruessner AC: 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). Rev Diabet Stud, 2011; 8(1): 6–16
39. Fridell JA, Joseph Tector A, Mangus RS et al: A new vascular approach to the modified multivisceral graft procurement. Clin Transplant, 2009; 23(6): 784–87
40. Cruz RJ Jr: Single-staple technique for pancreas allograft procurement. Ann Transplant, 2010; 15(2): 71–73
41. Suermann A, Vonend O, Schenker P et al: Plasma complement 3d levels in the early phase after pancreas transplantation. Ann Transplant, 2009; 14(3): 29–35
42. Ziaja J, Krol R, Chudek J et al: Intra-abdominal infections after simultaneous pancreas – kidney transplantation. Ann Transplant, 2011; 16(3): 36–43
43. Vantyghem MC, Balavoine AS, Caiazzo R et al: Diabetes cell therapy: a decade later. Minerva Endocrinol, 2011; 36(1): 23–39
44. Tchervenivanov N, Metrakos P, Kokugawa Y, Rosenberg L: Submucosal transplantation of pancreatic islets. Transplant Proc, 1994; 26(2): 680–81
45. Tchervenivanov N, Yuan S, Lipsett M et al: Morphological and functional studies on submucosal islet transplants in normal and diabetic hamsters. Cell Transplant, 2002; 11(6): 529–37
46. Caiazzo R, Gmyr V, Hubert T et al: Evaluation of alternative sites for islet transplantation in the minipig: interest and limits of the gastric submucosa. Transplant Proc, 2007; 39(8): 2620–23
47. Echeverri GJ, McGrath K, Bottino R et al: Endoscopic gastric submucosal transplantation of islets (ENDO-STI): technique and initial results in diabetic pigs. Am J Transplant, 2009; 9(11): 2485–96
48. Wszola M, Berman A, Fabisiak M et al: TransEndoscopic Gastric SubMucosa Islet Transplantation (eGSM-ITx) in pigs with streptozotocine induced diabetes – technical aspects of the procedure - preliminary report. Ann Transplant, 2009; 14(2): 45–50
49. Ng VL, Fecteau A, Shepherd R et al: Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a north american multicenter registry. Pediatrics, 2008; 122(6): e1128–35
50. Lodhi SA, Lamb KE, Meier-Kriesche HU: Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success. Am J Transplant, 2011; 11(6): 1226–35

51. Alamo JM, Barrera L, Marin LM et al: Results of liver transplantation with donors older than 70 years: a case-control study. Transplant Proc, 2011; 43(6): 2227–29
52. Schmeding M, Sauer I, Hartwig K et al: Aging of the liver graft and functional quality in the absence of recurrent disease: a 10 year histological follow-up. Ann Transplant, 2010; 15(1): 5–13
53. Northup PG, Abecassis MM, Englesbe MJ et al: Addition of adult-to-adult living donation to liver transplant programs improves survival but at an increased cost. Liver Transpl, 2009; 15(2): 148–62
54. Markiewicz-Kijewska M, Kalicinski P, Teisseyre J et al: Liver transplantation with ABO incompatible graft under immunoadsorption protocol – case report. Ann Transplant, 2010; 15(4): 68–71
55. Gelas T, McKiernan PJ, Kelly DA et al: ABO-incompatible pediatric liver transplantation in very small recipients: Birmingham's experience. Pediatr Transplant, 2011; 15(7): 706–11
56. Hernadez-Alejandro R, Wall W, Jevnikar A et al: Organ donation after cardiac death: donor and recipient outcomes after the first three years of the Ontario experience. Can J Anaesth, 2011; 58(7): 599–605
57. Dominguez-Gil B, Haase-Kromwijk B, Van Leiden H et al: Current situation of donation after circulatory death in European countries. Transpl Int, 2011; 24(7): 676–86
58. Tariciotti L, Rocha C, Perera MT et al: Is It Time to Extend Liver Acceptance Criteria for Controlled Donors After Cardiac Death? Transplantation, 2011; 92(10): 1140–46
59. Karp SJ, Johnson S, Evenson A et al: Minimising cold ischaemic time is essential in cardiac death donor-associated liver transplantation. HPB (Oxford), 2011; 13(6): 411–16
60. Bartlett A, Vara R, Muiesan P et al: A single center experience of donation after cardiac death liver transplantation in pediatric recipients. Pediatr Transplant, 2010; 14(3): 388–92
61. Loggi E, Micco L, Ercolani G et al: Liver Transplantation from Hepatitis B Surface Antigen Positive Donors: A Safe Way to Expand the Donor Pool. J Hepatol, 2011
62. Yataco M, Bonatti H, Machicao V et al: Long term survival and complications after liver transplantation in patients with chronic hepatitis B. Ann Transplant, 2010; 15(2): 27–34
63. Jaeck D, Boudjema K, Audet M et al: Auxiliary partial orthotopic liver transplantation (APOLT) in the treatment of acute liver failure. J Gastroenterol, 2002, 37(Suppl.13): 88–91
64. Mochizuki S, Kawashita Y, Eguchi S et al: Liver repopulation by transplanted hepatocytes in a rat model of acute liver failure induced by carbon tetrachloride and a partial hepatectomy. Ann Transplant, 2010; 15(4): 49–55
65. Wesson RN, Cameron AM: Stem cells in acute liver failure. Adv Surg, 2011; 45: 117–30
66. Rozga J, Malkowski P: Artificial liver support: quo vadis? Ann Transplant, 2010; 15(4): 92–101
