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# Chronic Progressive Calcineurin Nephrotoxicity: An Overstated Concept

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### Keywords

calcineurin; nephrotoxicity

It has long been believed that, for kidney transplant recipients, acute rejection episodes were a risk factor for, and a forerunner of, late graft dysfunction and graft loss. Thus, when the introduction of calcineurin inhibitor (CNI)-based immunosuppression was associated with a significant decease in acute rejection rates and improvement in short-term graft survival, there was optimism that there would be significant improvement in long-term graft survival rates. This hope has not been realized. At the same time, some CNI-immunosuppressed extra-renal transplant recipients have developed progressive native kidney dysfunction and renal failure. One possible explanation for these clinical observations is *chronic* CNI nephrotoxicity.

There is no doubt that *acute* CNI nephrotoxicity exists (reviewed in 1). Numerous reports attest to renal dysfunction or even anuria related to high CNI blood levels, and this toxicity has been associated with specific histologic lesions (1). The acute dysfunction, however, is usually reversible when the CNI is withdrawn (2). In contrast to acute nephrotoxicity, data supporting *chronic progressive* CNI-related nephrotoxicity is less clear (3, 4). Although some kidney and extrarenal transplant recipients develop late renal dysfunction, there have been no studies that define what proportion of this dysfunction is due to CNI use vs. other causes. Yet much of the *progressive* late graft dysfunction after a kidney transplant, or *progressive* native kidney dysfunction after an extrarenal transplant, has been attributed to CNI toxicity. In my opinion, the importance of progressive chronic CNI nephrotoxicity has been overstated as a cause of late renal dysfunction. This overemphasis on chronic CNI nephrotoxicity has resulted in negative consequences for our recipients. First, the diagnosis of “CNI toxicity” in individual patients has led to lowering of CNI doses (and levels); for some dose reduction had resulted in increased immunologic activity. Second, we have spent two decades attempting to minimize “CNI nephrotoxicity” instead of studying and minimizing other more prevalent causes of late dysfunction.

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CNIs have numerous side effects and there may be many reasons to consider minimization or elimination of CNI use. However, in the subsequent sections, I will suggest that: a) for the great majority of cases, the existing data does not support *chronic progressive* calcineurin nephrotoxicity, and b) there are other more plausible explanations for late kidney dysfunction after kidney and extrarenal transplantation.

## Problems with the data purported to show CNI nephrotoxicity

### a) Prospective randomized studies

There are major problems with the data purported to show progressive CNI nephrotoxicity after kidney transplantation. First, there are no prospective randomized studies that clearly demonstrate CNI nephrotoxicity to be responsible for a significant proportion of late graft dysfunction. Just the opposite—most studies have shown that CNI-free immunosuppression provides no long-term benefit (5-11). Yes, initial eGFR is better in recipients not taking CNIs. But there is no difference in the slope of eGFR vs. time in those taking or not taking CNIs. In addition, CNI-free protocols have their own drug-specific complications and limitations.

### b) Overdiagnosis of “CNI nephrotoxicity”

Second, there are no clinical or histologic parameters that are diagnostic of chronic CNI nephrotoxicity (1); as a consequence, CNI nephrotoxicity may be overdiagnosed. For CNI-immunosuppressed kidney transplant recipients who develop slow deterioration of graft function (or extrarenal-renal transplant recipients who develop native kidney dysfunction), a kidney biopsy is often not done and the clinical diagnosis of “CNI nephrotoxicity” is made. This diagnosis is then entered into the recipient's chart or into a database (including registry databases). Retrospective analyses of these databases attribute dysfunction and kidney failure to CNI nephrotoxicity. Alternatively, if a biopsy is done and shows fibrosis and atrophy, the pathologist, in the absence of any other specific diagnosis often interprets the biopsy as consistent with CNI nephrotoxicity. This was seen in the deterioration of kidney allograft function (DeKAF) study in which patients with new onset late kidney allograft dysfunction underwent percutaneous allograft biopsy (12). In 30% of the cases, the biopsy was interpreted as being consistent with CNI nephrotoxicity. For these recipients, if there were no circulating donor-specific antibody (DSA) and if histology showed no inflammation and was not C4d positive, prognosis was excellent.

