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REVIEW

Review of nonimmunological causes for deteriorated graft function and graft loss after transplantation

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Summary

Various factors determine the graft- and patient survival after transplantation. HLA-matching and immunological factors are of importance for the short- and long-term survival. Apart from these obvious determinants, nonimmunological factors play an important role in defining the baseline organ quality as well as the recipients' status. The influence of these parameters on graft- and patient survival is still underestimated and is a topic of debate. On account of the increasing acceptance of marginal-donor organs these events are of increasing importance for graft survival and long-term function. We review nonimmunological causes for deteriorated graft function and graft loss after solid organ transplantation.

Introduction

The fields of transplantation biology and immunology have flourished, embellished by progressive understanding of functional dynamics and inter-relationships of leukocyte populations and subpopulations. Parallel strides have been made in elucidating the T-cell receptor – major histocompatibility complex, the importance of co-stimulation, endothelial physiology, and the differential roles of cell surface molecules. At the same time, more effective immunosuppressive agents have become available with substantive improvements in clinical results after transplantation of several types of organs. But it has also become increasingly apparent that nonspecific, nonimmunological changes associated with organ injury may affect early and late allograft function both by themselves and in combination with host alloresponsiveness [1–5]. The bulk of evidence supporting the importance of such nonimmunological insults has accumulated through clinical and experimental studies.

The observation that organs from living, related donors perform in a consistently superior manner than those from deceased donors has persisted throughout the transplant experience [6]. Although the most obvious explanation involves histocompatibility differences between the donor and the host, a clue that antigen-independent injury may also be important has been the unexpected finding that survival rates of kidneys from living, unrelated donors are virtually identical to those of one haplotype-matched living, related sources and consistently better than those of mismatched deceased donor organs [7]. That the discrepancy between the results of deceased- and unrelated living donor grafts must be based on physiologic and not genetic variables has led investigators to focus on functional and structural changes related to nonspecific injury and to design strategies toward normalizing or stabilizing tissue function and structure before and after engraftment.

It has been hypothesized that allografted organs, particularly from less than optimal sources, may not be biologically inert at the time of placement but already programmed to initiate or amplify subsequent host responses. These potentially activated organs may provoke a continuum between the inflammatory changes from initial nonspecific insults and the onset of alloresponsiveness (Fig. 1) [8]. Several donor-associated factors implicated

