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REVIEW

Pretransplant identification of acute rejection risk following kidney transplantation*

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Summary

Lack of an accepted definition for 'high immunological risk' hampers individualization of immunosuppressive therapy after kidney transplantation. For recipient-related risk factors for acute rejection, the most compelling evidence points to younger age and African American ethnicity. Recipient gender, body mass, previous transplantation, and concomitant infection or disease do not appear to be influential. Deceased donation now has only a minor effect on rejection risk, but older donor age remains a significant predictor. Conventional immunological markers (human leukocyte antigen [HLA] mismatching, pretransplant anti-HLA alloantibodies, and panel reactive antibodies) are being reassessed in light of growing understanding about the role of donor-specific antibodies (DSA). At the time of transplant, delayed graft function is one of the most clear-cut risk factors for acute rejection. Extended cold ischemia time (≥24 h) may also play a contributory role. While it is not yet possible to establish conclusively the relative contribution of different risk factors for acute rejection after kidney transplantation, the available data point to variables that should be taken into account at the time of transplant. Together, these offer a realistic basis for planning an appropriate immunosuppression regimen in individual patients.

Introduction

Management of kidney transplant patients aims to achieve the minimum level of immunosuppression to prevent graft rejection. While the incidence of acute rejection has approximately halved in the last decade [1] and now affects only approximately 10–15% of patients in the first year post-transplant, depending on the immunosuppressive strategy [1,2], both cellular and antibody-mediated rejection continue to adversely affect allograft survival [3–5]. An analysis of over 27 000 adult kidney transplant patients from the United States Renal Data System (USRDS) showed that acute rejection was associated with a 1.6-fold increase in death-censored graft loss [3], while combined

cellular and antibody-mediated rejection may increase graft loss by as much as sixfold [4].

A reliable definition of immunological risk at the time of transplantation would refine clinicians' ability to individualize therapy and avoid acute rejection without excessive immunosuppression. It would also permit a more rational risk stratification of patients in clinical trials of immunosuppression regimens. Currently, however, there is no accepted definition of 'high immunological risk' and a lack of consensus regarding the importance of individual risk factors and cutoff points to define risk [6,7]. In recent randomized trials of immunosuppressive regimens undertaken in 'high immunological risk' populations, the criteria for inclusion varied considerably [8–12]. Efforts to develop a definition of high immunological risk are hampered by the fact that multicenter studies or registry databases are often necessary to provide adequate numbers for meaningful analysis, and the endpoint of such studies is typically all-cause or death-censored graft survival instead of acute rejection. Moreover, large-scale analyses have usually focused on the effect of one specific risk factor [e.g., obesity or cytomegalovirus (CMV) infection], while ignoring other potentially relevant factors. Lastly, studies of this type are rarely able to base assessments on biopsy-proven acute rejection and are instead obliged to rely on clinically suspected or treated rejection.

This article reviews factors that may contribute substantially to increased immunological risk and offers a qualitative grading of their likely impact, with the supporting evidence. Only variables that are known at the time of transplantation are considered because these determine the immunosuppression plan and, in clinical trials, risk categorization of patients. A systematic assessment and citation of all publications related to such a wide range of topics was not considered feasible. Instead, we focused on large-scale multivariate analyses where possible.

Recipient clinical characteristics

Of the various demographic and clinical characteristics of kidney transplant recipients that may influence the risk of acute rejection, the most compelling data relate to younger age [3,4,13–17]. Different cutoff points have been used, but 45–50 years appear to be a relevant threshold for a significant association with risk of rejection (Table 1). It should be borne in mind when determining the initial immunosuppressive regimen, however, that although the risk of rejection declines in older recipients, rejection appears to have a greater impact on risk of graft loss so adequate rejection prophylaxis may be particularly critical [20]. Evidence for an effect of gender after adjustment for confounding variables in multivariate analyses is by no means consistent [3,4,13–19] (Table 1), despite perceptions that female patients have a greater propensity for rejection. Obesity could potentially predispose to acute rejection due to an effect on immunosuppressive drug disposition. However, an analysis of United Network for Organ Sharing (UNOS) data undertaken specifically to examine the effect of body mass index (BMI) on outcomes reported that only the highest category of BMI ($\geq$35 kg/m^2) was associated with acute rejection at 1 year compared with normal weight (OR 1.20, 95% CI 1.04–1.39; $P = 0.014$) [15].

