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Published on: 01 Feb 2020 - Transplantation (Transplantation)

Topics: Dialysis and Kidney transplantation

Transplantation Publish Ahead of Print

DOI: 10.1097/TP.0000000000003012

The causes of kidney allograft failure: more than allo-immunity. A viewpoint paper.

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Authorship statement: EVL, JB, AVC and MN wrote the review paper.

The authors declare no conflicts of interest.

Funding: MN is supported by the Seventh Framework Programme (FP7) of the European Commission, in the HEALTH.2012.1.4-1 theme (grant number 305499); The Research Foundation Flanders (F.W.O.) and Flanders Innovation and Entrepreneurship (Agentschap Innoveren en Ondernemen) of the Flemish Government (grant numbers IWT.2015.0199 and T004417N) and KU Leuven (grant number C32/17/049). EVL holds a fellowship grant (1143919N) from The Research Foundation Flanders (F.W.O.) and MN is senior clinical investigator of The Research Foundation Flanders (F.W.O.) (1844019N).

Abbreviations:

AMR antibody-mediated rejection

BKV BK-virus

CMV cytomegalovirus

CNI calcineurin inhibitor

DGF delayed graft function

DSA donor-specific antibodies

ESRD end-stage renal disease

GNF glomerulonephritis

HLA human leucocyte antigen

IF/TA interstitial fibrosis / tubular atrophy

IRI ischemia/reperfusion injury

NODAT new onset diabetes after transplantation

PVAN polyomavirus-associated nephropathy

TCMR T-cell mediated rejection

Abstract

Kidney allograft failure is a serious condition as it implies the need for re-initiation of dialysis with associated morbidity and mortality, reduced quality of life and higher economic cost. Despite improvements in short-term survival of kidney allografts, this progress was not matched in long-term graft survival. In this viewpoint paper, we summarize the available literature on the causes of kidney allograft failure, both early and late, both nonimmune and allo-immune, to gain better insight in the causes of graft failure. Such insight is necessary to better target therapies or take preventative measures, that improve long-term outcome after kidney transplantation.

Introduction

Kidney allograft failure is a serious condition as it implies the need for re-initiation of dialysis with associated morbidity and mortality, reduced quality of life and higher economic cost. Data from the United States and Europe demonstrate that only 48% of patients are relisted for a repeat transplantation, with 61% of them being sensitized with HLA antibodies. The remaining majority of patients is not relisted and stays dialysis-dependent until death.[1] In addition, the success of repeat transplantation is hampered by the risk of HLA antibody sensitization after graft failure, the associated longer waiting time for a repeat transplantation, the increased risk of antibody-mediated rejection in sensitized patients and other complications after repeat transplantation.[2]

Despite improvements in short-term survival of kidney allografts, this progress was not matched in long-term graft survival.[3,4] Both United States and European registry data show relatively stable graft failure rates beyond the first year post transplantation since the late 1980s.[3-5] Also short-term improvements in death-censored graft survival have now decelerated, even when taking the increasing comorbidities of donor and recipients into account[4]. The rate of improvement of late graft failure has remained stable and modest over the past decades. Overall graft failure (including death with a functioning transplant) remains high at a rate of approximately 5% per year after the first year.[3]

Novel initiatives to improve long-term kidney allograft survival are therefore needed. However, in order to target late graft failure, this problem should be clearly defined and its causes elucidated. Recent data on the causes of kidney allograft failure show that graft failure due to acute rejection has become very rare in the first year after transplantation, occurring in only 0,4% of transplant recipients, as a result of the improvements in immunosuppressive regimens.[5] Acute rejection is only the fifth frequent cause of early graft failure after venous thrombosis,

death due to cardiovascular complications, primary nonfunction and death due to infectious complications.[5]

Here, we summarize the available literature on the causes of kidney allograft failure, both early and late, and suggest angles for further research aimed at improving graft survival. Given the extensiveness of contributors to graft loss and literature, this viewpoint can only touch superficially upon the most relevant topics.

Death with a functioning graft vs. loss of graft function

Premature death with a functioning graft is the most important reason for kidney allograft failure.[6,7] With the increasing acceptance of older recipients for kidney transplantation, age is indisputably one of, if not, the most important nonmodifiable risk factor for recipient death. However, recipient death with a functioning graft, when not premature, could be considered as the ultimate success of kidney transplantation and mortality rates are lower than when remaining on dialysis, even for older recipients.[8] Other pretransplant risk factors include diabetes mellitus, cardiovascular disease, patient functional status and the extent of dialysis exposure.[9,10] The causes of death vary by recipient age group[11] but the main causes of death are cardiovascular disease, malignancies and infections, all of which are also influenced by posttransplant variables, such as the use of immunosuppressive agents. The increased cardiovascular risk is influenced both by immunosuppressants with side effects like diabetes, hypertension, dyslipidemia and by the direct impact of impaired kidney function.[12-17] Both incidence and prevalence of cardiovascular disease are estimated to be 4 to 6 times higher than in the general population.[18,19] To improve patient survival after kidney transplantation, the search for less toxic drug regimens, improved prevention and timely diagnosis of cardiovascular disease, infections and malignancies, and better targeted therapies, are crucial. For most interventions in this context, no specific evidence is available in transplant recipients. Although the underlying risk profile and pathophysiology of the risk factors for death after transplantation

differ importantly from the general population, the lack of specific evidence necessitates extrapolation of data for the general populations to transplant recipients. The important progress made in these fields for the general population will hopefully also lead to significant improvements in patient survival after kidney transplantation.

Not only death with a functioning graft is ill-studied, even the causes of loss of kidney function, defined as return to dialysis or repeat kidney transplantation, and their relative contribution, have been evaluated only scarcely, from different perspectives and with different conclusions[20-23] (**Table 1, Figure 1**). The different inclusion criteria of these studies (including all graft losses versus only including patients with a biopsy proximal to graft loss) impede comparison and generalizability of the conclusions. Also, there are apparent differences between perceived causes of graft loss from indication versus protocol biopsies.[24] Many studies have determined risk factors for graft failure, but data on retrospective patient chart analysis of the patient-specific causes of graft failure are very limited. Using the Banff criteria for assessment of renal allograft histology, 2 cohort studies have given some insights in the causes of kidney transplant failure and suggest this is primarily explained by allo-immune processes (35% to 64%).[20,21]

Focusing on the Banff diagnostic criteria or histology as explanation of graft failure is however problematic for several reasons. First, late indication biopsies are not always performed prior to late graft failure. Only relying on early histological lesions as explanation for late graft failure could thus be misleading. Second, in early graft losses due to mechanical complications of primary-nonfunction, often no biopsy is performed. Third, in centers that systematically perform late protocol biopsies, the interpretation is influenced by survivor bias.[25,26]

In addition, exclusive focus on the available histological information rather than the less visible contributors to graft failure like aging, cardiovascular and metabolic disturbances, infections, pre- and postrenal causes etc. could lead to biased views, as these are all well-known risk factors of end-stage kidney disease (ESRD). These known causes of, and contributors to, ESRD remain

underreported in kidney transplant literature, although these factors are highly prevalent in the transplant population **(Table 2).**