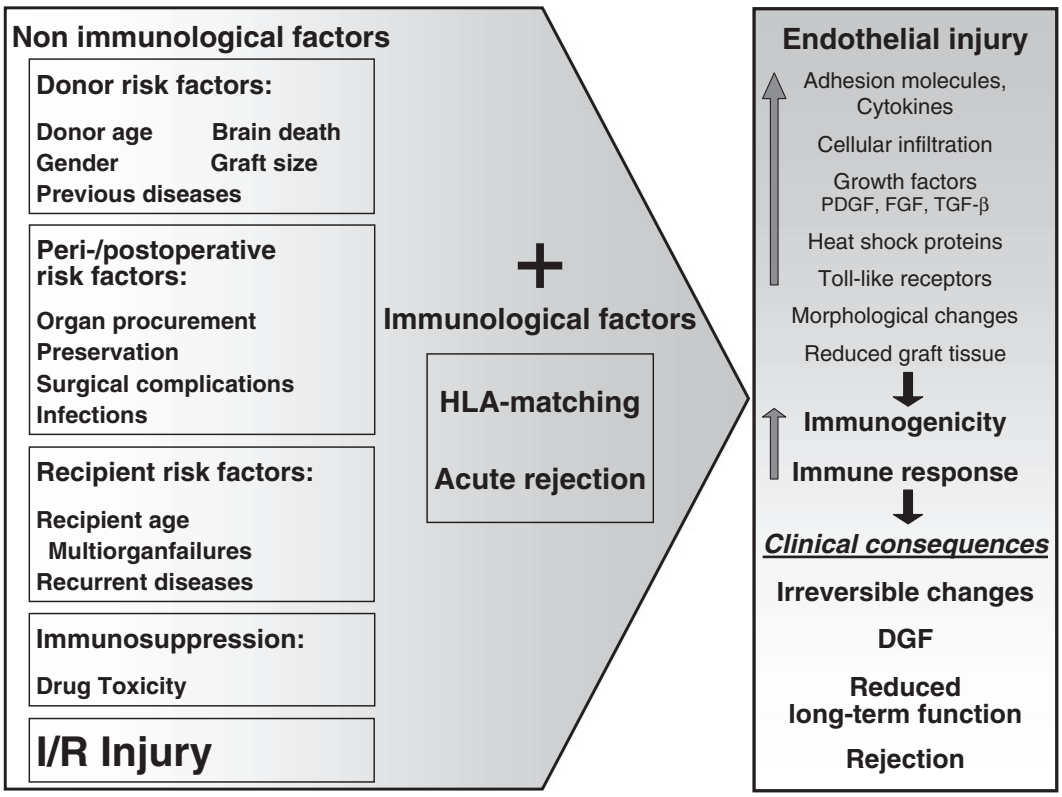

Figure 1 Factors influencing organ survival after transplantation – common pathway.

alone or in combination include age, hypertension, diabetes, the systemic effects of brain death (BD) and ischaemia/reperfusion (I/R) [7]. Nonetheless, because of the continuously increasing divergence between the availability of appropriate organs and those demanding them, a 'marginal donor pool' or 'alternative transplant list' has been established [9]. Donors >60 years are used increasingly, including those with diagnosed diseases but acceptable organ quality [10–12]. Organs sometimes accepted may also include those from younger individuals supported with high doses of inotropic agents after BD, >20% donor/recipient weight mismatch and prolonged ischaemia.

It has become clear that the inflammatory response associated with donor factors may provoke or trigger an increased level of acute host alloreactivity [13]. The continuum between nonspecific injury and episodes of acute immunological rejection may explain synergistic effects on the outcome of affected organs. Both events together produce a significantly less favourable graft outcome over the long term than if either of them were to occur separately or neither of the phenomena is experienced by the graft recipient [14]. The presence of nonimmunological risk factors may also affect the subsequent events. Thus, initial acute rejection predisposes to chronic rejection, while delayed graft function (DGF) may initiate a programmed inflammatory and fibrotic process within the organ which leads to chronic allo-immune injury as well as chronic nonimmune injury.

Several initially nonimmunological parameters have been associated with late graft dysfunction. However, it is not always possible to investigate one of these factors isolated from the other, as there is a close interaction between nonimmunological and immunological factors. The loss of graft function can be a multifactorial process which started before organ recovery during the treatment of the potential organ donor or is a result of a single event such as a surgical complication.

Brain death-associated ischaemia as a risk factor

The observation that living-donor organs show a better function and outcome than organs from deceased donors can not be fully explained away by shorter cold ischaemia time and better immunological preconditions [15,16]. BD, as a factor without obvious correlation to the specific-recipient immunological pathways is still an underestimated risk factor uniquely relevant to the deceased donor. BD is a catastrophic event, defined as irreversible injury of cerebrum, cerebellum and brain stem. Subse-

quently, BD is associated with rapid swings in blood pressure, hypo- and hypertension, coagulopathies, pulmonary changes, hypothermia and electrolyte aberrations. An initial period of excessive parasympathetic activity with low blood pressure is followed by a sympathetic activity with extensive high plasma levels of catecholamines, extreme systemic arterial hypertension and tachycardia. This is followed by a phase of severe reduction in sympathetic outflow with impairment of the inotropic and chronotropic state of the heart [17–20]. These circulatory changes, vasoconstriction and vasodilatation, lead to significantly reduced organ perfusion with severe ischaemia of the graft before recovery [17,18,21]. The question, if the state of BD is a risk factor on its own or in combination with the imminent ischaemia, cannot be answered finally. Furthermore, BD and the associated alterations stimulate different cell types to release pro- and anti-inflammatory cytokines with significant up-regulation of cytokine mRNA and increased leukocyte infiltration in tissues [9,22–26]. In addition, the altered and immunologically activated grafts trigger a more intense host inflammatory response with increased I/R injury and an increased rate of acute rejection [8,9]. Pro-inflammatory factors associated with BD such as hemodynamic instability, cytokine release and cellular infiltrates lead to structural and functional changes in somatic organs before recovery [17–20,27]. Donor BD does not only result in increased inflammation but also contributes substantially to a decreased function of these grafts compared to ideal living donors. Clinical studies showed that organs from BD donors indeed experience a higher rate of rejection episodes and DGF [28] associated with altered pro-inflammatory gene expression profiles. In regard to the increased utilization of 'marginal organs' the initial graft injury associated with risk factors around the donor procedure seem to be even more important.