Few studies have included an adequate number of non-Caucasian recipients to evaluate the effect of race, but two very large registry analyses of United States populations by Cole *et al.* [3] and Gore *et al.* [15] both convincingly

Table 1. Recipient risk factors for acute rejection after kidney transplantation based on multivariate analysis.

Reference	Data source	Year of transplant	*n*	Younger age	Gender	African American	High BMI	Retransplant	CMV serology/ infection
Dunn *et al*. [4]	Single center	2004–2007	587	✓ *(<50 years)*	X	–	–	X	–
Cole *et al*. [3]	USRDS	1995–2002	27 707	✓ *(<45 years)*	✓ (male)	✓	X	n/a	–
Øien *et al*. [13]	Single center	1994–2004	739	✓ *(<50 years)*	✓ (female)	–	–	n/a	–
Quiroga *et al*. [14]	Single center	1990–1998	518	✓	–	–	–	X	X
Gore *et al*. [15]	OPTN	1997–1999	27 377	✓	✓ (female)	✓	✓ (morbid obesity)	–	–
Pallardó Mateu *et al*. [16]	Multicenter	1990–1998	3365	✓ *(<60 years)*	X	–	–	X	✓
Mota *et al*. [17]	Single center	1985–1999	866	✓ *(<45 years)*	–	–	X	–	–
Sagedal *et al*. [18]	Single center	1994–1997	477	X	X	–	–	X	X
Boom *et al*. [19]	Single center	1983–1997	734	X	X	–	–	X	–

✓, indicates that a significant association was observed; X, indicates that no significant association was observed; –, indicates that no assessment was made; n/a, not applicable; BMI, body mass index; CMV, cytomegalovirus; OPTN, Organ Procurement and Transplant Network; USRDS, United States Renal Data System.

Cutoff values for continuous variables are shown in italics.

demonstrated that black recipients are 22–25% more likely to experience rejection than white recipients, a difference that was statistically significant in both studies. A comparison of rejection rates by Schold *et al.*, based on 112 120 kidney transplant patients in the Scientific Renal Transplant Registry (SRTR) in the United States has suggested that this difference may be confined to younger patients: among patients aged 18–33 years, the adjusted OR for acute rejection in African Americans versus white recipients was 1.33 (95% CI 1.12–1.57), but diminished with age and became nonsignificant in patients >65 years [21]. Gore *et al.* also observed a significant reduction in risk in Hispanic versus non-Hispanic recipients (parameter estimate -0.28, $P = 0.01$), but corroborative data are lacking. It should be noted that none of these studies included nonclinical factors in their models, such as socioeconomic status, level of education, or access to health care (other than health insurance in the study by Schold *et al.*), which are known to influence compliance [22] and thus rejection risk.

Perhaps surprisingly, several studies have shown no significant association between previous kidney transplantation and risk of rejection [4,14,16,18,19,23]. Each of these analyses, however, adjusted rejection rates for at least one marker of sensitization in the multivariate analysis (presence of panel reactive antibodies [PRA], HLA mismatch, or donor-specific antibodies [DSA]) that is, retransplantation *per se* was not a risk factor but the accompanying HLA immunization must of course be taken into account (See Recipient immunological characteristics). The conventional view that patients with a prior failed transplant are more prone to rejection may be based on data from the 1980s [24], before current immunosuppressive agents were available. Interrogation of data on 823 patients who lost a kidney allograft to BK virus infection during 2004–2008 has shown the one-year rejection rate after retransplantation to be only 7% [25]. Furthermore, a multivariate analysis of a French cohort has demonstrated that although second transplants had a higher risk of late graft failure (hazard ratio 2.18), there was no significant difference in the occurrence of acute rejection or steroid-resistant acute rejection [23].