Finally, we need to be cautious about singling out 1 possible explanation as the sole cause of loss of allograft function. Especially in late allograft failure many pathologic processes can be present simultaneously, which makes late graft failure a multifactorial process. Multivariate models that illustrate that different factors are independent predictors of graft outcome support the multifactorial nature of graft failure. Several histological processes change over time and active and chronic cumulative injuries coincide and accumulate, which makes the interpretation of late biopsies very challenging.[27]

Causes of loss of graft function

Nonallo-immune injury mechanisms

Irrespective of the underlying cause, the development and extent of chronic tubulo-interstitial damage (IF/TA) seems to be a very important prognostic factor.[22] Tubular atrophy, interstitial fibrosis and glomerulosclerosis are the hallmarks of nephron loss, which is a multifactorial process of both immunological and nonimmunological mechanisms. Interstitial fibrosis and tubular atrophy (IF/TA) is a nonspecific pathological finding in kidney biopsies, reflecting a final common pathway of different injury processes. Nephron damage leads to compensatory hyperfiltration and glomerular hypertension in the remaining functioning nephrons, initiating apoptosis, inflammation, and fibrosis that gradually increase, not only in glomeruli but also in tubules and interstitium. This leads to a vicious circle of further renal functional deterioration.[28,29] **(Figure 2)**

For a long time, calcineurin nephrotoxicity was considered an important nonimmunological cause of progressive fibrosis after transplantation.[30-32] Studies testing this hypothesis, by minimizing or avoiding calcineurin inhibitors, showed conflicting results with better renal function in some studies but increased rejection and donor-specific antibodies in others.[33,34]

These findings and more insights in other pathophysiological processes (allo-immune, see below) cast doubts on the role of calcineurin inhibitor nephrotoxicity as the major cause of late kidney allograft failure. Nevertheless, and although it remains difficult to quantify its relative contribution, it is likely that the almost universal use of calcineurin inhibitors in kidney transplantation contributes to graft functional decline and ultimately graft failure.[30] However, it is important to realize that these contributions to graft damage are considerably outweighed by the advantage they offer, as was illustrated by the historical improvement in short-term survival rates after the introduction of these powerful immunosuppressive drugs.[3,35]

Glomerulonephritis in the transplant kidney, either recurring or de novo, represents a second category of nonallo-immune causes of graft failure.[36,37] Up to 20 to 50% of kidney transplant recipients have glomerulonephritis as the primary kidney disease.[38,39] Recurrence of native kidney disease in the transplanted organ is a well-recognized cause of graft failure, although reported recurrence rates vary widely (2.6%-50%), depending also on the initial disease, and recurrence increases with time after transplantation[38-44]. Another important aspect to consider in the varying recurrence rates is that only a fraction of failing native kidneys were biopsied for confirmation of the cause of failure. Similarly, rates of graft loss attributed to glomerulonephritis vary widely (1.1 to 55%). [37,39,40,43,45-48]

Viral diseases represent another class of nonallo-immune causes of graft failure, especially the human polyomavirus BK (BKV), which causes polyomavirus-associated nephropathy (PVAN) in up to 10% of renal transplant recipients.[49,50] In literature, PVAN is deemed as the cause of graft failure in 5-15% of graft losses.[20,22,51] PVAN damages the allograft by direct tubular injury with tubulo-interstitial inflammation, which can lead to development of IF/TA in >60% of cases.[51-53] PVAN is managed by reducing immunosuppression, however this reduction might paradoxically enhance rejection episodes and development of de novo donor-specific antibodies.[54]

Pretransplant diabetes and new onset diabetes after transplantation (NODAT) are prevalent in the transplant population (6-17% for pretransplant diabetes and up to 53% for NODAT).[55-57] A recent study of our group demonstrated rapid occurrence of mesangial matrix expansion in insulin-dependent pretransplant diabetes patients, already within the first 5 years after transplantation.[55] This might even be an underestimation, as a recent study from Denic et al. illustrated that using manual morphometry, mesangial matrix expansion predicted graft failure that was not predicted when these lesions were scored by Banff.[58] As many centers don't perform late protocol biopsies, the lesions of diabetic nephropathy are systematically missed. Diabetes nephropathy after kidney transplantation is therefore potentially underestimated as contributor to late graft failure.

Next to diabetes, other recipient-related cardiovascular risk factors likely play an important role in kidney allograft failure (**Figure 2**). Risk factors associated with cardiovascular complications after transplantation are, amongst others, male sex, age, arterial hypertension before transplantation, longer pretransplant dialysis, cardiovascular events before transplantation, posttransplant diabetes mellitus, increased pulse pressure after transplantation and intake of corticosteroids.[59] The pathophysiology of cardiovascular disease in renal transplant recipients is complex and involves endothelial dysfunction, arterial stiffness as well as diastolic and systolic heart failure, developed during the progression of chronic kidney disease. Kidney transplantation results only in a partial recovery of these mechanisms resulting in a persistently high cardiovascular risk, possibly due to ongoing exposure to chronic kidney disease-related risk factors (in case of impaired transplant function) or transplantation-specific risk factors (immunosuppressive therapy). Observational data suggest that the degree of microvascular endothelial dysfunction 3 months after transplantation predicts long-term allograft survival.[60] Whereas endothelial dysfunction reflects damage of the intimal layer of the vessel wall (atherosclerosis), an altered structure of the medial layer (arteriosclerosis) will result in arterial

stiffness. Whether persisting higher arterial stiffness after transplantation is independently associated with worse allograft outcome needs to be elucidated in large prospective trials.[61,62] Kidney transplantation improves both cardiac structure and systolic function.[63,64] However, patients with persistent left ventricular hypertrophy in the fifth year posttransplantation, exhibit a higher risk of graft failure than those with left ventricular hypertrophy regression or no pretransplant left ventricular hypertrophy.[65] In elderly transplant recipients, a positive history of heart failure at the time of transplantation predicts not only survival but also graft failure.[66] Also, kidney allograft failure in the context of the cardio-renal syndrome is a well-defined cause of graft loss, especially related to diastolic dysfunction rather than systolic dysfunction,[67] but remains largely understudied. As there seems to be a high prevalence of diastolic dysfunction in renal transplant recipients (up to 53%),[63,68,69] this topic merits further investigation. A causal relationship is plausible from a mechanistic viewpoint, but observational data should be interpreted with caution due to considerable confounding and bias.

The kidney allograft vasculature in se is also prone to deterioration, further contributing to allograft loss. Arteriolar hyalinosis lesions are considered to be the hallmark of calcineurin inhibitor nephrotoxicity, however these lesions are not specific and occur independent of calcineurin inhibitor use.[70] As these lesions increase over time, they might reflect a component of general accelerated aging. This impact of aging or replicative senescence, associated with telomere shortening, was also suggested in the progression of renovascular disease in native kidneys.[71] In early allograft biopsies, these lesions most likely represent preexisting donor-derived factors.[70]

Other nonimmune events that are not infrequently the cause of graft loss include intercurrent medical and surgical illnesses, unrelated to the allograft.[20,21] Finally, not all nonallo-immune graft injury observed after transplantation is the consequence of posttransplant events. Both donor-related (cause of death, donor age, donor kidney size and quality) and transplant

procedure-related (poor organ management, ischemia-reperfusion injury, surgical complications) factors can lead to nephron loss and chronic injury.[72-75] A maladaptive injury repair of the early transplant-related kidney injury can also initiate later allo-immune responses like a late B lymphocyte response relating to renal dysfunction and fibrosis, as was recently shown by Cippa et al.[76] With the recent evolution towards better preservation techniques and prevention of delayed graft function, it is important to realize that these factors, despite their significant associations with outcome, are presumably more contributors rather than single causes of graft failure. It remains impossible to exactly quantify the contribution of these graft quality-related factors to long-term graft failure in the individual patients, and to attribute these as cofactors in graft failure.