Ischaemia/reperfusion injury and delayed graft function

Ischaemia/reperfusion is an important and initially nonimmunological factor influencing graft outcome in various organs [29–32]. Originally considered as an event surrounding organ procurement, preservation and revascularization, it has recently been associated with donor conditions such as BD and the nonheart-beating donor. Occurring early in the transplant process, it initiates a cascade of molecular and cellular events including the release of pro-inflammatory mediators and attraction of various cell types infiltrating the tissues initiating progressive immunological processes. Ischaemia and reperfusion are distinct events. The time period that cells, tissues and organs can remain undamaged or viable without blood supply is finite but may vary between organs and between species. Cooling slows but cannot prevent their progressive dysfunction and destruction of cellular integrity. Reperfusion, in contrast, restores oxygen and viability to the tissues. At the same time, much of the injury associated with I/R is on account of events associated with reperfusion, referred to as the 'reflow paradox' with leukocytes slowing and sticking to vascular endothelial cells. These initial interactions cause the so-called rolling effect which leads to progressive slowing of leukocyte traffic along the vascular wall, adherence of these circulating cells to the endothelium and their ultimate infiltration into graft tissue.

Ischaemia/reperfusion injury affects all organs, its most obvious manifestation associated with transplantation is initial DGF, defined as a temporary divergence between the functional capacity of the engrafted organ and fulfilment of the physiologic needs of the recipient. Such a condition may increase the complexities of clinical care, particularly uncertainties in assessing the coincident presence of acute immunological injury with its concurrent need for invasive and noninvasive diagnostic tests, prolonged hospitalization, delayed rehabilitation, and higher costs. Primary dysfunction is associated with a high rate of organ failure, early retransplantation and death.

The impact of gender and age

Donor age has been described as a risk factor for graft survival in different studies and is commonly regarded as a detrimental factor for graft survival. Traditionally, donor age more than 50 years has been considered a risk factor. This is still valid for lung, heart, small bowel and pancreas grafts; however, for kidneys and livers the age limit was relaxed in the recent years and organs from older donors are transplanted with increasing frequencies. Recent publications showed more promising results after transplantation of livers of donors <60 years compared to that of individuals >60 years into recipients who did not experience an acute rejection episode in their graft [33–35]. These results lead to an increasing acceptance of older donor livers over the last years [36]. However, donor age seems to be one of the most important progression factors for the development of chronic organ dysfunction. Kidneys from older donors for example have an increased incidence of acute interstitial rejections [37]. Once a rejection occurs these organs are less capable to deal with the repair of damage accompanied by the transplant procedure, resulting in a higher rate of DGF [38]. As a consequence of multiple injuries and insufficient repair, the graft parenchymal cells may undergo premature senescence and aging. The lesions observed in aging organs are very similar to the morphologic changes

observed in organs with chronic alterations after transplantation. The loss of glomeruli in the aged kidney, for example, is irreversible and leads to progressive changes with increasing renal failure rates over the long term compared to younger donors' kidneys. Following inflammatory processes, triggered by a reduced number of functioning nephrons may contribute to a progressive exhaustion of the remaining nephrons leading to further loss of glomeruli [39–41]. These phenomena of premature aging of the grafts are also observed in hearts and lungs where arteriosclerosis and bronchiolitis are common problems. In contrast, the liver with its capacity of regeneration of hepatic cells seems to be an exception, nonetheless an increased rate of early and progressive bile duct complications in terms of ITBL is observed after transplantation of older donors' livers (P. Neuhaus, H.J. Schlitt, K.W. Sauch personal communication).

Apart from donor age, the gender of the donor seems to be of importance for the long- term function after transplantation. Most strikingly noticed in renal transplantation, the gender and graft size are known to influence the outcome. Women in general have smaller kidneys with approximately 15% fewer nephrons than male kidneys, leading to a negative correlation over the long term based on a reduced mean glomerular volume. Again hyperfiltration based on a less than ideal body mass/kidney mass ratio may lead to progressive exhaustion of the transplanted organ. However, recent publications pointed out that donor age and organ size seem to be more important for graft survival and long-term function than donor sex [42–46].