Multivariate analyses have not consistently shown pretransplant CMV-positive serology or CMV infection to be a significant predictor for rejection (Table 1). The impact of post-transplant CMV infection on risk of rejection remains a matter for debate. It has recently been shown that positive serostatus of the donor, particularly in CMV-seropositive recipients, negatively impacts long-term graft survival but not the occurrence of acute rejection [26]. Less clear-cut is whether concomitant HIV infection raises the risk of rejection: large registry analyses from 1996 [27] and 1997–2004 [28] observed no effect, but a more recent meta-analysis of 254 patients from 12 case series [29], and single-center reports [30–32], has reported high rates of rejection by year 1 (31–55%). In a series of 150 HIV-positive patients undergoing kidney transplantation at a single center, the incidence of acute rejection at one and 3 years, respectively, was 31% and 41% [32]. It is not clear why rejection may be more frequent in HIV-positive recipients; dysregulation of the immune system or inadequate immunosuppression have been suggested as possible causes [33]. For hepatitis C virus (HCV) infection, recipient positivity was not a predictor of acute rejection in the large USRDS analysis by Cole *et al.* [3] or in multicenter [16] or single-center studies [34,35], but in a single-center retrospective analysis of 2269 patients over the period 1991–2007 which assessed both recipient and donor serostatus, R+/D- status was a significant predictor of acute rejection versus R-/D- (adjusted hazard ratio 1.7, 95% CI 1.2–2.5) [36]. In a multi-center study from Spain which assessed 4304 patients transplanted during 1990–2002, the subpopulation of 587 HCV-positive patients exhibited a higher rate of acute rejection than HCV-negative recipients but included a higher proportion of retransplanted and immunized patients [37]. Overall, there are insufficient data to establish coinfection with HIV or HCV as significant predictors of rejection.

No other clinical characteristics of the recipient appear to exert a relevant effect on immunological risk. After adjustment for confounding factors, diabetes mellitus shows no association with acute rejection [4,14]. One multivariate analysis of SRTR data from patients transplanted during 2002–2009 included coronary artery disease and peripheral vascular disease as potential confounders and found no relation with risk of rejection [21]. There are limited data to indicate that the cause of end-stage renal disease [3] and duration of pretransplant dialysis (using a cutoff point of 6 months) [4] are not influential. Time on dialysis prior to transplantation, however, is a relatively complex issue to explore as although longer exposure to dialysis *per se* may not increase the risk of acute rejection, medical consequences such as greater risk of blood transfusion can promote sensitization. Dialysis patients have been shown to have increased antidonor T-cell alloreactivity [38].

One other area, which exerts a major impact on risk of rejection, is patient adherence to the medication regimen. In a recent review, Prendergast and Gaston identified a series of factors associated with medication nonadherence after kidney transplantation, including younger age (<25 years), male gender, non-Caucasian ethnicity, poor perception and understanding of treatment benefits, complex regimens or more distressing side effects, longer time post-transplant, and economic or physical impediments to obtaining medication [22]. While the likelihood of nonad-

herence is not generally taken into account when planning the immunosuppressive regimen at the time of transplant, use of intravenous immunosuppression (e.g., belatacept) has been proposed as an option in young nonadherent patients [39].