Allo-immune injury mechanisms

The seminal analyses by Nankivell et al. on protocol biopsy histology over time after transplantation reported on the rapid decline in rejection, and a steep increase in chronic injury over time after transplantation.[25] From this, rejection became less often recognized as cause of graft failure, and calcineurin inhibitor nephrotoxicity gained attention as contributor to graft failure (see above). Until 1993, interstitial fibrosis and tubular atrophy was called "chronic rejection" according to Banff consensus, suggesting an underlying allo-immune cause. Nevertheless, as chronic injury cannot be attributed exclusively to rejection and nonimmune phenomena play an important role, this term was first changed into "chronic allograft nephropathy" and since 2005 "interstitial fibrosis/tubular atrophy" (IF/TA) was implemented as a more descriptive term in the Banff classification.[77] The contribution of allo-immune phenomena to IF/TA has long been overshadowed by the perceived importance of calcineurin inhibitor nephrotoxicity. In recent years however, increasing evidence suggests the impact of continuous allo-immune responses on late IF/TA and late kidney allograft failure.

Two major subtypes of rejection are currently identified. The last 2 decades, acute cellular (T-cell mediated) rejection (TCMR) is reported only rarely as a direct cause of graft failure.[21] Chronic TCMR was suggested more recently and remains ill defined, making it difficult to capture its prevalence and contribution to graft failure.[78] Acute and chronic antibody-mediated rejection (AMR), which are better defined than TCMR with a more specific histological presentation, are more recognized as causes of graft failure, both on the short and long term.

T-cell mediated rejection (TCMR) as cause of graft failure

Acute TCMR is present in up to 24% of indication biopsies in the first months after transplantation but its prevalence progressively decreases over time.[21,25] Acute TCMR is rare at 10 years posttransplantation.[21,26,79] By successfully preventing most episodes of acute TCMR with the use of potent immunosuppressive therapy and effective antirejection treatment with corticosteroids and ATG, the importance of acute TCMR for rapid graft failure has decreased in the last two decades. Still, the importance of acute TCMR should not be underestimated, since we know the associations with graft failure from more historical studies[80-82] and also recently it was shown that even less severe T cell inflammation in surveillance biopsies associates with increased scarring and graft functional decline.[83] Another recent study found that posttransplant DSA are associated with increased TCMR episodes, and patients who had both DSA and TCMR had increased graft loss on 4-year follow-up.[84] Moreover, TCMR could be a potentiating event for development of de novo antibodies and chronic injury.[85-89]

The latest update of the Banff classification introduced "chronic active TCMR."[78] The impact of inflammation in atrophic areas (i-IFTA) on graft outcome was illustrated in several studies.[21,85,86,90,91] I-IFTA is related to under-immunosuppression and is typically preceded by episodes of acute TCMR.[86] Persisting i-IFTA after treatment of acute TCMR associates with progressive IFTA and decreased allograft survival.[85,86] Although the suggestion that chronic active TCMR is related to graft failure, the infirm definition, the nonvalidated diagnostic

thresholds, and the notion that many, also nonimmune, renal pathologies are accompanied by inflammation, make chronic active TCMR a challenging entity, both in terms of its allo-immune nature and its association with outcome. Moreover, the response of chronic active TCMR to increased immunosuppression has not yet been studied. From this, the relative contribution of allo-immune phenomena to the phenotype of chronic active TCMR, and of chronic active TCMR as cause of kidney allograft failure, and the benefits and harms of targeting it as an allo-immune phenomenon remain to be elucidated.

Borderline changes as cause of graft failure

Borderline changes represents a separate category in the Banff classification and is defined by foci of tubulitis with limited interstitial inflammation, or interstitial inflammation with no or only mild tubulitis and represent a more prevalent category than TCMR.[92,93] Over the years, the diagnostic threshold of borderline rejection was lowered. The incorporation of i0 in the criteria for borderline changes was introduced in the 2005 meeting report,[77] but is currently contested. In an international survey, the majority of responding pathologists required at least minor interstitial infiltration (i1) for diagnosis of borderline changes,[94] Recent evidence confirms isolated tubulitis (t1i0, t2i0 and t3i0) to be a distinct entity compared to inflamed borderline TCMR, with benign subsequent histology, not affecting outcome and heterogeneous etiology.[95] Data from the same group in a recent single-center study indicated the clinical significance of inflamed borderline rejection (with exclusion of isolated tubulitis) with associations with renal dysfunction, subsequent fibrosis, subsequent rejection, allograft failure and even patient mortality.[93] Very likely, future updates of the Banff classification will again incorporate both tubulitis and interstitial inflammation (below the thresholds for acute TCMR) in the diagnostic criteria for borderline changes. The relative contribution of borderline changes to graft failure remains unclear.

Antibody-mediated rejection (AMR) as cause of graft failure

Since its recognition as a distinct diagnostic entity in 1997, important progress has been made in the diagnosis of AMR. The 3 initial diagnostic features of AMR included morphologic evidence of acute tissue injury, presence of donor specific antibodies (DSA) and positive C4d staining in peritubular capillaries as a marker for complement involvement. These features were refined in the following Banff meeting reports with more sensitivity and stratification of graft loss risk by the more recent criteria.[96] Generally, AMR is initiated by DSA, either to HLA antigens or less commonly, but also less easily detectable, to other donor-recipient mismatched antigens.[97]

AMR and some individual lesions (transplant glomerulopathy and microvascular inflammation) are recognized as important risk factors for graft failure, both when accompanied with clinical kidney dysfunction as when detected subclinically.[20-23,98] The lack of proven effective treatments to prevent or treat AMR is part of the explanation for the strong association with impaired survival.[99-101]

AMR histology with identified HLA-DSA

HLA-DSA are sometimes present before transplantation, arising from blood transfusions, pregnancies or previous transplants. The prevalence of preexisting HLA-DSA in kidney transplant recipients ranges from 10.5 to 22.9%,[55,98,102] dependent on the center acceptance of higher-risk sensitized patients and specific kidney allocation programs that avoid such transplants.[103-105] The incidence of de novo HLA-DSA after transplantation ranges from 6.5% to 16%, dependent on background risk factors, therapeutic adherence, immunosuppressive drug minimization and time after transplantation.[88,89,106-109] De novo HLA-DSA usually occur later after transplantation as a result of suboptimal immunosuppression and nonadherence and have shown to be more deleterious than preformed HLA-DSA.[102,110-112] Nonadherence is strongly linked to AMR and overall graft loss[84,110,113] but remains difficult to capture correctly.

Although HLA-DSA and the development of AMR are among the strongest risk factors identified for graft failure in cohort studies, the large majority of patients don't have nor develop HLA-DSA. Therefore, HLA-DSA cannot be considered as contributing to allograft failure in the large HLA-DSA negative fraction of graft failures.