Donor and recipient associated diseases

It has become increasingly obvious that graft quality, influenced by a variety of donor- and recipient-associated factors, may be critical for both, its short- and long-term functions. Factors implicated in long-term graft dysfunction alone or in combination include the systemic effects of diabetes and hypertension. Recipient hypertension has been shown in clinical studies to perturb significantly the function and structure of grafts, and represents a major risk factor for chronic graft changes predominantly in transplanted kidney and heart grafts including glomerulosclerosis, arteriosclerosis and interstitial fibrosis. Both high systolic and diastolic blood pressure have been shown to be significant predictors of long-term graft survival. Hypertension, as well as hyperlipidaemia may promote arteriosclerosis within graft vessels and lead to significant intimal thickening of the vessel wall, the classical signs of chronic changes in transplanted organs. Secondary graft damage induced by acute rejection episodes on account of an increased endothelial activation, which is observed in hypertensive organs, supports the ongoing nonspecific activation of the graft by recipients risk factors. It is difficult to differentiate, however, between effects that are caused by immunological and by nonimmunological factors, as both have a common pathway post-transplantation. However, hypertension developing after transplantation is nearly universal and reflects several pathogenic mechanisms. Apart from an altered vascular reactivity and vasoconstriction related to CNI administration, the side-effects of steroids may contribute. Additionally in kidney transplantation, allografts from hypertensive donors seem to experience more frequent and severe rejection episodes. In addition, it is shown experimentally that organs from genetically hypertensive animals may transfer hypertension to normotensive recipients. Clinical observations emphasize these experimental findings. There are only limited data available describing the influences of donor- and recipient hypertension on transplanted livers and lungs, most importantly however it poses a considerable long-term cardiovascular risk for the transplant recipient [47–51].

Diabetes mellitus may lead to lesions again most obvious in transplanted kidneys such as glomerular mesangial fibrosis, focal lymphocytic infiltration, diffuse interstitial fibrosis, atrophic tubular lesions and sclerosis of vascular intima, which is of importance in all transplanted organs [52]. All these changes seem to have a strong correlation with the incidence of DGF and long-term survival. Therefore for kidney transplants originating form diabetic or hypertensive donors a baseline biopsy is advisable. In recent publications a strong correlation between the lack of ATN in the baseline biopsy and immediate graft function was reported [53].

An additional significant risk factor for graft survival is the development of dyslipidaemia and recipient obesity. After heart transplantation the long- term survival is strongly associated with the development of a particular type of coronary arteriosclerosis, the so called cardiac allograft vasculopathy (CAV). There is growing evidence that the pathogenesis of this entity is a combination of immunological mechanisms in a setting of nonimmunological risk factors. Arteriosclerotic changes may be of utmost importance for transplanted hearts but are also a significant risk factor for all types of transplants.

Recent evidence suggests the negative impact of pretransplant obesity of the recipient on DGF, immunologically-mediated graft loss and the development of chronic changes in the graft. Naturally, the subsequent progression of cardiovascular diseases as well as the frequency of surgical complications is increased in obese recipients [54].

Donor obesity seems to be predominantly a major problem in liver transplantation associated with signifi-

cant steatosis in donor organs. In transplanted livers, this condition leads, in spite of the regenerative potencies of hepatic cells, to progressive fibrosis and a negative influence on the outcome. Especially when such a graft is transplanted to a patient with hepatitis C virus (HCV) infection the function of the graft is limited seriously [55,56]. With the acceptance of grafts from less than optimal sources, which have a reduced resistance to unspecific injury, donor factors are gaining an increasing importance. Multivariable linear regression analysis also demonstrated that an increasing number of transplantations, with the addition of donor risk factors such as age, dyslipidaemia, blood pressure etc., was directly associated with poorer outcome after transplantation [38,57–59].

However apart from donor factors, the importance of recipient risk factors is stressed by the fact that for renal recipients the waiting time on dialysis is the strongest independent risk factor for renal transplant outcome. 5- and 10-year graft survival rates were significantly worse in paired kidney recipients who had undergone more than 24 months of dialysis (58% and 29% respectively) compared to paired kidney recipients who had undergone less than 6 months of dialysis (78% and 63% respectively) [60].