Recipient immunological characteristics

One of the most well-established risk factors for acute rejection is the degree of HLA mismatching. Hazard ratios in the range of 1.39–3.78 have been described for one or more HLA-A, -B and -DR mismatches [3,13,15], and 1.81–2.7 [14,18,19] for one or more HLA-DR mismatches. Discrepancies in the impact of a mismatching may be due to disparities in immunosuppressive strategies and population characteristics. For example, ischemia–reperfusion injury is greater in deceased donor grafts compared with living donor grafts, increasing the expression of donor HLA antigens, raising the alloimmune response and the risk of acute rejection. However, while a single HLA-A, -B, or -DR mismatch has not always been found to significantly predict acute rejection [16,18], the association becomes irrefutable as the number of HLA-A, -B, and -DR mismatches increases [3,4,13]. The presence of pretransplant alloantibodies against HLA class I and/or II has been shown convincingly to increase the risk of acute rejection during the first 3 months post-transplant, based on prospective data collected by the Collaborative Transplant Study (CTS) (OR 2.53, $P < 0.001$) [40].

Recent years have seen intense interest in the role of DSA as a predictor of rejection. A meta-analysis by Mohan *et al.* [41] has confirmed that the presence of pretransplant DSAs, be they class I, II, or both, is strongly associated with the occurrence of acute antibody-mediated rejection (relative risk 1.98, 95% CI 1.36, 2.89). DSA titer correlates with risk of acute antibody-mediated rejection [42]. A threshold of 3000 for peak pretransplant DSA detected by the Luminex technique may be indicative of increased risk [43], but this is not necessarily reproducible in different laboratories. Suitable cutoff points using other detection techniques, notably positive cross-match on flow cytometry in recent or historical serum samples and a positive historical complement-depended cytotoxicity (CDC) cross-match, have not been established. Further data—including information on different types of DSA such as C1q fixing—are required for reliable risk stratification based on DSA levels.

The presence of PRA >0% has been a widely accepted marker for acute rejection risk after kidney transplantation [6] based on retrospective [16,18,19,44] and prospective [45] data, and PRA level is uniformly included as a criteria for 'high-risk' patients in clinical trials [8–12]. Unexpectedly, Cole *et al.* did not observe a significant association between PRA >30% (11.9% of patients) and risk of acute rejection in their USRDS population of 27 707 kidney transplants from 1995 to 2002 [3], although multivariate analyses in smaller populations have found an increase in risk in the range of 1.2–2.7-fold using thresholds of >0% [18], >15% [16] and >50% [19]. The risk associated with PRA, however, is likely to be mediated by DSA, and as a result, PRA level *per se* may in fact not be important. In a retrospective analysis of 587 kidney transplants performed at a single center, Dunn *et al.* [4] observed that PRA >0% was not significantly related to either antibody-mediated or cellular rejection in the absence of DSA. When DSA was included in a multivariate model, PRA >0% was no longer significantly associated with antibody-mediated rejection, but of course different immunosuppressive regimens in the high-and low-risk patients may have clouded the issue [4]. However, some sensitized patients, while DSA-negative, are characterized by high levels of circulating antibodies against non-HLA antigens such as autoantigens or major histocompatibility complex (MHC) class I-related chain A (MICA), which can contribute to post-transplant rejections [46]. Sánchez-Zapardiel *et al.* [47] recently observed in a series of 727 kidney transplants that preformed anti-MICA antibodies (present in 15% of patients) independently increased the risk of acute rejection and enhanced the deleterious effect of positive PRA status early after transplantation. In addition, the presence of alloantigen-specific memory B cells, in the context of no detectable circulating DSAs prior to transplantation, poses a risk of post-transplant rejections by promoting the activation of naïve T cells [48]. New tests are under evaluation (B-cell ELISpot) for the identification of such alloantigen-specific memory B cells.

The CD30 molecule belongs to the tumor necrosis factor receptor (TNF-R) superfamily. In activated T cells, the membrane-bound CD30 molecule is proteolytically cleaved, thereby generating a soluble form (sCD30), which can be measured in serum. It has been suggested that pre- or post-transplant levels of sCD30 represent a biomarker for graft rejection associated with an impaired outcome for transplanted patients [48]. Thus, sCD30 seems to reflect the pretransplant activation status of the T cells and thereby allows identification of high-risk recipients.