Moreover, not all HLA-DSA are equally deleterious. Pretransplant DSA often disappear early posttransplantation and are not detrimental for graft outcome.[104,114,115] Especially low median fluorescence intensity (MFI) DSA and non-DQ HLA-DSA easily resolve.[114] There are inconsistent findings on graft outcome in patients with resolved DSA in literature.[104,115-117] Recently, a study by our group showed that, although patients with resolved versus persistent pretransplant DSA had an equally high incidence of AMR in the first 3 months posttransplantation (53.6% and 58.8%, respectively), this was not reflected in worse graft outcome in patients with resolved pretransplant DSA[114] when compared to patients without HLA-DSA. Although the association between HLA-DSA positive AMR and graft outcome is strong and well confirmed, attributing this automatically as sole or primary cause for graft failure in a patient is perhaps an overstatement, especially if HLA-DSA are of class I, low MFI and disappear over time.

AMR histology without identified HLA-DSA

There is increasing attention for cases with the histology of AMR (primarily microcirculation inflammation) in the absence of detectable HLA-DSA. With increasingly sensitive detection assays for anti-HLA DSA, it is hard to believe that these cases merely represent cases where clinically important anti-HLA DSA are missed by our detection methods. The possibility that non-HLA DSA, which are not routinely tested and therefore remain unnoticed, can initiate AMR is gaining attention and evidence.[97,118-122] However, as recent studies suggest that the spectrum of non-HLA antibodies could be wider than anticipated,[97,120] and no screening assays are validated yet for routine clinical use, the relative importance of these antibodies as cause of

AMR remains unclear. Moreover, recent data from our group suggest that these HLA-DSA negative cases represent a distinct entity, with more transient histology of AMR, less C4d deposition and better outcome.[102] Whether HLA-DSA negative cases of AMR histology, presumably due to non-HLA antibodies, should be considered as a distinct cause of graft failure, is unclear. Further work is necessary to establish this phenotype in more detail, including investigation on potential antibody-independent initiation of microcirculation inflammation, as recently suggested by e.g. the association with NK cell missing self.[123]

Difficulties in identifying the causes of graft failure

Next to the challenges in the definition of the separate diagnostic categories of kidney allograft injury and in the identification of the exact underlying biological processes, an even bigger challenge remains establishing the cause(s) of graft failure at the individual patient level. Although several studies reported on the causes of graft failure by identifying 1 single disease per patient, this approach seems overly simplistic. Especially in late graft failure, different pathologies co-occur. We previously showed that in the last biopsy before graft failure, 1 in 4 biopsies had more than 1 co-existing specific disease.[22] On the other hand, 16% of patients did not have any specific diagnosis in the last biopsy performed, but did have a specific disease in a prior biopsy. Interstitial fibrosis and tubular atrophy (IF/TA) as well as glomerulosclerosis are highly prevalent in patients with a specific diagnosis prior to graft failure.[22] Different disease processes wax and wane over time, but culminate in progressive chronic injury and nephron loss, which is often no longer reflecting the primary disease process but a final common pathology. Only relying on the last biopsy to establish the cause of graft failure is therefore not sufficient, and the whole patient's history should be taken into account. However, for reporting and study purposes inevitably 1 cause is singled out, as is also the case in reports of native kidney disease failures.[124]

A potential aid in establishing the patient-specific cause of graft failure is indeed the evaluation of disease trajectories over time, e.g. by integrating information from systematic protocol biopsies performed over a longer follow-up period (not only in the first year after transplantation). As lesions are not always reaching the Banff diagnostic thresholds, it could be important to consider the relative severity of the individual lesions simultaneously. This is currently not reflected in the Banff classification, which remains a dichotomous classification (disease present or absent) and does not allow for a more continuous evaluation of trajectories of injuries. This contrasts with the natural disease courses, which are characterized by time-dependent fluctuations or progression, evolving over time. The lack of emphasis on chronic injury of the Banff consensus also makes it difficult to identify the progression of chronic injury as a cause of graft failure.

Finally, this review and the available studies on causes of graft failure almost exclusively focus on known causes of graft failure, related to the histopathologic entities we diagnose in kidney transplant biopsies. In many failing kidney allografts very early or late after transplantation no biopsies are performed and no knowledge on the complete histopathological picture is available. Especially in recipients who are not considered eligible for relisting for a repeat transplant, there is less need to determine the cause of graft failure. This creates some bias in the current literature on the causes of graft failure which likely underrepresent older patients or patients with important comorbidities. This bias could lead to an overestimation of the importance of histologic, and certainly allo-immune injury in the causes of graft failure, and an underestimation of the contribution of nonimmune risk factors for end-stage renal disease.

Future directions

In this review, we summarized the causes of graft failure as they are currently acknowledged. There is a possibility that these causes and their relative share in graft failure change over time. This was illustrated with the improved short-term graft survival after the introduction of powerful immunosuppressants tackling T-cell mediated rejection in the early decades of clinical transplantation. Also, patient populations include increasingly elderly recipients, with more comorbidities potentially contributing to graft failure. It is imaginable that with better therapeutic strategies, introduction of new immunosuppressants or better screening pretransplant leading to better matching, a similar shift in the causes of graft failure can occur.

In summary, the causes of graft failure are heterogeneous, multifactorial and time-dependent. Many disease processes culminate into the final common histological picture of irreversible chronic damage. Up to now, the relative importance of disease trajectories over time, including subclinical injury and nonallo-immune processes, is insufficiently studied in this context. More in depth analyses of the causes of graft failure, that take into account these considerations and avoid systematic bias, is necessary. For this, future international efforts should be aimed at setting minimal requirements for the prospective standardized collection of clinical and histological parameters in each case of kidney allograft failure. Gaining better insight in the causes of graft failure is important to better target therapies, or take preventative measures, that improve long-term outcome after kidney transplantation.

REFERENCES

1. Rose C, Schaeffner E, Frei U, et al. A Lifetime of Allograft Function with Kidneys from Older Donors. *J Am Soc Nephrol.* 2015;26(10):2483-2493.
2. Ghyselen L, Naesens M. Indications, risks and impact of failed allograft nephrectomy. *Transplant Rev (Orlando).* 2019;33(1):48-54.
3. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant.* 2011;11(3):450-462.
4. Coemans M, Süsal C, Döhler B, et al. Analyses of the short- and long-term graft survival after kidney transplantation in Europe between 1986 and 2015. *Kidney Int.* 2018;94(5):964-973.
5. Helanterä I, Räihä J, Finne P, et al. Early failure of kidney transplants in the current era-a national cohort study. *Transpl Int.* 2018;31(8):880-886.
6. Gill JS, Rose C, Pereira BJ, et al. The importance of transitions between dialysis and transplantation in the care of end-stage renal disease patients. *Kidney Int.* 2007;71(5):442-447.
7. Cosio FG, Hickson LJ, Griffin MD, et al. Patient survival and cardiovascular risk after kidney transplantation: the challenge of diabetes. *Am J Transplant.* 2008;8(3):593-599.
8. Arcos E, Pérez-Sáez MJ, Comas J, et al. Assessing the Limits in Kidney Transplantation: Use of Extremely Elderly Donors and Outcomes in Elderly Recipients. *Transplantation.* 2019.
9. Bui K, Kilambi V, Rodrigue JR, et al. Patient Functional Status at Transplant and Its Impact on Posttransplant Survival of Adult Deceased-donor Kidney Recipients. *Transplantation.* 2019;103(5):1051-1063.

