1. Adenovirus-associated hemorrhagic cystitisin a pediatric renal transplant recipient
Pediatr Transplantation 2007; 11: 568-571.
Keswani M., Moudgil A.

ABSTRACT

Adenovirus infection has been associated with the development of hemorrhagic cystitis in bone marrow transplant recipients. However, limited information exists regarding adenovirus-associated hemorrhagic cystitis in solid organ transplantation, especially in renal transplant recipients. In most cases, the disease is self-limited. However, some patients may have a protracted course. Although no particular antiviral agent has been identified as the gold standard of therapy, cidofovir has been found to be effective in a number of bone marrow transplant recipients. In this study, we report a five-yr-old boy who presented with adenovirus-associated hemorrhagic cystitis 68 days after renal transplant and was successfully treated with reduction of immunosuppression and an intermediate dose of intravenous cidofovir.

2. An aggressive systematic strategy for acute respiratory distress syndrome caused by severe pneumonia after renal transplantation

Transplant International 2006;19(2):110-6.

Sun Q., Liu Z.H., Chen J., Ji S., Tang Z., Cheng Z., Ji D., Li L.S.

ABSTRACT

Acute respiratory distress syndrome (ARDS) caused by pneumonia after renal transplantation was usually associated with overimmunosuppression and high mortality rate. We evaluated the efficacy of an aggressive systemic protocol including strategies improving body's immune function. Twenty-one recipients were enrolled in this study. Patients were subjected to a protocol including (i) withdrawal of most immunosuppressants, (ii) early use of immunoenhancers and continuous renal replacement therapy (CRRT), (iii) reasonable administration of antibiotic regimen, (iv) prompt mechanical ventilating strategy, and (v) adequate nutrition. Immunosuppressants were adjusted according to the value of CD4+, CD8+T lymphocytes in peripheral blood. CRRT was conducted at once when patients were admitted to the intensive care unit (ICU), regardless the graft function. Thirteen (62%) survived and eight died finally. This is a high survival rate for this kind of patients. Eighteen patients had received thymosin treatment. All patients who survived experienced renal allograft dysfunction during CRRT, but when CRRT stopped, the function of all grafts gradually recovered. No acute rejection episodes were documented during the treatment. The aggressive systemic protocol including strategies improving the body's immune function and CRRT can improve the outcome of patients with ARDS after renal transplantation. The count of CD4+, CD8+T lymphocytes of peripheral blood is useful in the adjustment of immunosuppressants and the prediction of patient outcome.

3. Balancing efficacy and toxicity of kidney transplant immunosuppression.
Transplant Proc. 2009;41(8):3393-5.
Naesens M., Lerut E., Sarwal M., Van Damme B., Vanrenterghem Y., Kuypers D.R.

ABSTRACT
Late renal allograft loss is mainly the result of progressive histological damage. Both underimmunosuppression (rejection phenomena) and overimmunosuppression (calcineurin inhibitor nephrotoxicity) contribute to the progression of chronic histological damage. The current study was performed to elucidate the complementary impact of immune and nonimmune phenomena on renal allograft histology and function. By performing protocol biopsies, it was demonstrated that clinical and subclinical acute cellular rejection phenomena continue to play important roles, despite the use of the powerful combination of tacrolimus, mycophenolate mofetil, and steroids. Next to immune phenomena, the importance of nonimmune factors in renal allograft histological evolution was shown in protocol biopsy studies. Both in adult and in pediatric renal allograft recipients, the characteristics of the donor kidney (donor age, size discrepancy) appeared to be major determinants of the histological and functional evolution. This impact of donor characteristics was not only important in the immediate peritransplantation period, it was also shown that higher donor age increased the risk for progressive posttransplant histological injury and calcineurin inhibitor nephrotoxicity. Systemic levels of tacrolimus, if kept within a relatively narrow target window, were not associated with a risk for calcineurin inhibitor nephrotoxicity. However, we observed a significant association between renal allograft histology and P-glycoprotein (ABCB1) gene polymorphisms and expression, suggesting a role of this protein in the individual susceptibility to calcineurin inhibitor nephrotoxicity. Finally, the interplay between immune and nonimmune phenomena was demonstrated by the association between donor origin (deceased versus living) and local renal complement gene expression, by using whole-genome expression microarrays.