67. Memon I, Klein CL: Impact of hepatorenal syndrome and liver transplantation. Curr Opin Organ Transplant, 2011; 16(3): 301–5
68. Sedra AH, Strum E: The role of intraoperative hemodialysis in liver transplant patients. Curr Opin Organ Transplant, 2011; 16(3): 323–25
69. Scouras NE, Matsusaki T, Boucek CD et al: Portopulmonary hypertension as an indication for combined heart, lung, and liver or lung and liver transplantation: literature review and case presentation. Liver Transpl, 2011; 17(2): 137–43
70. Guarrera JV, Henry SD, Samstein B et al: Hypothermic machine preservation in human liver transplantation: the first clinical series. Am J Transplant, 2010; 10(2): 372–81
71. Dondero F, Paugam-Burtz C, Danjou F et al: A randomized study comparing IGL-1 to the University of Wisconsin preservation solution in liver transplantation. Ann Transplant, 2010; 15(4): 7–14
72. Eurich D, Seehofer D, Veltzke-Schlieker W et al: Successful endoscopic and surgical management of non-anastomotic biliary strictures after liver transplantation – case report. Ann Transplant, 2009; 14(1): 47–51
73. Koch RO, Kaser A: Genetic insights into non-anastomotic biliary strictures after orthotopic liver transplantation. Liver International, 2011; 31(8): 1065–67
74. Czuprynska MM, Wawrzynowicz-Syczewska M, Jureczko L et al: Preemptive administration of recombinant factor VII (rVIIa) in patients transplanted due to fulminant Wilson's disease. Ann Transplant, 2010; 15(3): 7–10
75. Trzebicki J, Flakiewicz E, Kosieradzki M et al: The use of thromboelastometry in the assessment of hemostasis during orthotopic liver transplantation reduces the demand for blood products. Ann Transplant, 2010; 15(3): 19–24
76. Hong JC, Yersiz H, Busuttil RW: Where are we today in split liver transplantation? Curr Opin Organ Transplant, 2011; 16(3): 269–73
77. Clavien PA, Lesurtel M, Bossuyt PM et al: Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol, 2011
78. Ekong UD: The long-term liver graft and protocol biopsy: do we want to look? What will we find? Curr Opin Organ Transplant, 2011; 16(5): 505–8
79. Knight SR, Morris PJ: Steroid sparing protocols following nonrenal transplants; the evidence is not there. A systematic review and meta-analysis. Transpl Int, 2011; 24(12): 1198–207
80. Sanchez-Fueyo A: Hot-topic debate on tolerance: Immunosuppression withdrawal. Liver Transpl, 2011, 17(Suppl.3): S69–73
81. Haddad EM, McAlister VC, Renouf E et al: Cyclosporin versus tacrolimus for liver transplanted patients. Cochrane Database Syst Rev, 2006(4): CD005161
82. Dopazo C, Rodriguez R, Llado L et al: Successful conversion from twice-daily to once-daily tacrolimus in liver transplantation: observational multicenter study. Clin Transplant, 2011
83. Romero FA, Razonable RR: Infections in liver transplant recipients. World J Hepatol, 2011; 3(4): 83–92
84. van de Berg PJ, Heutinck KM, Raabe R et al: Human cytomegalovirus induces systemic immune activation characterized by a type 1 cytokine signature. J Infect Dis, 2010; 202(5): 690–99
85. Pacholczyk M, Lagiewska B, Lisik W et al: Invasive fungal infections following liver transplantation - risk factors, incidence and outcome. Ann Transplant, 2011; 16(3): 14–16
86. U.S. Department of Health and Human Services HRaSA, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD.: 2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1994-2008.. In.: U.S. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD.; 2009
87. Beath S, Pironi L, Gabe S et al: Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. Transplantation, 2008; 85(10): 1378–84
88. Wunderlich H, Brockmann JG, Voigt R et al: DTG procurement guidelines in heart beating donors. Transpl Int, 2011; 24(7): 733–57
89. Matsumoto CS, Kaufman SS, Fishbein TM: Inclusion of the colon in intestinal transplantation. Curr Opin Organ Transplant, 2011; 16(3): 312–15
90. Wu G, Selvaggi G, Nishida S et al: Graft-versus-host disease after intestinal and multivisceral transplantation. Transplantation, 2011; 91(2): 219–24
91. Ueno T, Fukuzawa M: Current status of intestinal transplantation. Surg Today, 2010; 40(12): 1112–22
92. Abu-Elmagd KM, Costa G, Bond GJ et al: Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg, 2009; 250(4): 567–81
93. Adeyi OA, Costa G, Abu-Elmagd KM, Wu T: Rotavirus infection in adult small intestine allografts: a clinicopathological study of a cohort of 23 patients. Am J Transplant, 2010; 10(12): 2683–89
94. Mercer DF: Hot topics in postsmall bowel transplantation: noninvasive graft monitoring including stool calprotectin and plasma citrulline. Curr Opin Organ Transplant, 2011; 16(3): 316–22
95. Farmer DG, Venick RS, Colangelo J et al: Pretransplant predictors of survival after intestinal transplantation: analysis of a single-center experience of more than 100 transplants. Transplantation, 2010; 90(12): 1574–80