10. Gill JS, Rose C, Joffres Y, et al. Variation in Dialysis Exposure Prior to Nonpreemptive Living Donor Kidney Transplantation in the United States and Its Association With Allograft Outcomes. *Am J Kidney Dis.* 2018;71(5):636-647.

11. Oniscu GC, Brown H, Forsythe JL. How old is old for transplantation? *Am J Transplant.* 2004;4(12):2067-2074.

12. Liefeldt L, Budde K. Risk factors for cardiovascular disease in renal transplant recipients and strategies to minimize risk. *Transpl Int.* 2010;23(12):1191-1204.

13. Fellström B, Jardine AG, Soveri I, et al. Renal dysfunction is a strong and independent risk factor for mortality and cardiovascular complications in renal transplantation. *Am J Transplant.* 2005;5(8):1986-1991.

14. Soveri I, Snyder J, Holdaas H, et al. The external validation of the cardiovascular risk equation for renal transplant recipients: applications to BENEFIT and BENEFIT-EXT trials. *Transplantation.* 2013;95(1):142-147.

15. Badve SV, Palmer SC, Strippoli GFM, et al. The Validity of Left Ventricular Mass as a Surrogate End Point for All-Cause and Cardiovascular Mortality Outcomes in People With CKD: A Systematic Review and Meta-analysis. *Am J Kidney Dis.* 2016;68(4):554-563.

16. Hryniewiecka E, Zegarska J, Zochowska D, et al. Cardiovascular Disease in Kidney Transplantation and Its Association With Blood Concentrations of Cyclosporine and Cyclosporine Metabolites. *Transplant Proc.* 2018;50(6):1850-1854.

17. Neale J, Smith AC. Cardiovascular risk factors following renal transplant. *World J Transplant.* 2015;5(4):183-195.

18. Aakhus S, Dahl K, Widerøe TE. Cardiovascular disease in stable renal transplant patients in Norway: morbidity and mortality during a 5-yr follow-up. *Clin Transplant.* 2004;18(5):596-604.

19. Oterdoom LH, de Vries AP, van Ree RM, et al. N-terminal pro-B-type natriuretic peptide and mortality in renal transplant recipients versus the general population. *Transplantation.* 2009;87(10):1562-1570.

20. El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. *Am J Transplant.* 2009;9(3):527-535.

21. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant.* 2012;12(2):388-399.

22. Naesens M, Kuypers DR, De Vusser K, et al. The histology of kidney transplant failure: a long-term follow-up study. *Transplantation.* 2014;98(4):427-435.

23. Chand S, Atkinson D, Collins C, et al. The Spectrum of Renal Allograft Failure. *PLoS One.* 2016;11(9):e0162278.

24. Stegall MD, Gaston RS, Cosio FG, et al. Through a glass darkly: seeking clarity in preventing late kidney transplant failure. *J Am Soc Nephrol.* 2015;26(1):20-29.

25. Nankivell BJ, Borrows RJ, Fung CL, et al. The natural history of chronic allograft nephropathy. *N Engl J Med.* 2003;349(24):2326-2333.

26. Stegall MD, Cornell LD, Park WD, et al. Renal Allograft Histology at 10 Years After Transplantation in the Tacrolimus Era: Evidence of Pervasive Chronic Injury. *Am J Transplant.* 2018;18(1):180-188.

27. Van Loon E, Lerut E, Naesens M. The time dependency of renal allograft histology. *Transpl Int.* 2017;30(11):1081-1091.

28. Yang B, El Nahas AM, Thomas GL, et al. Caspase-3 and apoptosis in experimental chronic renal scarring. *Kidney Int.* 2001;60(5):1765-1776.

29. Schnaper HW. Remnant nephron physiology and the progression of chronic kidney disease. *Pediatr Nephrol.* 2014;29(2):193-202.

30. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol.* 2009;4(2):481-508.

31. Nankivell BJ, P'Ng CH, O'Connell PJ, et al. Calcineurin Inhibitor Nephrotoxicity Through the Lens of Longitudinal Histology: Comparison of Cyclosporine and Tacrolimus Eras. *Transplantation.* 2016;100(8):1723-1731.

32. Jevnikar AM, Mannon RB. Late kidney allograft loss: what we know about it, and what we can do about it. *Clin J Am Soc Nephrol.* 2008;3(Suppl 2):S56-67.

33. Sharif A, Shabir S, Chand S, et al. Meta-analysis of calcineurin-inhibitor-sparing regimens in kidney transplantation. *J Am Soc Nephrol.* 2011;22(11):2107-2118.

34. Lim WH, Eris J, Kanellis J, et al. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. *Am J Transplant.* 2014;14(9):2106-2119.

35. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med.* 2004;351(26):2715-2729.

36. Kotanko P, Pusey CD, Levy JB. Recurrent glomerulonephritis following renal transplantation. *Transplantation.* 1997;63(8):1045-1052.

37. Cosio FG, Cattran DC. Recent advances in our understanding of recurrent primary glomerulonephritis after kidney transplantation. *Kidney Int.* 2017;91(2):304-314.

38. Briganti EM, Russ GR, McNeil JJ, et al. Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med.* 2002;347(2):103-109.

39. Allen PJ, Chadban SJ, Craig JC, et al. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. *Kidney Int.* 2017;92(2):461-469.

40. Hariharan S, Savin VJ. Recurrent and de novo disease after renal transplantation: a report from the Renal Allograft Disease Registry. *Pediatr Transplant.* 2004;8(4):349-350.

41. Toledo K, Pérez-Sáez MJ, Navarro MD, et al. Impact of recurrent glomerulonephritis on renal graft survival. *Transplant Proc.* 2011;43(6):2182-2186.

42. Moroni G, Longhi S, Quaglini S, et al. The impact of recurrence of primary glomerulonephritis on renal allograft outcome. *Clin Transplant.* 2014;28(3):368-376.

43. An JN, Lee JP, Oh YJ, et al. Incidence of post-transplant glomerulonephritis and its impact on graft outcome. *Kidney Res Clin Pract.* 2012;31(4):219-226.

44. Odum J, Peh CA, Clarkson AR, et al. Recurrent mesangial IgA nephritis following renal transplantation. *Nephrol Dial Transplant.* 1994;9(3):309-312.

45. Charpentier B, Hiesse C, Marchand S, et al. De novo and recurrent diseases: recurrent glomerulopathies. *Transplant Proc.* 1999;31(1-2):264-266.

46. Fairhead T, Knoll G. Recurrent glomerular disease after kidney transplantation. *Curr Opin Nephrol Hypertens.* 2010;19(6):578-585.

47. Mulay AV, van Walraven C, Knoll GA. Impact of immunosuppressive medication on the risk of renal allograft failure due to recurrent glomerulonephritis. *Am J Transplant.* 2009;9(4):804-811.

48. Gourishankar S, Leduc R, Connett J, et al. Pathological and clinical characterization of the 'troubled transplant': data from the DeKAF study. *Am J Transplant.* 2010;10(2):324-330.

49. Hirsch HH, Randhawa P, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. *Am J Transplant.* 2013;13(Suppl 4):179-188.

50. Lamarche C, Orio J, Collette S, et al. BK Polyomavirus and the Transplanted Kidney: Immunopathology and Therapeutic Approaches. *Transplantation.* 2016;100(11):2276-2287.