### c) Concerns regarding late graft dysfunction and graft loss after kidney transplantation

It has been noted that although CNI-based immunosuppression has resulted in significant improvement of short-term outcome, there has been little parallel improvement in long-term outcome. This observation has been interpreted as suggesting that any early survival gain is countered by CNI nephrotoxicity. However, there is an alternate explanation. Half-lives (the length of time until 50% of grafts surviving 1 year subsequently fail) have not changed (or have increased) since the introduction of CNIs (13). Therefore, for recipients on CNIs whose grafts survive 1 year, there is no decrease in long-term graft survival (vs historical CNI-free protocols) —suggesting that *chronic progressive* CNI nephrotoxicity is not affecting the grafts.

Why then might CNIs result in improving early but not long-term graft survival? One possibility is that although CNIs decrease acute rejection rates (and increase early graft survival), they have no, or minimal, impact on other factors responsible for late graft dysfunction and late graft loss (e.g., noncompliance, recurrent disease, chronic antibody-mediated rejection).

### d) Progression of histologic lesions on protocol biopsy after kidney transplant

Major support for the concept of chronic CNI nephrotoxicity after kidney transplantation came from Nankivell et al. who reported on sequential biopsies in 120 simultaneous kidney-pancreas recipients immunosuppressed with cyclosporine (CSA), prednisone, and azathioprine (AZA) (14). Nankivell et al. described the progressive development of glomerulosclerosis, periglomeruli fibrosis, and totally sclerosed glomeruli. Of note, the 10-year death-censored graft survival for their patient population was 95%; mean serum creatinine level was 1.6 +/- 0.5 mg/dl. Therefore, although histologic abnormalities certainly developed, the long-term outcome was excellent. Importantly, there are numerous problems with Nankivell et al.'s interpretation of their data. First, this was not a randomized series; all recipients were on CNIs. The development of histologic lesions may have been due to CNIs but also could have been due to other common factors. Second, there were relatively few late observations; the median histologic follow-up was 3.9 +/- 3.3 years. Third, and perhaps most important, subclinical rejection remained a significant clinical problem in their series, occurring in 19.5% of biopsies done 2 to 5 years posttransplant, and 12.3% of biopsies done 6 to 10 years posttransplant. Thus, it is quite plausible that the development of progressive histologic lesions was due to ongoing subclinical rejection. Finally, two-thirds of the fibrosis that was present at 10 years had already appeared by 1 year; there was little progression beyond this point.

Perhaps the most powerful observation challenging Nankivell et al's interpretation comes from a subsequent paper by the same group in which they reported on sequential biopsies in a second cohort of recipients (15). This cohort was different in that mycophenolate mofetil (MMF) replaced AZA in the immunosuppressive protocol. The authors noted that the MMF-treated recipients had decreased acute rejection and decreased need for OKT3 treatment (vs. the earlier cohort). In addition, this was associated with “limited chronic interstitial fibrosis, striped fibrosis, and peri-glomeruli fibrosis ($p < 0.05$ to .001), mesangial matrix accumulation ($p < 0.01$), chronic glomerulopathy scores ($p < 0.05$), and glomerulosclerosis ($p < 0.05$).” Nankivell et al. reported that the “MMF-treated patients had reduced arterial hyalinosis, striped fibrosis, and tubular microcalcification.” Therefore, they reported a significant minimization of the lesions they associated with CNI nephrotoxicity by using MMF instead of AZA while maintaining CSA use (and decreasing their rates of rejection, and presumably of subclinical rejection).

In contrast to Nankivell et al., other clinical series have not shown CNI nephrotoxicity to be responsible for a significant proportion of late graft dysfunction. Humar et al. reported graft survival for CNI-immunosuppressed kidney recipients after excluding those with death with function, technical failure, primary nonfunction, and recurrent disease (16). The actuarial 10-year graft survival for those with no rejection was 91% (vs. 45% for those with ≥1 rejection) ($p=.001$). CNI toxicity was a rare cause of graft loss in either group. El-Zoghby et al. reported on 330 graft losses in 1,317 recipients (17). Of the 330, 138 (43.4%) were lost due to death with function, 39 (11.8%) were lost due to primary nonfunction, and 156 (46.3%) were lost due to other causes (18). The latter group was subdivided by cause: glomerular disease (37%), fibrosis and atrophy (31%), medical or surgical causes (16%), acute rejection (12%), and unclassifiable (5%). Of those with fibrosis and atrophy (representing 15% of the total population of graft loss), only 1 case was attributed to CNI nephrotoxicity. Others have shown no subsequent progressive deterioration of function when transplant biopsies showed only fibrosis and atrophy (and no inflammation). Only those grafts with evidence of active inflammation at the time of graft biopsy progressed to graft failure (18 -19).