Memory T cells generated in response to environmental stimuli (e.g., previous transplant, blood transfusion, viral infections) become more prevalent with age and can cross-react with alloantigens from the donor graft, despite no previous exposure to tissue from that donor. The presence of cross-reactive, donor-specific memory T cells increases the risk of immunological injury to the graft. In a small series of 19 deceased and living donor kidney transplant recipients, Heeger *et al.* [49] demonstrated that the pretransplant frequency of donor-specific memory T cells, as assessed by levels of allospecific cytokines, correlated

with the subsequent risk of acute rejection. More recently, the same group retrospectively assessed 118 consecutive recipients of a kidney allograft from a deceased donor aged >50 years and found the incidence of acute rejection to be 36% vs. 14% in patients with or without donor-specific lymphocytes ($P = 0.009$) [50]. Defining the allospecific immune response prior to transplantation may in the future contribute to identification of donor–recipient pairs at high risk of rejection. Standardization and cross-validation of such assays have been recently performed, both in Europe [51] and the USA [52].

Donor clinical characteristics

In the early 1990s, the one-year incidence of acute rejection was approximately 10% lower in recipients of a kidney graft from a living donor than a deceased donor [1], but the difference has since narrowed to only 1–2% [1,53] due to factors such as improved immunosuppression and closer matching for deceased donor grafts. Living related donation does not appear to reduce the risk of acute rejection versus living unrelated donation, despite a significantly higher donor–recipient HLA disparity in recipients of a graft from living unrelated donors [54,55].

Several multivariate analyses of risk factors for acute rejection have included increased donor age as a potential variable [13,14,16–18,56,57]. In addition, there is an association between increased donor age and subclinical rejection on protocol renal allograft biopsies [58]. In the majority of cases, donor age was included as a continuous variable, with no cutoff point [14,16–18,56,57], the exception being a prospective single-center study of 739 patients which reported donor age ≥65 years to be a significant predictor for acute rejection [13]. Tullius *et al.* analyzed UNOS data from 108 118 deceased donor kidney transplants during 1995–2008 with the aim of investigating the effect of donor age on transplant outcomes [56]. They observed a significant association between increasing donor age and acute rejection, but this effect was less marked than for younger recipient age. For example, the incidence of acute rejection was 18.2% vs. 24.5% with donors aged 18–29 vs. 60–69 years, compared with 28.7% vs. 15.7% for recipients in the same age groups.

Donor gender *per se* has not been shown to influence rates of rejection in two large retrospective cohorts [16,19], although a prospective analysis of 739 living donor recipients undertaken to assess the effect of donor gender observed that male donors were associated with a trend to

Table 2. Donor demographics and clinical characteristics as risk factors for acute rejection after kidney transplantation based on multivariate analysis.

Reference	Data source	Year of transplant	*n*	Older donor age	Donor–recipient demographic mismatch	Brain death (versus circulatory death)	Cause of death
Tan *et al*. [62]	Registry	1988–2006	188 508	–	X (gender mismatch)	–	–
Ferrari *et al*. [63]	Registry	1991–2006	2364	–	X (age mismatch)	–	–
Tullius *et al*. [56]	Registry	1995–2008	108 188	✓	–	–	–
Naesens *et al*. [58]	Single center	2004–2006	120	✓ (subclinical)	–	–	–
Øien *et al*. [13]	Single center	1994–2004	739	✓ (*≥65 years*)	–	–	–
Quiroga *et al*. [14]	Single center	1990–1998	518	✓	–	–	X (trauma) X (cardiovascular disease)
Pallardó Mateu *et al*. [16]	Multicenter	1990–1998	3365	X	–	–	X (trauma)
Sánchez-Fructuoso *et al*. [61]	Single center	1996–2002	372	–	–	–	✓ (cerebrovascular disease)
Mota *et al*. [17]	Single center	1985–1999	866	X	–	–	✓ (cardiovascular disease)
Sagedal *et al*. [18]	Single center	1994–1997	477	✓	–	✓ (increased in DBD)	–
De Fijter *et al*. [57]	Single center	1983–1993	514	✓	–		–

Cutoff values for continuous variables are shown in italics.
✓, indicates that a significant association was observed; X, indicates that no significant association was observed; –, indicates that no assessment was made; DBD, donation after brain death.

fewer early acute rejection episodes (OR 0.80; 95% CI 0.73–1.16; $P = 0.063$) [13].