4. Biochemical monitoring of mTOR inhibitor-based immunosuppression following kidney transplantation: a novel approach for tailored immunosuppressive therapy.

Kidney Int. 2005;68(6):2593-8.

Hartmann B., Schmid G., Graeb C., Bruns C.J., Fischereder M., Jauch K.W., Heeschen C., Guba M.

ABSTRACT

Background: Immunosuppressive therapy with the mammalian target of rapamycin (mTOR) inhibitors requires a fine balance between allograft maintenance and drug-related side effects.
Methods: In this study we examined the feasibility of monitoring TOR inhibitor-based immunosuppression by assessment of the phosphorylation status at the Thr(389) site of the p70S6 kinase in peripheral blood mononuclear cells (PBMCs). At total of 36 patients with renal transplants and 8 healthy controls were enrolled.
Results: We found that sirolimus treatment was associated with a pronounced inhibition of p70S6 kinase phosphorylation, as compared to healthy donors or otherwise immunosuppressed patients. In sirolimus-treated patients, phosphorylation of the p70S6 kinase was significantly inhibited when sirolimus trough levels were > 6 ng/mL. In contrast, for trough levels <6 ng/mL, the degree of inhibition of p70S6 kinase phosphorylation showed a high degree of interindividual variability. We recorded a total of five clinical relevant rejection episodes in this patient category. Intriguingly, rejecters uniformly maintained a high degree of phosphorylation independent of the sirolimus trough level whereas non-rejecters showed a significant inhibition of phosphorylation.
Conclusion: Therefore, the phosphorylation status of the p70S6 kinase appears to provide more relevant information on the desired effect of sirolimus in target cells as compared to trough level measurements. Moreover, this assay provides an opportunity to safely titer down sirolimus levels to avoid overimmunosuppression and, on the other hand, to identify patients with insufficient TOR inhibitor therapy that are at risk for rejection.

5. BK Polyomavirus Subtype III in a Pediatric Renal Transplant Patient with Nephropathy.
J Clin Microbiol. 2013; 51(12): 4255–4258.
Kapusinszky B., Chen S.F., Sahoo M.K., Lefterova M.I., Kjelson L., Grimm P.C., Kambham N., Concepcion W., Pinsky B.A.

ABSTRACT
BK polyomavirus (BKV) is an emerging pathogen in immunocompromised individuals. BKV subtype III is rarely identified and has not previously been associated with disease. Here we provide the whole-genome sequence of a subtype III BKV from a pediatric kidney transplant patient with polyomavirus-associated nephropathy.

6. BK virus infection: an update on diagnosis and treatment.
Nephrol Dial Transplant. 2015;30(2):209-17
Sawinski D, Goral S.

ABSTRACT
BK virus, first isolated in 1971, is a significant risk factor for renal transplant dysfunction and allograft loss. Unfortunately, treatment options for BK virus infection are limited, and there is no effective prophylaxis. Although overimmunosuppression remains the primary risk factor for BK infection after transplantation, male gender, older recipient age, prior rejection episodes, degree of human leukocyte antigen mismatching, prolonged cold ischemia time, BK serostatus and ureteral stent placement have all been implicated as risk factors. Routine screening for BK has been shown to be effective in preventing allograft loss in patients with BK viruria or viremia. Reduction of immunosuppression remains the mainstay of BK nephropathy treatment and is the best studied intervention. Laboratory-based methods such as ELISPOT assays have provided new insights into the immune response to BK and may help guide therapy in the future. In this review, we will discuss the epidemiology of BK virus infection, screening strategies, treatment options and future research directions.