### e) Concerns regarding development of renal dysfunction after extrarenal transplants

A major argument for the existence of chronic CNI nephrotoxicity has been the development of kidney dysfunction in extrarenal transplants. Myers et al. first reported that 12-month posttransplant eGFR was significantly lower in 17 CSA-immunosuppressed heart transplant recipients than in CNI-free historical controls (20). However, the CSA doses used by Myers et al were extraordinarily high—the dose at transplant was 17.5 mg per day and the trough levels ranged from 300 to 350 ng/dl for the first 4 months posttransplant and were still 164±18 ng/ml at 2 years posttransplant (21). Even with these trough levels, the renal function in the majority of patients remained stable.

More recently, Ojo et al. described the cumulative incidence of chronic renal failure among 69,000 patients receiving extrarenal organ transplant and reported to the OPTN database (22). Multivariate analysis showed the important risk factors for renal dysfunction to be increasing age, pretransplant hepatitis C, diabetes mellitus, postoperative acute renal failure, female gender, and hypertension. Use of a CNI was not significant. Also of note was that the rate of development of chronic renal failure was not related to organ-specific CNI target levels. For example, liver transplant recipients who are targeted for relatively low short- and long-term levels had a much higher rate of chronic renal failure over the first 10 years than did lung, heart, or heart-lung transplant recipients (who are targeted for higher CNI levels).

Recent single-center analyses have similarly noted that CNI use was not a risk factor for chronic renal dysfunction. In heart transplant recipients (n=352), Hamour et al. reported that risk factors for low eGFR were need for postoperative renal replacement therapy, pretransplant diabetes, increasing recipient age, and female recipient or donor gender (23). CNI use was not shown to have a long-term impact on renal function. Navarro-Manchon et al. reported that elevated pretransplant serum creatinine, CMV infection, and diabetes were risks for posttransplant renal dysfunction after heart transplantation; interestingly, use of an interleukin-2 receptor inhibitor and MMF (vs. AZA) were protective (24).

Liver failure, itself, is associated with renal dysfunction. Numerous series have shown glomerular lesions at autopsy (12% to 100%, with an overall rate of 45%) in patients with liver cirrhosis (25, 26). In 2 liver transplant studies, a kidney biopsy was done at the time of transplantation (26, 27). Both studies showed significant rates of histologic abnormalities. In Axelson et al.'s study (n=23), 8 had glomerular lesions, 2 IgA nephropathy, 1 angio capillary GN type 1, and 12 had minor glomerular abnormalities (26). In McGuire et al.'s study (n=30 with hepatitis C-induced cirrhosis), only 1 had no histologic abnormalities (27). Of the 30, 12 had MPGN type I, 7 had IgA nephropathy, 6 had angio glomerulonephritis, and 4 had minor glomerular abnormalities.

In other liver transplant studies, a kidney biopsy has been done at the time of new-onset late renal dysfunction. Phillebout et al. reported on 26 patients with posttransplant kidney biopsies done at a mean of 4.8 ± 0.7 years posttransplant; of these, 5 had renal failure pretransplant, 8 had pre-existing diabetes, and 9 had hypertension (28). The authors noted multiple significant histologic lesions including: severe arterial lesions in 65%, hydroxy starch nephropathy in 50%, thrombotic microangiopathy in 46%, diabetic lesions in 34%, and FSGS in 34%. Those with hepatitis C recurrence had worse glomerular lesions. More recently, Kim et al. reported on 80 kidney biopsies done at a mean time 5 years posttransplant; all biopsies showed glomerular lesions (29). Kim et al. concluded, “Our findings suggest that chronic kidney disease post orthotopic liver transplant may only rarely be ascribed to CNI toxicity and instead has a complex and varied pathologic basis.” Sanchez et al. followed long-term (15-year) renal function after liver transplantation (30). They showed that the lower the GFR is after transplant, the sooner renal failure develops. However, for most recipients, function was stable for the 15-year follow-up.