51. Drachenberg CB, Papadimitriou JC, Chaudhry MR, et al. Histological Evolution of BK Virus-Associated Nephropathy: Importance of Integrating Clinical and Pathological Findings. *Am J Transplant.* 2017;17(8):2078-2091.

52. Nankivell BJ, Renthawa J, Sharma RN, et al. BK Virus Nephropathy: Histological Evolution by Sequential Pathology. *Am J Transplant.* 2017;17(8):2065-2077.

53. Menter T, Mayr M, Schaub S, et al Pathology of resolving polyomavirus-associated nephropathy. *Am J Transplant.* 2013;13(6):1474-1483.

54. Sawinski D, Forde KA, Trofe-Clark J, et al. Persistent BK viremia does not increase intermediate-term graft loss but is associated with de novo donor-specific antibodies. *J Am Soc Nephrol.* 2015;26(4):966-975.

55. Coemans M, Van Loon E, Lerut E, et al. Occurrence of Diabetic Nephropathy After Renal Transplantation Despite Intensive Glycemic Control: An Observational Cohort Study. *Diabetes Care.* 2019;42(4):625-634.

56. Díaz JM, Gich I, Bonfill X, et al. Prevalence evolution and impact of cardiovascular risk factors on allograft and renal transplant patient survival. *Transplant Proc.* 2009;41(6):2151-2155.

57. Balla A, Chobanian M. New-onset diabetes after transplantation: a review of recent literature. *Curr Opin Organ Transplant.* 2009;14(4):375-379.

58. Denic A, Morales MC, Park WD, et al. Using computer-assisted morphometrics of 5-year biopsies to identify biomarkers of late renal allograft loss. *Am J Transplant.* 2019.

59. Vanrenterghem YF, Claes K, Montagnino G, et al. Risk factors for cardiovascular events after successful renal transplantation. *Transplantation.* 2008;85(2):209-216.

60. Dahle DO, Midtvedt K, Hartmann A, et al. Endothelial dysfunction is associated with graft loss in renal transplant recipients. *Transplantation.* 2013;95(5):733-739.

61. Korogiannou M, Xagas E, Marinaki S, et al. Arterial Stiffness in Patients With Renal Transplantation; Associations With Co-morbid Conditions, Evolution, and Prognostic Importance for Cardiovascular and Renal Outcomes. *Front Cardiovasc Med.* 2019;6:67.

62. Cheddani L, Radulescu C, Chaignon M, et al. From arterial stiffness to kidney graft microvasculature: Mortality and graft survival within a cohort of 220 kidney transplant recipients. *PLoS One.* 2018;13(5):e0195928.

63. Hamidi S, Kojuri J, Attar A, et al. The effect of kidney transplantation on speckled tracking echocardiography findings in patients on hemodialysis. *J Cardiovasc Thorac Res.* 2018;10(2):90-94.

64. Gong IY, Al-Amro B, Prasad GVR, et al. Cardiovascular magnetic resonance left ventricular strain in end-stage renal disease patients after kidney transplantation. *J Cardiovasc Magn Reson.* 2018;20(1):83.

65. An JN, Kim YH, Park JB, et al. The reciprocal interaction between LV remodelling and allograft outcomes in kidney transplant recipients. *Heart.* 2015;101(22):1826-1833.

66. Hatamizadeh P, Molnar MZ, Streja E, et al. Recipient-related predictors of kidney transplantation outcomes in the elderly. *Clin Transplant.* 2013;27(3):436-443.

67. Waiser J, Knebel F, Rudolph B, et al. Renal allograft loss caused by cardiorenal syndrome: frequency and diagnosis. *Transplantation.* 2015;99(6):1208-1215.

68. Ravera M, Rosa GM, Fontanive P, et al. Impaired Left Ventricular Global Longitudinal Strain among Patients with Chronic Kidney Disease and End-Stage Renal Disease and Renal Transplant Recipients. *Cardiorenal Med.* 2019;9(1):61-68.

69. Rumman RK, Ramroop R, Chanchlani R, et al. Longitudinal assessment of myocardial function in childhood chronic kidney disease, during dialysis, and following kidney transplantation. *Pediatr Nephrol.* 2017;32(8):1401-1410.

70. Bröcker V, Schubert V, Scheffner I, et al. Arteriolar lesions in renal transplant biopsies: prevalence, progression, and clinical significance. *Am J Pathol.* 2012;180(5):1852-1862.

71. De Vusser K, Pieters N, Janssen B, et al. Telomere length, cardiovascular risk and arteriosclerosis in human kidneys: an observational cohort study. *Aging.* 2015;7(10):766-775.

72. Zukowski M, Bohatyrewicz R, Biernawska J, et al. Cause of death in multiorgan donors and its relation to the function of transplanted kidneys. *Transplant Proc.* 2009;41(8):2972-2974.

73. Debout A, Foucher Y, Trébern-Launay K, et al. Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. *Kidney Int.* 2015;87(2):343-349.

74. Mogulla MR, Bhattacharjya S, Clayton PA. Risk factors for and outcomes of delayed graft function in live donor kidney transplantation - a retrospective study [published online June 17, 2019]. *Transpl Int*. doi: 10.1111/tri.13472.

75. Cippà PE, Sun B, Liu J, et al. Transcriptional trajectories of human kidney injury progression. *JCI Insight.* 2018;3(22):1-12.

76. Cippà PE, Liu J, Sun B, et al. A late B lymphocyte action in dysfunctional tissue repair following kidney injury and transplantation. *Nat Commun.* 2019;10(1):1157.

77. Solez K, Colvin RB, Racusen LC, et al. Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). *Am J Transplant.* 2007;7(3):518-526.

78. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant.* 2018;18(2):293-307.

79. Halloran PF, Chang J, Famulski K, et al. Disappearance of T Cell-Mediated Rejection Despite Continued Antibody-Mediated Rejection in Late Kidney Transplant Recipients. *J Am Soc Nephrol.* 2015;26(7):1711-1720.

80. Matas AJ, Gillingham KJ, Payne WD, et al. The impact of an acute rejection episode on long-term renal allograft survival (t1/2). *Transplantation.* 1994;57(6):857-859.

81. Joseph JT, Kingsmore DB, Junor BJ, et al. The impact of late acute rejection after cadaveric kidney transplantation. *Clin Transplant.* 2001;15(4):221-227.

82. Wu K, Budde K, Schmidt D, Neumayer HH, et al. Pathologic characteristics of early or late acute cellular rejection and outcome after kidney transplant. *Exp Clin Transplant.* 2014;12(4):314-322.

83. Mehta R, Bhusal S, Randhawa P, et al. Short-term adverse effects of early subclinical allograft inflammation in kidney transplant recipients with a rapid steroid withdrawal protocol. *Am J Transplant.* 2018;18(7):1710-1717.

84. Cherukuri A, Mehta R, Sharma A, et al. Post-transplant donor specific antibody is associated with poor kidney transplant outcomes only when combined with both T-cell-mediated rejection and et aladherence. *Kidney Int.* 2019;96(1):202-213.

85. Nankivell BJ, Shingde M, Keung KL, et al. The causes, significance and consequences of inflammatory fibrosis in kidney transplantation: The Banff i-IFTA lesion. *Am J Transplant.* 2018;18(2):364-376.

86. Lefaucheur C, Gosset C, Rabant M, et al. T cell-mediated rejection is a major determinant of inflammation in scarred areas in kidney allografts. *Am J Transplant.* 2018;18(2):377-390.