7. BK virus nephropathy complicated with meningoencephalitis after kidney transplantation.
Pediatr Transplant. 2014;18(2):E48-51.
Rocha A., Faria S., Costa T., Marques L., Freitas C., Mota C.

ABSTRACT
BK disease is an opportunistic infection in organ transplant recipients and patients with other cellular immunodeficiencies. To the best of our knowledge, we report the second case of BK meningoencephalitis associated with nephropathy in a kidney transplant recipient. A 15-yr-old boy underwent a cadaveric kidney transplant without complications; however, 11 wk after the transplantation, he was admitted to the hospital for graft dysfunction and cytopenia, which were confirmed by BK nephropathy (plasma viral replication and histological evidence). Four days after his hospital admission, he developed a high-grade fever and headache. CSF analysis revealed pleocytosis with a positive PCR for BK virus. Reduction in immunosuppression and supportive care conducting cycles of immunoglobulin and cidofovir were successful in treating the patient. BK meningoencephalitis should be considered in kidney transplant recipients who present with signs and symptoms of meningoencephalitis.

8. Calcineurin Inhibitors Associated Posterior Reversible Encephalopathy Syndrome in Solid Organ Transplantation: Report of 2 Cases and Literature Review.

Medicine (Baltimore). 2016;95(14):e3173

Song T., Rao Z., Tan Q., Qiu Y., Liu J., Huang Z., Wang X., Lin T.

ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is a rare neurologic side effect of calcineurin inhibitors (CNIs) with poorly understood clinical features.We report cases of 2 patients with PRES developing after kidney transplantation and summarize PRES clinical features through a literature review.The 1st case was a 28-year-old man who received a kidney transplant from a deceased donor. Initial immunosuppressive therapy consisted of tacrolimus/mycophenolate mofetil/prednisolone. He developed headache and blurred vision with visual field loss15 days after transplantation and generalized seizures 4 days later. The 2nd case was a 34-year-old man who received a living kidney transplant. His initial immunosuppressive therapy comprised tacrolimus/mycophenolate mofetil/prednisolone. Two months after transplantation, he developed seizures. Both patients were diagnosed with PRES based on neurological symptoms and magnetic resonance imaging (MRI) findings; they recovered after switching from tacrolimus to either a cyclosporine or a lower tacrolimus dose. CNI-associated PRES is an acute neurological syndrome with seizures, encephalopathy, visual abnormalities, headache, focal neurological deficits, and nausea/vomiting. It is always accompanied by hypertension. A fluid-attenuated inversion recovery signal MRI scan typically shows reversible subcortical white matter changes in the posterior cerebral hemisphere that usually occur within the 1st month after transplantation. CNI-associated PRES has a generally favorable prognosis with early diagnosis and prompt treatment including alternating or discontinuing CNIs and blood pressure control.CNI-associated PRES should be considered in patients exhibiting acute neurological symptoms after transplantation. Early diagnosis and immediate treatment are critical for a favorable prognosis.

9. Calcineurin-inhibitor-free immunosuppression based on the JAK inhibitor CP-690,550: a pilot study in de novo kidney allograft recipients.

Am J Transplant. 2009;9(8):1936-45.

Busque S., Leventhal J., Brennan DC., Steinberg S., Klintmalm G., Shah T., Mulgaonkar S., Bromberg J.S., Vincenti F., Hariharan S., Slakey D., Peddi V.R., Fisher R.A., Lawendy N., Wang C., Chan G.