In CNI-treated pancreas recipients, long-term histologic follow-up of native kidneys showed that between 5 and 10 years posttransplant there was significant improvement in the histology (31).

The strongest data to support CNI nephrotoxicity is the data from CNI-treated patients with autoimmune diseases (32). However, even here there is controversy: a) some autoimmune disease are associated with kidney lesions; b) when used, CNIs are often associated with reduced renal function in a small percent of patients, and c) usually renal function returns to normal if CNIs are stopped or reduced (32-4).

## Data refuting chronic CNI nephrotoxicity

### a) CNI-free protocols have not shown an advantage

There is considerable data that refutes *chronic* CNI nephrotoxicity. First, in prospective randomized studies of CNI-containing vs. CNI-free protocols, there has been no long-term benefit for the CNI-free groups (5-11). A number of studies have randomized recipients on antibody, MMF, and prednisone to CNI vs. sirolimus. Larson et al. reported no difference between groups at 12 or at 24 months in patient survival, graft survival, acute rejection rates, measured GFR, and no difference in histology on protocol biopsies (5). Buchler et al. reported no difference in 12-month patient survival, graft survival, acute rejection rates, or eGFR (6). Similarly, Glotz et al. reported lower 12-month graft survival in the sirolimus group and no significant difference in GFR (7). In the Symphony study, Ekberg et al. randomized patients treated with MMF and prednisone to 4 arms: standard dose cyclosporine, or IL-2R induction with low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus (8). The worst results were seen in the CNI-free arm. More recently, 2 large trials randomized recipients on antibody, MMF, and prednisone to CNI vs. Belatacept (9, 10). The CNI-treated recipients had higher serum creatinine levels and lower GFR. However, in both groups, creatinine and GFR were stable over 2 years.

### b) Stable renal function in recipients on long-term CNIs

A second line of evidence refuting chronic CNI nephrotoxicity is that many recipients have done well on long-term CNIs. Kandaswamy et al. reported on 1,263 patients with graft survival ≥1 year and remaining on CNIs (3). In this group, mean serum creatinine level and calculated creatinine clearance were stable through 20 years. Thus, CNI nephrotoxicity, if real, certainly does not affect all grafts.

### c) Alternative explanations for chronic graft dysfunction

Perhaps most important is that there are alternative explanations for most late renal dysfunction. The concept of *chronic* CNI nephrotoxicity evolved in an era where our diagnostic armamentarium was not nearly as sophisticated as it is today. It was known that acute CNI nephrotoxicity existed. Therefore, it is not surprising that when CNI-treated transplant recipients developed late renal dysfunction, it was attributed to CNIs. However, even during that era, alternative explanations existed. Those for extrarenal transplant recipients are described above.

In kidney transplantation, it has been known since the early 1990s that recipients having ≥1 acute rejection episodes were at increased risk for late graft dysfunction and graft loss (35). Humar et al. showed that 10-year graft survival, in the absence of an acute rejection episode, was excellent (16); Nankivell et al. minimized “CNI nephrotoxicity” by using a more powerful (CNI-based) immunosuppressive regime and decreasing subclinical rejection (15). In the 1990s, Rush et al. documented the negative impact of untreated subclinical rejection on long-term graft outcome, and this has been confirmed by others (36). And, patients

having protocol biopsies or biopsies for dysfunction have had no subsequent decline in renal function if the biopsies showed no evidence of active inflammation (or recurrent disease) (18, 19). Of importance, since by Banff criteria inflammation in area of scarring was not scored, the degree of inflammation in most studies may have been underreported. Mannon et al. recently showed that inflammation and tubulitis in regions of fibrosis and atrophy were strongly correlated with each other ($p<0.0001$), and that inflammation solely in these areas was strongly associated with death-censored graft failure when compared to recipients whose biopsies had no inflammation (even after adjusting for the presence of interstitial fibrosis, tubular atrophy, serum creatinine at the time of biopsy, time to biopsy, and *i* score (37). Mengel et al. reported that scoring of total inflammation (i.e., in both scarred and non-scarred areas) was a better predictor of graft survival than the Banff i-score and all current diagnostic Banff categories (reviewed in 38). Thus, historically, immune-mediated damage may have been underappreciated, and the progressive graft dysfunction erroneously attributed to CNIs.