87. El Ters M, Grande JP, Keddis MT, et al. Kidney allograft survival after acute rejection, the value of follow-up biopsies. *Am J Transplant.* 2013;13(9):2334-2341.

88. Schinstock CA, Cosio F, Cheungpasitporn W, et al. The Value of Protocol Biopsies to Identify Patients With De Novo Donor-Specific Antibody at High Risk for Allograft Loss. *Am J Transplant.* 2017;17(6):1574-1584.

89. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant.* 2012;12(5):1157-1167.

90. Mannon RB, Matas AJ, Grande J, et al. Inflammation in areas of tubular atrophy in kidney allograft biopsies: a potent predictor of allograft failure. *Am J Transplant.* 2010;10(9):2066-2073.

91. Mengel M, Reeve J, Bunnag S, et al. Scoring total inflammation is superior to the current Banff inflammation score in predicting outcome and the degree of molecular disturbance in renal allografts. *Am J Transplant.* 2009;9(8):1859-1867.

92. de Freitas DG, Sellarés J, Mengel M, et al. The nature of biopsies with "borderline rejection" and prospects for eliminating this category. *Am J Transplant.* 2012;12(1):191-201.

93. Nankivell BJ, Agrawal N, Sharma A, et al. The clinical and pathological significance of borderline T cell-mediated rejection. *Am J Transplant.* 2019;19(5):1452-1463.

94. Becker JU, Chang A, Nickeleit V, et al. Banff Borderline Changes Suspicious for Acute T Cell-Mediated Rejection: Where Do We Stand? *Am J Transplant.* 2016;16(9):2654-2660.

95. Nankivell BJ, P'Ng CH, Chapman JR. Does tubulitis without interstitial inflammation represent borderline acute T cell mediated rejection? *Am J Transplant.* 2019;19(1):132-144.

96. Solar-Cafaggi D, Marino L, Uribe-Uribe N, et al. Antibody-mediated rejection in the Banff classifications of 2007 and 2017: A comparison of renal graft loss prediction capability. *Transpl Immunol.* 2018;51:40-44.

97. Reindl-Schwaighofer R, Heinzel A, Kainz A, et al. Contribution of non-HLA incompatibility between donor and recipient to kidney allograft survival: genome-wide analysis in a prospective cohort. *Lancet.* 2019;393(10174):910-917.

98. Loupy A, Vernerey D, Tinel C, et al. Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts. *J Am Soc Nephrol.* 2015;26(7):1721-1731.

99. Loupy A, Lefaucheur C. Antibody-Mediated Rejection of Solid-Organ Allografts. *N Engl J Med.* 2018;379(12):1150-1160.

100. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation.* 2012;94(8):775-783.

101. Wan SS, Ying TD, Wyburn K, et al. The Treatment of Antibody-Mediated Rejection in Kidney Transplantation: An Updated Systematic Review and Meta-Analysis. *Transplantation.* 2018;102(4):557-568.

102. Senev A, Coemans M, Lerut E, et al. Histological picture of antibody-mediated rejection without donor-specific anti-HLA antibodies: Clinical presentation and implications for outcome. *Am J Transplant.* 2019;19(3):763-780.

103. Viglietti D, Loupy A, Vernerey D, et al. Value of Donor-Specific Anti-HLA Antibody Monitoring and Characterization for Risk Stratification of Kidney Allograft Loss. *J Am Soc Nephrol.* 2017;28(2):702-715.

104. Redondo-Pachón D, Pérez-Sáez MJ, Mir M, et al. Impact of persistent and cleared preformed HLA DSA on kidney transplant outcomes. *Hum Immunol.* 2018;79(6):424-431.

105. Heidt S, Haasnoot GW, van Rood JJ, et al. Kidney allocation based on proven acceptable antigens results in superior graft survival in highly sensitized patients. *Kidney Int.* 2018;93(2):491-500.

106. Kauke T, Oberhauser C, Lin V, et al. De novo donor-specific anti-HLA antibodies after kidney transplantation are associated with impaired graft outcome independently of their C1q-binding ability. *Transpl Int.* 2017;30(4):360-370.

107. Calp-Inal S, Ajaimy M, Melamed ML, et al. The prevalence and clinical significance of C1q-binding donor-specific anti-HLA antibodies early and late after kidney transplantation. *Kidney Int.* 2016;89(1):209-216.

108. Wiebe C, Kosmoliaptsis V, Pochinco D, et al. A Comparison of HLA Molecular Mismatch Methods to Determine HLA Immunogenicity. *Transplantation.* 2018;102(8):1338-1343.

109. Lachmann N, Niemann M, Reinke P, et al. Donor-Recipient Matching Based on Predicted Indirectly Recognizable HLA Epitopes Independently Predicts the Incidence of De Novo Donor-Specific HLA Antibodies Following Renal Transplantation. *Am J Transplant.* 2017;17(12):3076-3086.

110. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. *Am J Transplant.* 2015;15(11):2921-2930.

111. Bray RA, Gebel HM, Townsend R, et al. De novo donor-specific antibodies in belatacept-treated vs cyclosporine-treated kidney-transplant recipients: Post hoc analyses of the randomized phase III BENEFIT and BENEFIT-EXT studies. *Am J Transplant.* 2018;18(7):1783-1789.

112. Aubert O, Loupy A, Hidalgo L, et al. Antibody-Mediated Rejection Due to Preexisting versus. *J Am Soc Nephrol.* 2017;28(6):1912-1923.

113. Halloran PF, Reeve JP, Pereira AB, et al. Antibody-mediated rejection, T cell-mediated rejection, and the injury-repair response: new insights from the Genome Canada studies of kidney transplant biopsies. *Kidney Int.* 2014;85(2):258-264.

114. Senev A, Lerut E, Van Sandt V, et al. Specificity, strength, and evolution of pretransplant donor-specific HLA antibodies determine outcome after kidney transplantation [published online May 6, 2019]. *Am J Transplant.* doi: 10.1111/ajt.15414.

115. Kimball PM, Baker MA, Wagner MB, et al. Surveillance of alloantibodies after transplantation identifies the risk of chronic rejection. *Kidney Int.* 2011;79(10):1131-1137.

116. Zecher D, Bach C, Staudner C, et al. Characteristics of donor-specific anti-HLA antibodies and outcome in renal transplant patients treated with a standardized induction regimen. *Nephrol Dial Transplant.* 2017;32(4):730-737.

117. Caillard S, Becmeur C, Gautier-Vargas G, et al. Pre-existing donor-specific antibodies are detrimental to kidney allograft only when persistent after transplantation. *Transpl Int.* 2017;30(1):29-40.

118. Dragun D, Müller DN, Bräsen JH, et al. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. *N Engl J Med.* 2005;352(6):558-569.

119. Lefaucheur C, Viglietti D, Bouatou Y, et al. Non-HLA agonistic anti-angiotensin II type 1 receptor antibodies induce a distinctive phenotype of antibody-mediated rejection in kidney transplant recipients. *Kidney Int.* 2019;96(1):189-201.

120. Steers NJ, Li Y, Drace Z, et al. Genomic Mismatch at. *N Engl J Med.* 2019;380(20):1918-1928.

121. Delville M, Lamarthée B, Pagie S, et al. Early Acute Microvascular Kidney Transplant Rejection in the Absence of Anti-HLA Antibodies Is Associated with Preformed IgG Antibodies against Diverse Glomerular Endothelial Cell Antigens. *J Am Soc Nephrol.* 2019;30(4):692-709.