ABSTRACT

This randomized, pilot study compared the Janus kinase inhibitor CP-690,550 (15mg BID [CP15] and 30mg BID [CP30], n = 20 each) with tacrolimus (n = 21) in de novo kidney allograft recipients. Patients received an IL-2 receptor antagonist, concomitant mycophenolate mofetil (MMF) and corticosteroids. CP-690,550 doses were reduced after 6 months. Due to a high incidence of BK virus nephropathy (BKN) in CP30, MMF was discontinued in this group. The 6-month biopsy-proven acute rejection rates were 1 of 20, 4 of 20 and 1 of 21 for CP15, CP30 and tacrolimus groups, respectively. BKN developed in 4 of 20 patients in CP30 group. The 6-month rates of cytomegalovirus disease were 2 of 20, 4 of 20 and none of 21 for CP15, CP30 and tacrolimus groups, respectively. Estimated glomerular filtration rate was >70 mL/min at 6 and 12 months (all groups). NK cells were reduced by ≤77% in CP-690,550-treated patients. In the CP-690,550 arms, there were modest lipid elevations and a trend toward more frequent anemia and neutropenia during the first 6 months. These data suggest that coadministration of CP-690,550 30 mg BID with MMF is associated with overimmunosuppression. At 15 mg BID, the efficacy/ safety profile was comparable to the tacrolimus control group, excepting a higher rate of viral infection.
Further dose-ranging evaluation of CP-690,550 is warranted.

10. Clearance of BK Virus Nephropathy by Combination Antiviral Therapy With Intravenous Immunoglobulin.

Transplant Direct. 2017; 3(4): e142.

Kable K., Davies C.D, O'connell P.J, Chapman J.R., and Nankivell B.J.

ABSTRACT

Background: Reactivation of BK polyoma virus causes a destructive virus allograft nephropathy (BKVAN) with graft loss in 46%. Treatment options are limited to reduced immunosuppression and largely ineffective antiviral agents. Some studies suggest benefit from intravenous immunoglobulin (IVIG).

Methods: We evaluated effectiveness of adjuvant IVIG to eliminate virus from blood and tissue, in a retrospective, single-center cohort study, against standard-of-care controls. Both groups underwent reduced immunosuppression; conversion of tacrolimus to cyclosporine; and mycophenolate to leflunomide, oral ciprofloxacin, and intravenous cidofovir.

Results: Biopsy-proven BKVAN occurred in 50 kidneys at 7 (median interquartile range, 3-12) months after transplantation, predominantly as histological stage B (92%), diagnosed following by dysfunction in 46%, screening viremia in 20%, and protocol biopsy in 34%. After treatment, mean viral loads fell from 1581 ± 4220 × 103 copies at diagnosis to 1434 ± 70 639 midtreatment, and 0.138 ± 0.331 after 3 months ($P < 0.001$). IVIG at 1.01 ± 0.18 g/kg was given to 22 (44%) patients. The IVIG group more effectively cleared viremia (hazard ratio, 3.68; 95% confidence interval, 1.56-8.68; $P = 0.003$) and BK immunohistochemistry from repeated tissue sampling (hazard ratio, 2.24; 95% confidence interval, 1.09-4.58; $P = 0.028$), and resulted in faster (11.3 ± 10.4 months vs 29.1 ± 31.8 months, $P = 0.015$) and more complete resolution of viremia (33.3% vs 77.3%, $P = 0.044$). Numerically, fewer graft losses occurred with IVIG (27.3% vs 53.6% for control, $P = 0.06$), although graft and patient survivals were not statistically different. Acute renal dysfunction requiring pulse corticosteroid was common (59.1% vs 78.6%, $P = 0.09$), respectively, after immunosuppression reduction.

Conclusions: Combination treatment incorporating adjuvant IVIG was more effective eliminating virus from BKVAN, compared with conventional therapy. Validation by multicenter randomized trial is needed.

11. Direct and Indirect Effects of Cytomegalovirus-Induced γδ T Cells after Kidney Transplantation

Front Immunol. 2015;6:3

Couzi L., Pitard V., Moreau J.F., Merville P., and Déchanet-Merville J.