Recently, with the development of sensitive technology to measure development of donor-specific antibody and to diagnose antibody-mediated rejection (AbMR), there has been a revolution in our understanding of chronic graft dysfunction after kidney transplantation. Studies by Worthington et al. and Terasaki et al. have shown an association of circulating anti-HLA antibodies and chronic graft loss (39, 40) and Terasaki and Cai have suggested that donor specific anti-HLA antibody (DSA) is responsible for most cases of late graft loss (40). Kidney transplant recipients with capillaritis (seen in AbMR, and not scored in the original Banff classification) have worse long-term posttransplant outcome (41) as do recipients who are C4d positive (12, 42). A series of studies by the Edmonton group suggested that ABMR was the major cause of graft loss: 1) de novo DSA was associated with microcirculatory changes (in the biopsy) and subsequent graft failure; and 2) a significant subset of ABMB was C4d negative (reviewed in 38). Separately, and similar to the studies on subclinical cell-mediated rejection (36), Loupy et al. reported that subclinical AbMR (in 3-month protocol biopsies) was associated with increased IFTA and lower GFR at 1 year (43). As noted above, this and other types of chronic progressive graft functional deterioration may not have been affected by CNIs, and, in fact, erroneously attributed to CNIs. Hopefully, with better characterization of the many causes of chronic progressive kidney dysfunction, future studies will better delineate the role (or lack of) chronic CNI toxicity.

## Conclusion

It is possible that *chronic* progressive CNI nephrotoxicity exists, but it is not clear that it is a predominant cause of late kidney dysfunction after kidney or extrarenal transplantation. There is no doubt that there are other side effects associated with CNIs that justify development protocols that minimize or eliminate CNI use. But, before additional studies are done to minimize chronic “CNI nephrotoxicity,” it will be important to better characterize its prevalence. Otherwise, the importance of chronic “CNI nephrotoxicity” will continue to be overstated as a cause of late kidney dysfunction after transplantation.

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## References


1. Naesens M, Kuypers DRJ, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol. 2009; 4:481–508. [PubMed: 19218475]
2. Curtis, JJ. Cyclosporine-induced hypertension. In: Laragh, JH.; Brenner, BM., editors. Hypertension: Pathophysiology, Diagnosis, and Management. New York, NY: Raven Press; 1990. p. 1829-1835.
3. Kandaswamy R, Humar A, Casingal V, Gillingham KJ, Ibrahim H, Matas AJ. Stable kidney function in the second decade after kidney transplantation while on cyclosporine-based immunosuppression. Transplantation. 2007; 83(6):722–726. [PubMed: 17414704]
4. Gaston RS. Chronic calcineurin inhibitor nephrotoxicity: Reflections on an evolving paradigm. Clin J Am Soc Nephrol. 2009; 4:2029–2034. [PubMed: 19850771]
5. Larson TS, Dean PG, Stegall MD, Griffin MD, Textor SC, Schwab TR. Complete avoidance of calcineurin inhibitors in renal transplantaiton: a randomized trial comparing sirolimus and tacrolimus. Am J Transplant. 2006; 6:514–522. [PubMed: 16468960]
6. Büchler M, Caillard S, Barbier S, Thervet E, Toupance O, Mazouz H, et al. Sirolimus versus cyclosporine in kidney recipients receiving thymoglobulin®, mycophenolate mofetil and a 6-month course of steroids. Am J Transplant. 2007; 7:2522–2531. [PubMed: 17868057]
7. Glotz D, Charpentier B, Abramovicz D, Lang P, Rostaing L, Fifle G, et al. Thymoblobulin induction and sirolimus versus tacrolimus in kidney transplant recipients receiving mycophenolate mofetil and steroids. Transplantation. 2010; 89(12):1511–7. [PubMed: 20386144]
8. Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A, et al. ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007; 357:2562–2575. [PubMed: 18094377]
9. Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P. A phase III study of Belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT Study). Am J Transplant. 2010; 10:535–546. [PubMed: 20415897]
10. Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J. A phase III study of Belatacept versus cyclosporine in kidney transplants from extended donors (BENEFIT-EXT Study). Am J Transplant. 2010; 10:547–557. [PubMed: 20415898]
11. Ekberg H, Grinyo J, Nashan B, Vanrenterghem Y, Vincenti F, Voulgari A. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: The CAESAR study. Am J Transplant. 2007; 7:560–570. [PubMed: 17229079]
12. Gaston RS, Cecka JM, Kasiske BL, Fieberg AM, Leduc R, Cosio FC, et al. Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. Transplantation. 2010; 90:68–74. [PubMed: 20463643]
13. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant. 2004; 4:1289–1295. [PubMed: 15268730]
14. Nankivell BJ, Borrows RJ, Fung CL-S, O'Connell PJ, Allen RDM, Chapman J. The natural history of chronic allograft nephropathy. N Engl J Med. 2003; 349:24–33.
15. Nankivell BJ, Wavamunno MD, Borrows RJ, Vitalone M, Fung CL-S, Allen RDM, et al. Mycophenolate mofetil is associated with altered expression of chronic renal transplant histology. Am J Transplant. 2007; 7:366–376. [PubMed: 17283486]
16. Humar A, Hassoun A, Kandaswamy R, Payne W, Sutherland DER, Matas A. Immunologic factors: the major risk for decreased long-term renal allograft survival. Transplantation. 1999; 68(12): 1842–1846. [PubMed: 10628761]
17. El-Zoghby ZM, Stegall MD, Lager DJ, Kremers WK, Amer H, Gloor JM, et al. Identifying specific causes of kidney allograft loss. Am J Transplant. 2009; 9:527–535. [PubMed: 19191769]
18. Cosio FG, Grande JP, Wadei H, Larson TS, Griffin MD, Stegall MD. Predicting subsequent decline in kidney allograft function from early surveillance biopsies. Am J Transplant. 2005; 5(10):2464–72. [PubMed: 16162196]