It is difficult to disentangle the effect of expanded criteria donor (ECD) grafts on rejection risk from the effect of older donor age, as by definition, ECD grafts are from older recipients. As ECD donors are typically matched to older recipients [56], there may be no increase in immunological risk of ECD donors overall, as reported by multivariate analyses in two large series [59,60]. Specific identification of acute rejection risk according to other ECD characteristics, such as donor blood pressure and kidney function, has not been performed.

The few studies that have investigated whether donor cause of death influences risk of rejection have selectively examined only one or two causes [14,16,17,61] (Table 2). No comprehensive analysis has yet been undertaken. While there are single-center data suggesting a significant association between rejection and cardiovascular disease [17] or cerebrovascular disease [61], methodological limitations and the absence of corroborative data restrict their validity. Donation after brain death, similarly, has not shown a consistent relation with the risk of acute rejection [60,61,64–69], although confounding variables make this difficult to prove conclusively. Two large cohort studies on the UK transplant registry had conflicting results regarding the risk of acute rejection in kidneys donated after brain death or circulatory death. In the first study [68], the incidence of acute rejection at 3 months after transplantation was significantly higher in recipients of kidneys donated after brain death than in recipients of kidneys donated after circulatory death (24% vs. 17%, $P < 0.0001$), whereas in the more recent study [69], acute rejection risk was not different (13% vs. 12%). It remains unclear whether this discrepancy results from evolving practice in immunosuppression or relates to yet unidentified factors.

Donor–recipient demographic matching

In their large analysis of UNOS data, Tullius and colleagues demonstrated convincingly that there is a pronounced interaction between recipient and donor age. For example, older recipients (>60 years) have a low risk of rejection that is further reduced if they receive a graft from a younger donor (18–20 years) (10–15%). Conversely, a younger recipient (18–29 or 30–39 years) with a donor aged >60 years has a 30–40% risk of acute rejection. Findings were confirmed by multivariate analysis. This age-specific analysis may be more relevant than data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), which suggested that donor–recipient age mismatching does not affect risk of rejection [63]. In the ANZDATA analysis, all donor–recipient pairs were grouped together if the age difference was below -10, between -10 and 20, 20–29, or ≥30 years. Thus, for example, the category of -10 years could include recipients aged 30 years or >70 years, which is associated with widely differing rejection risk according to the UNOS data [56], casting doubt on the results.

Mismatching of donor–recipient gender, in contrast, does not seem relevant for acute rejection risk [62] although it is a significant risk factor for graft loss even after adjustment for sensitization status [62]. A retrospective study of 195 516 deceased donor recipients showed that after adjustment for recipient and donor gender, female recipients of male deceased donor kidneys exhibited a small but significantly increased risk of graft failure and patient mortality in the first year post-transplant compared with all other recipient–donor gender combinations [70], a finding partially confirmed elsewhere [71]. This effect may

Table 3. Qualitative assessment of pretransplant risk factors for acute rejection in kidney transplant recipients. Variables considered most relevant for assessment of immunological risk status are shown in italics.