With respect to liver transplantation, after the introduction of the MELD (Model for End-Stage Liver Disease) in Eurotransplant, as a consequence, severely ill patients are receiving a graft on priority [61]. The MELD score is significantly higher if the patient awaiting a liver transplant is suffering from kidney failure or chronic renal insufficiency. As a consequence, more patients with multi-organ failure are transplanted and the outcome determined by recipient factors is accordingly inferior compared to patients with a single organ failure. Likewise, kidney transplantation patients with end-stage liver disease should be transplanted early in the process to provide a satisfactory patient and organ survival. However, major benefits provided by transplantation are limited by multi-organ failure and severe co-morbidities in the recipient leading to early graft loss, retransplantation and death of the patient. A similar situation is observed for lung and heart transplants where severely ill patients receiving an organ late in the process have an inferior outcome compared to patient transplanted in more favourable condition.

The role of recurrent disease over the graft survival after organ transplantation may be difficult to assess. In transplanted kidneys about 1% of graft failure in adults and 5% in children are predominantly from recurrent disease [62,63]. For a disease to recur in the allograft following organ failure implies that a milieu persists in the recipient that leads to graft involvement. The recurrence might be expected mostly for metabolic diseases as oxalosis, amyloidosis, immunological diseases with immune aggregates such as IgA nephropathy or metabolic disorders such as diabetes mellitus. In these instances, it is difficult to differentiate between the contribution of recurrent disease and the chronic processes referred to as chronic alloimmune injury, as the morphologic alterations show striking resemblance.

Vascular complications over the short and long term

Arterial and venous thromboses after transplantation are the most frequent vascular complications. The incidence has been reported to range between 4% and 25% [64–66]. Clinical symptoms of arterial thrombosis may be different depending on the type of graft and on the time of occurrence. In livers, the ischaemic damage after arterial thrombosis may lead to insufficiencies of the biliary anastomosis in the early phase, later to strictures and intrahepatic bilomas or abscesses [64,67]. In kidneys and other organs such a complication is usually associated with an early graft loss and retransplantation. Factors, which are possibly responsible for development of arterial thrombosis, are apart from the surgical technique, immunological factors such as anticardiolipin antibodies, reperfusion injuries and coagulopathies. Further risk factors are multiple transplants, recipient-negative cytomegalovirus (CMV) status, arterial anastomosis to an old conduit and multiple arterial anastomoses [68–71]. Varotti *et al.* [72] found in the analysis of a 17-year experience, that donor age is an independent risk factor associated with an increased rate of arterial thrombosis, demonstrating a significantly higher incidence of this fatal complication in grafts of donors older than 60 years. Generally, the therapeutical options are the surgical thrombectomy and retransplantation. Even in asymptomatic patients, it is suggested to approach a revascularization of the thrombosed vessel leading to an increased rate of graft salvage. Nevertheless in symptomatic patients, the surgical revascularization was associated with 40% mortality after liver transplantation suggesting the early retransplantation as first choice [73].

Renal arterial stenosis is a common complication after solid-organ transplantation with a reported incidence of up to 23% [74]. This complication normally occurs within 3 months to 2 years after transplantation, and can result in graft failure, hypertension, and the complete occlusion of the vessel. Causes for the onset of vascular stenosis are surgical technique, vessel lesions during the preservation and/or kinking and angulation of the artery [75]. Hyperlipidaemia of the donor or recipient is a further common reason for the development of arterial atherosclerotic stenosis.

Vascular thrombosis is the most common cause of graft failure after combined pancreas/kidney transplantation. Apart from the increased immunogenicity and the complications after pancreatitis, this organ has a low blood flow based on collateral circulation as a further risk factor for development of thrombotic complications [76–80].

Infections

Despite modern immunosuppressive regimens, infections with a large group of pathogens are still a serious problem after solid-organ transplantation leading to organ failure and death of the patient [81–84]. Viral infections are common and important causes of opportunistic infections after transplantation with immediate influence on graft function and survival. There is a close association between acute rejection and infection both triggering immune activation and furthermore tissue injury and impaired graft function. Various factors facilitating viral infections after transplantation include, apart from immunosuppression and rejection therapy, the age of the recipient, the viral status of the recipient and the donor-organ quality [85].