19. Matas AJ, Leduc R, Rush D, Cecka JM, Connett J, Fieberg A, et al. Histopathologic clusters differentiate subgroups within the nonspecific diagnoses of CAN or CR: preliminary data from the DeKAF study. Am J Transplant. 2010; 10:315–323. [PubMed: 20041864]
20. Myers BD, Ross J, Newton L, Luetscher J, Perlroth M. Cyclosporine-associated chronic nephropathy. NEJM. 1984; 311(11):699–705. [PubMed: 6382005]
21. Myers BD, Sibley R, Newton L, Tomlanovich SJ, Boshkos C, Stinson E, et al. The long-term course of cyclosporine-associated chronic nephropathy. Kidney Int. 1988; 33:590–600. [PubMed: 3283402]
22. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. NEJM. 2003; 349:931–940. [PubMed: 12954741]
23. Hamour IM, Omar F, Lyster HS, Palmer A, Banner NR. Chronic kidney disease after heart transplantation. Nephrol Dial Transplant. 2009; 24:1655–1662. [PubMed: 19168463]
24. Navarro-Manchón J, Martinez-Dolz, Bonet LA, Sánchez-Lázaro I, Raso RR, Grima EZ, et al. Predictors of renal dysfunction at 1 year in heart transplant patients. Transplantation. 2010; 89(8): 977–982. [PubMed: 20405579]
25. Wagrowska-Danilewicz M, Danilewicz M, Sikorska B. glomerular and interstitial renal findings in patients with liver cirrhosis with normal renal function. The histomorphometric study. Gen Diagn Pathol. 1996; 141:353. [PubMed: 8780935]
26. Axelsen RA, Crawford DHG, Endre ZH, Lynch SV, Balderson GA, Strong RW, et al. Renal glomerular lesions in unselected patients with cirrhosis undergoing orthotopic liver transplantation. Pathology. 1995; 27:237–246. [PubMed: 8532390]
27. McGuire BM, Julian GA, Bynon JS, Cook WJ, King SJ, Curtis JJ, et al. Brief Communication: Glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. Ann Int Med. 2006; 144(10):735–741. [PubMed: 16702589]
28. Pillebout E, Nochy D, Hill G, Conti F, Antoine C, Calmus Y, et al. Renal histopathological lesions after orthotopic liver transplantation (OLT). Am J Transplant. 2005; 5:1120–1129. [PubMed: 15816895]
29. Kim JY, Akalin E, Dikman S, Gagliardi R, Schiano T, Bromberg J, et al. The variable pathology of kidney disease after liver transplantation. Transplantation. 2010; 89(2):215–221. [PubMed: 20098285]
30. Sanchez EQ, Melton LB, Chinnakotla S, Randall HB, McKenna GJ, Ruiz R, et al. Tranpslantation. 2010; 89(2):232–235.
31. Fioretto P, Steffes MW, Sutherland DER, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med. 1998; 339:115–7. [PubMed: 9654544]
32. Bagnis CI, DuMontcel ST, Beaufils H, Jouanneau C, Jaudon MC, Maksud P, et al. Long-term renal effects of low-dose cyclosporine in uveitis-treated patients: follow-up study. J Am Soc Nephrol. 2002; 13:2962–2968. [PubMed: 12444215]
33. Tappeiner C, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. Eye. 2009; 23:1192–1198. [PubMed: 18551142]
34. Ponticelli C. Cyclosporine: from renal transplantation to autoimmune diseases. Ann NY Acad Sci. 2005; 1051:551–558. [PubMed: 16126995]
35. Almond PS, Matas A, Gillingham K, Dunn DL, Payne WD, Gores P, et al. Risk factors for chronic rejection in renal allograft recipients. Transplantation. 1993; 55(4):752–6. [PubMed: 8475548]
36. Rush D, Nickerson P, Gough J, McKenna R, Grimm P, Cheang M, Trpkov K, Solez K, Jeffery J. Beneficial effects of treatment of early subclinical rejection: a randomized study. J Am Soc Nephrol. 1998; 9(11):2129–34. [PubMed: 9808101]
37. Mannon RB, Matas AJ, Grande J, Leduc R, Connett J, Kasiske B, et al. for the DeKAF Investigators. Inflammation in areas of tubular atrophy in kidney allograft biopsies: a potent predictor of allograft failure. Am J Transplant. In Press.
38. Halloran PF, de Freitas DG, Einecke G, Famulski KS, Hidalgo LG, Mengel M, et al. An integrated view of molecular changes, histopathology, and outcomes in kidney transplants. Amer J Transplant. In Press.