	Quality of evidence	Impact
Recipient clinical characteristics		
Younger age	*Good*	*Strong**
Gender	Moderate	No
Black race	*Moderate*	*Strong*
High BMI	Weak	No
Retransplantation	Moderate	No
CMV infection	Weak	No
HIV infection	Weak	No
HCV infection	Weak	No
Recipient immunological characteristics		
HLA mismatch	*Good*	*Strong*
Presence of anti-HLA antibodies	*Good*	*Strong*
Presence of pretransplant DSA	*Good*	*Strong*
DSA titer	*Moderate*	*Strong*
Panel reactive antibodies	*Moderate*	*Moderate*
Donor clinical characteristics		
Deceased donor	*Moderate*	*No*
Older donor age	*Good*	*Moderate†*
Donor–recipient age matching	*Moderate*	*Strong‡*
Donor–recipient gender matching	Moderate	No
Extended criteria donor	Poor	No§
Cause of death	Poor	No
Nonheart-beating	Moderate	No
Transplant-related factors		
Cold ischemia time	Moderate	Weak¶
Delayed graft function	*Good*	*Strong*

BMI, body mass index; CMV, cytomegalovirus; DSA, donor-specific antibodies; ECD, expanded criteria donor; HCV, hepatitis C virus; HLA, human leukocyte antigen.

*Various cutoff points, typically <45–50 years.

†Continuous effect.

‡Older donor/younger recipient confers higher risk.

§Older age in ECD donors confers higher risk.

¶If ≥24 h.

be related to an alloimmune response to H-Y antigens derived from the Y chromosome, which could act as a minor histocompatibility antigen in female recipient/male donor transplants.

Transplant-related factors

Delayed graft function (DGF) is one of the most clear-cut risk factors for acute rejection after kidney transplantation. It is estimated to confer an increased rejection risk of between 38% and 81% compared to patients with immediate function [14,16,17,19,72,73]. Yarlagadda *et al.* [73] undertook a meta-analysis of 33 studies involving 151 594 kidney transplant recipients to investigate the relation between DGF and graft outcomes and found the relative risk of acute rejection with DGF to be 1.38 (95% CI 1.29–1.47), the most robust of the available analyses. Thus, risk factors for DGF should be considered when planning the immunosuppressive regimen. In an analysis of over 25 000 deceased donor kidney transplant patients in the UNOS database, independent risk factors for DGF were older recipient age, male gender, African American ethnicity, elevated PRA level, long cold ischemia time, and diabetes mellitus [74].Not all risk factors for DGF, however, are independent risk factors for acute rejection (see above).

Longer cold ischemia time could potentially contribute to the risk of rejection by exacerbating ischemia–reperfusion injury [75] and increasing the risk of DGF [76]. Available analyses of cold ischemia time as a continuous variable have not shown a significant association after adjustment for confounding variables [14,16,18,19], but a relatively high cutoff point may be required to demonstrate an effect. In a study of UNOS data from 27 377 patients undertaken to examine the association between obesity and outcomes, Gore and colleagues found cold ischemia time $\geq$24 h to be significantly associated with risk of acute rejection ($P = 0.002$) [15].

Conclusion

It is not possible to establish conclusively the relative contribution of different risk factors for acute rejection after kidney transplantation. Adequately powered registry studies and meta-analyses based on recent patient cohorts have not comprehensively evaluated risk factors using acute rejection as the endpoint and are hampered by an absence of data on biopsy-proven acute rejection. Single-center studies, while offering more rigorous designs, have generally focused on only one risk factor and are necessarily based on smaller populations. However, with these caveats in mind, a qualitative assessment of the probable impact of leading risk factors can be developed (Table 3). It seems reasonable to propose that younger recipient age, African American ethnicity, and older donor age be taken into account when assessing immunological risk pretransplant, complemented by increasing HLA mismatch, the presence of HLA alloantibodies and PRA status, and the presence of DSA (ideally with DSA titer). Taking these variables into account at the time of transplant would provide a realistic basis for planning an appropriate immunosuppression regimen in individual patients. This list does not, of course, take into account post-transplant contributory factors, particularly adherence.

The accuracy of immunological risk assessment could be improved by a well-planned registry analysis incorporating these parameters into a model of risk factors for acute rejection. Such an analysis would inevitably by limited by the absence of data on biopsy-proven rejection and more novel variables such as DSA titer, however, and it would be helpful if registry data collection procedures could in the future be expanded to include this information.

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