Cytomegalovirus is the most important infectious complication after transplantation. Active CMV infection is diagnosed in 40–70% of all allografted patients during the first 3 months after transplantation [85–87]. Immunosuppression suppressing particularly T-lymphocyte function has set the stage for CMV as an opportunistic agent [85,86]. In heart-allograft recipients, CMV myocarditis may be an important cause of cardiac dysfunction. CMV contributes to the risk of graft rejection and is able to predispose transplant recipients to life-threatening super-infections with a variety of microbial agents, including pneumocystis carinii, different fungi as well as EBV-mediated post-transplant lymphoproliferative disorder (PTLD). Allograft rejection often precedes CMV infection, either the virus acts as an adjuvant and triggers allograft rejection or allograft rejection activates a latent virus infection. However, increased expression of MHC antigens in the allograft, especially class II has been shown during allograft rejection and also in association with CMV infection [85,88]. Additionally in heart transplant recipients, there is a close association between the onset of CAV and CMV infection [51]. Additionally, urinary tract infection is one of the most common problems after renal transplantation followed by an deterioration of graft function and urosepsis. These conditions are known to trigger rejection episodes and activate latent CMV infection. The placement of ureteric stents, acute rejection episodes, CMV disease, mycophenolate mofetil (MMF) as primary immunosuppression and urologic malformation are independent predictive factors for acute graft pyelonephritis [89,90].

In kidney transplantation, nephropathy-associated BKV has been identified as a serious cause of allograft failure and loss. BKV nephropathy is a rare complication after renal transplantation with a prevalence of 1–5% and allograft loss reported in 45% of the affected patients. Risk factors for this infection are recurrent acute rejection episodes and intense immunosuppressive regimens. So far no treatment regimen for BKV-positive recipients has been established. A reduction of the immunosuppressive therapy seems to be the best therapeutic option [91,92]. Apart from infectious complications viral infections can also alter the immunogenicity of endothelial cells and lead to thrombotic complications resulting in a higher rate of arterial complications after the transplantation of CMV-seropositive donor livers in CMV-seronegative recipients [85,93,94].

Hepatitis C virus as one of the major causes for cirrhosis and subsequently liver transplantation regularly leads to hepatic re-infection after grafting. Detection of HCV by polymerase chain reaction (PCR) has shown, that re-infection of the transplanted liver by HCV is 100% in a time-dependent fashion. The reported incidence of HCV re-infection detected by histologic examination varies from 14% to 72% [95–97]. Recurrent Hepatitis C is a major cause for loss of graft function and eventually of graft failure and retransplantation [98]. So far, the optimal immunosuppressive regimen for HCV-positive liver transplant recipients remains controversial. In addition, standard therapeutical regimens for the treatment of acute rejection in HCV-positive recipients has not been established yet and remains controversial on account of the risk of accelerating and intensifying HCV-infections by an increased immunosuppressive therapy [99]. The CMV co-infection is associated with high levels of TNF-α, a pro-inflammatory mediator itself, leading to unspecific allograft activation. Additionally, a significantly increased risk for HCV-positive transplant recipients to develop cirrhosis in allografts after co-infection with CMV has been reported [100–106].

Drug-related side-effects

The impact of immunosuppressive agents on long-term graft structure and function is conjectural. The nephrotoxic effects of calcineurin inhibitors as well as accelerated graft arteriosclerosis have been linked to the use of these drugs. An even more serious problem is the onset of PTLD after long-term application of immunosuppressive drugs, which significantly limits patient- and graft survival.

The availability of different immunosuppressive agents with different modes of action and different side-effect

profiles offer the opportunity to tailor the immunosuppressive therapy with regard to recipient-related as well as donor-associated characteristics and risk factors. The selection of different immunosuppressants is based on efficacy, side-effect profiles, and recipient- and donor-related factors. Clearly, the transplant clinician now has a greater choice in the selection and application of immunosuppressants with the opportunity for an individualized immunosuppression. This approach may improve long-term graft function and reduce side-effects including significantly increased rates of malignomas for the duration of immunosuppression [107,108].