39. Worthington JE, McEwen A, McWilliam LJ, Picton ML, Martin S. Association between C4d staining in renal transplant biopsies, production of donor-specific HLA antibodies, and graft outcome. Transplantation. 2007; 83:398–403. [PubMed: 17318071]

40. Terasaki PI, Cai J. Human leukocyte antigen antibodies and chronic rejection: from association to causation. Transplantation. 2008; 86:377–383. [PubMed: 18698239]

41. Gibson IW, Gwinner W, Brőcker, Sis B, Riopel J, Roberts ISD, et al. Peritubular capillaritis in renal allografts: prevalence, scoring system, reproducibility and clinicopathological correlates. Am J Transplant. 2008; 8:819–825. [PubMed: 18261174]

42. Feucht HE, Schneeberger H, Hillebrand G, Burkhardt K, Weiss M, Riethmüller G, et al. Capillary deposition of C4d complement fragment and early renal graft loss. Kidney Int. 1993; 43(6):1333–8. [PubMed: 8315947]

43. Loupy A, Suberbielle-Boissel C, Hill GS, Lefaucheur C, Anglicheau D, Zuber J, et al. Outcome of subclinical antibody-mediated rejection in kidney transplant recipients with preformed donor-specific antibodies. Am J Transplant. 2009; 9(11):2561–70. [PubMed: 19775320]

## Abbreviations

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| **CNI** | calcineurin inhibitor |
| **eGFR** | estimated glomerular filtration rate |
| **DSA** | donor-specific antibody |
| **CSA** | cyclosporine |
| **AZA** | azathioprine |
| **OKT3** | Muromonab-CD3 (trade name Orthoclone OKT3) |
| **CMV** | cytomegalovirus |
| **MMF** | mycophenolate mofetil |
| **MPGN** | membranoproliferative glomerulonephritis |
| **FSGS** | focal segmental glomerulosclerosis |
| **IL-2R** | interleukin-2 receptor |
| **ABMR** | antibody-mediated rejection |