122. Kamburova EG, Gruijters ML, Kardol-Hoefnagel T, et al. Antibodies against ARHGDIB are associated with long-term kidney graft loss [published online June 13, 2019]. *Am J Transplant.* doi: 10.1111/ajt.15493.

123. Koenig A, Chen C-C, Marçais A. Missing self triggers NK cell-mediated chronic vascular rejection of solid organ transplants. Nature Communications. 2019. In Press.

124. Kramer A, Pippias M, Noordzij M, et al. The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2016: a summary. *Clinical Kidney Journal.* 2019:1-19.

125. Kasiske BL, Anjum S, Shah R, et al. Hypertension after kidney transplantation. *Am J Kidney Dis.* 2004;43(6):1071-1081.

126. Singh R, Geerlings SE, Peters-Sengers H, et al. Incidence, risk factors, and the impact of allograft pyelonephritis on renal allograft function. *Transpl Infect Dis.* 2016;18(5):647-660.

127. Giral M, Pascuariello G, Karam G, et al. Acute graft pyelonephritis and long-term kidney allograft outcome. *Kidney Int.* 2002;61(5):1880-1886.

128. Kamath NS, John GT, Neelakantan N, et al. Acute graft pyelonephritis following renal transplantation. *Transpl Infect Dis.* 2006;8(3):140-147.

129. Pellé G, Vimont S, Levy PP, et al. Acute pyelonephritis represents a risk factor impairing long-term kidney graft function. *Am J Transplant.* 2007;7(4):899-907.

130. Fiorante S, Fernández-Ruiz M, López-Medrano F, et al. Acute graft pyelonephritis in renal transplant recipients: incidence, risk factors and long-term outcome. *Nephrol Dial Transplant.* 2011;26(3):1065-1073.

131. Gołębiewska J, Dębska-Ślizień A, Zadrożny D, et al. Acute graft pyelonephritis during the first year after renal transplantation. *Transplant Proc.* 2014;46(8):2743-2747.

132. Fervenza FC, Lafayette RA, Alfrey EJ, et al. Renal artery stenosis in kidney transplants. *Am J Kidney Dis.* 1998;31(1):142-148.

133. Dimitroulis D, Bokos J, Zavos G, et al. Vascular complications in renal transplantation: a single-center experience in 1367 renal transplantations and review of the literature. *Transplant Proc.* 2009;41(5):1609-1614.

134. Rouvière O, Berger P, Béziat C, et al. Acute thrombosis of renal transplant artery: graft salvage by means of intra-arterial fibrinolysis. *Transplantation.* 2002;73(3):403-409.

135. Giustacchini P, Pisanti F, Citterio F, et al. Renal vein thrombosis after renal transplantation: an important cause of graft loss. *Transplant Proc.* 2002;34(6):2126-2127.

136. Bach D, Wirth C, Schott G, et al. Percutaneous renal biopsy: three years of experience with the biopty gun in 761 cases--a survey of results and complications. *Int Urol Nephrol.* 1999;31(1):15-22.

Figure Legends

Figure 1. Literature overview of reported causes of death-censored graft failure. This figure reports the causes annotated to death-censored graft failures from 4 different studies. More information on these studies is given in Table 1. As illustrated, causes vary importantly between studies, due to different study perspectives and designs and differences in definitions. PVAN=polyoma-virus associated nephropathy.

Figure 2. Schematic overview of risk factors for allograft loss, distinguishing recipient-related factors (analogous to risk factors in native kidneys) from transplant-related factors, that can be nonimmunological and immunological. All these factors can contribute to allograft injury with nephron loss, further initiating a vicious circle of harmful hyperfiltration of the remnant nephrons resulting in accelerated nephron loss and fibrosis.

ESRD= end-stage renal disease. IRI=ischemia-reperfusion injury. DGF= delayed graft function. CNI=calcineurin inhibitor. PVAN= polyoma-virus associated nephropathy. CMV=cytomegalovirus.

Tables

Table 1. Overview of studies reporting causes of graft failure.

Study	Sample size	Timing	Follow-up	Biopsy indication	Biopsy timing ~graft loss	Death with function/ PNF/ DCGF	Early/Late	Causes identified
El-Zoghby 2008 [20]	1317 recipients 330 graft losses	Transplanted between 1996-2006	50.3+-32.6 months	Protocol & indication	68% within 1y – 84% within 2y	138/39/153	Not separated but subanalysis in function of time given	37% glomerular diseases (GNF/transplant glomerulopathy) 31% IFTA 16% Medical/surgical 12% acute rejection 5% unkown
Sellares 2012 [21]	315 recipients 74 graft losses	Biopsied between 2004-2008 Dates of transplantation not mentioned	Median 17 months (6d-32y)	Only indication	Follow-up after biopsy: median 24.6 months (0.3-36.9)	14/0/60	Not separated	N=56 evaluated (4 missing information) 64% AR (all AMR) 18% GNF 7% PVAN 11% medical/surgical
Naesens 2014 [22]	1197 recipients 664 graft losses	Transplanted between 1991-2001	14.5±2.80 years	Only indication	3.2±3.9 (range, 0–16.4) years 46% within 2 years	351/0/313	Not separated	N=144 last indication biopsies within the last 2 years before graft failure 36.1% acute rejection 30.6% no specific disease (14.5% IFTA>1) 16.7% transplant glomerulopathy 11.8% GNF 4.86% PVAN
Chand 2016 [23]	171 DCGF studied	Failures between 2008-2014. Transplanted 1990-201?	0-36y	Only indication	The mean time between biopsy and graft failure was 4±2 weeks for failures within 1 year, 4±3 months for	0/33/138	Split first month/1m-1y /1y-5y/5y-10y/>10y	<1m: PNF due to vascular thrombosis or donor quality/preservation injury Beyond 1m in patients with proximate biopsy (N=97):

	failures within 5 years, 7±4 months for failures within 10 years, and 14±5 months for failures beyond 10 years.	29.9% IFTA 27.8% AMR 22.7% recurrent disease 14.4% TCMR 5.1% PVAN

Table 2. Causes of end-stage renal disease in native kidneys (as reported in ERA-EDTA Registry Annual Report 2016, data for all countries for incident patients accepted for renal replacement therapy in 2016, at day 1[124]) and prevalence in the kidney transplant population.

Diagnostic category	Prevalence as cause of ESRD in native kidneys	Prevalence after kidney transplantation
Diabetes mellitus	23%	Pretransplant diabetes: 6-17%[55,56] New onset diabetes after transplantation: 2-53%[57]
Glomerulonephritis/ Glomerulosclerosis	15%	2.6-50% recurrence of glomerulonephritic disease[40-42]
Hypertension	13%	55.5%-93%[17,56,125]
Autosomal dominant polycystic disease	6%	/
Pyelonephritis	6%	10–22%[126-131]
Renal vascular disease	2%	Renal artery stenosis 1-23%[132,133] Renal artery thrombosis: 0.5-3.5%[134] Renal vein thrombosis : 0.5-4%[135] Biopsy-induced vascular injuries: 1-18%[136]
Miscellaneous	15.0%	/
Unknown/missing	20%	/

Figure 1

Figure 2