Since the introduction of calcineurin inhibitors, the frequency of acute rejection episodes has significantly decreased. Long-term graft outcome is predominantly determined by late patient death caused by cardiovascular complication and chronic graft deterioration [109–111]. Therefore, in choosing the primary immunosuppression, preference should be given to immunosuppressive regimens with a low cardiovascular risk profile. Over the past years, standard immunosuppressive protocols were based on the calcineurin inhibitors tacrolimus and cyclosporin A. Both drugs were combined in most instances with steroids or a variety of other concomitant immunosuppressants. Apart from nephrotoxicity, calcineurin inhibitors seem to be associated with hyperlipidaemia and hypertension. Therefore combination therapies and the utilization of a variety of drugs in low dosages may offer the opportunity to balance the required immunosuppressive effect with diminished or absent side-effects, taking into account the risk profile of the organ recipient. The absence of nephrotoxicity and its antiproliferative potencies make rapamycin an attractive alternative for the widely used calcineurin inhibitors. On the other hand, the pronounced hyperlipidaemia seems to be an additional risk factor for those categories of patients with an already increased cardiovascular morbidity and mortality. As drug-related side-effects are also developing based on patients' susceptibility, even the conversion of the basic immunosuppressive regimen should be considered on account of drug-related side-effects. Indeed patients with pronounced side-effects obviously caused by a calcineurin inhibitor benefit in most instances from the conversion to the alternative calcineurin inhibitor [112].

Patients with an expected strong immune response as strongly mismatched recipients, or those who lost their first graft on account of aggressive acute rejection with high titers of circulating antibodies should receive induction therapies with antibodies. In these instances the use of tacrolimus as long-term suppression is recommended, as it is proven to have a greater immunosuppressive potency, which can even reverse rejections occurring after cyclosporin A application [113].

Recent clinical and experimental findings demonstrated that organs from marginal donors, as well as those from brain-dead donors are immunologically activated. Those organs show an increased damage as a consequence of I/R injury, a higher frequency of rejection episodes with reduced long-term graft function [2,114,115]. Donor treatment in terms of immunosuppressants applied to the organ donor may improve the success of graft outcome. These findings have been shown in experimental models with improved kidney survival and long-term function after donor treatment with calcineurin inhibitors, steroids or adhesion-molecule blocking antibodies. Recent clinical investigations demonstrated beneficial effects after high dose steroid and hormone applications in brain dead organ donors [116,117]. It seems recommendable that immunosuppressive therapies should start before transplantation with treatment of the organ donor, as inflammatory changes occur early after BD and immunosuppressive drugs administered with the transplant procedure are frequently not sufficient to prevent unspecific damages.

Noncompliance

Compliance is a multifactorial factor, which significantly influences the long-term outcome after solid organ transplantation [118]. Based on the fact that the immunosuppressive drugs are not taken in a timely fashion or in the worst case not at all, the patient's immune system is not suppressed sufficiently and the immunological factors damage the organ. Noncompliance in the first place is a nonimmunological factor leading to severe immunological implications. The reported prevalence of noncompliance varies for all solid-organ transplants from 2% to 39%. Furthermore, noncompliance is the second-most frequent cause for graft loss beyond the first 3 months after transplantation [119].

Causes for noncompliance are complex (i.e. education status, frequency of drug intake, relationship between physician and patient, drug side-effects, other diseases). Noncompliance leads to loss of graft function with subsequently retransplantation in approximately 13.5% of the noncomplier [120].

Summary

Nonimmunological factors play an important role for the outcome and graft survival after transplantation. Apart from the recipients' immune status and co-morbidities, the quality of the transplanted graft seems to be crucial for short- and long-term survival after transplantation. Organs from marginal donors, as well as those from brain-dead donors are immunologically activated. Those

organs show an increased damage as a consequence of I/R injury, a higher frequency of rejection episodes with reduced long-term graft function. It seems recommendable that immunosuppressive therapies and approaches to improve the organ quality should start before transplantation.

The objectives of future studies should be to assess whether immunomodulation by specific and unspecific donor-treatment does improve the donor organ quality by reduction of inflammatory changes and acute host alloresponsiveness.

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Authorship

JP: wrote paper, proof reading, literature search. SW: wrote paper, proof reading, literature search. PN: wrote paper, proof reading. AP: wrote paper, proof reading.

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