ABSTRACT

Despite effective anti-viral therapies, cytomegalovirus (CMV) is still associated with direct (CMV disease) and indirect effects (rejection and poor graft survival) in kidney transplant recipients. Recently, an unconventional T cell population (collectively designated as Vδ2neg γδ T cells) has been characterized during the anti-CMV immune response in all solid-organ and bone-marrow transplant recipients, neonates, and healthy people. These CMV-induced Vδ2neg γδ T cells undergo a dramatic and stable expansion after CMV infection, in a conventional "adaptive" manner. Similarly, as CMV-specific CD8+ αβ T cells, they exhibit an effector/memory TEMRA phenotype and cytotoxic effector functions. Activation of Vδ2neg γδ T cells by CMV-infected cells involves the γδ T cell receptor (TCR) and still ill-defined co-stimulatory molecules such as LFA-1. A multiple of Vδ2neg γδ TCR ligands are apparently recognized on CMV-infected cells, the first one identified being the major histocompatibility complex-related molecule endothelial protein C receptor. A singularity of CMV-induced Vδ2neg γδ T cells is to acquire CD16 expression and to exert an antibody-dependent cell-mediated inhibition on CMV replication, which is controlled by a specific cytokine microenvironment. Beyond the well-demonstrated direct anti-CMV effect of Vδ2neg γδ T cells, unexpected indirect effects of these cells have been also observed in the context of kidney transplantation. CMV-induced Vδ2neg γδ T cells have been involved in surveillance of malignancy subsequent to long-term immunosuppression. Moreover, CMV-induced CD16+ γδ T cells are cell effectors of antibody-mediated rejection of kidney transplants, and represent a new physiopathological contribution to the well-known association between CMV infection and poor graft survival. All these basic and clinical studies paved the road to the development of a future γδ T cell-based immunotherapy. In the meantime, γδ T cell monitoring should prove a valuable immunological biomarker in the management of CMV infection.

Keywords: antibody-mediated rejection, cancer, cytomegalovirus, gamma-delta T cells, lymphocytes, renal transplantation

12. Preformed frequencies of cytomegalovirus (CMV)-specific memory T and B cells identify protected CMV-sensitized individuals among seronegative kidney transplant recipients.

Clin Infect Dis. 2014;59(11):1537-45

Lúcia M., Crespo E., Melilli E., Cruzado J.M., Luque S., Llaudó I., Niubó J., Torras J., Fernandez N., Grinyó J.M., Bestard O.

ABSTRACT

Background: Cytomegalovirus (CMV) infection remains a major complication after kidney transplantation. Baseline CMV risk is typically determined by the serological presence of preformed CMV-specific immunoglobulin (Ig) G antibodies, even though T-cell responses to major viral antigens are crucial when controlling viral replication. Some IgG-seronegative patients who receive an IgG-seropositive allograft do not develop CMV infection despite not receiving prophylaxis. We hypothesized that a more precise evaluation of pretransplant CMV-specific immune-sensitization using the B and T-cell enzyme-linked immunospot assays may identify CMV-sensitized individuals more accurately, regardless of serological evidence of CMV-specific IgG titers.

Methods: We compared the presence of preformed CMV-specific memory B and T cells in kidney transplant recipients between 43 CMV IgG-seronegative (sR(-)) and 86 CMV IgG-seropositive (sR(+)) patients. Clinical outcome was evaluated in both groups.

Results: All sR(+) patients showed a wide range of CMV-specific memory T- and B-cell responses. High memory T- and B-cell frequencies were also clearly detected in 30% of sR(-) patients, and those with high CMV-specific T-cell frequencies had a significantly lower incidence of late CMV infection after prophylactic therapy. Receiver operating characteristic curve analysis for predicting CMV viremia and disease showed a high area under the receiver operating characteristic curve (>0.8), which translated into a high sensitivity and negative predictive value of the test.

Conclusions: Assessment of CMV-specific memory T- and B-cell responses before kidney transplantation among sR(-) recipients may help identify immunized individuals more precisely, being ultimately at lower risk for CMV infection.

13. Excessive immunosuppression in kidney transplant patients: prevalence and outcomes.
Transplant Proc. 2012;44(8):2381-3.
Sanders-Pinheiro H., da Silveira S.T., Carminatti M., Braga L.S., Marsicano E.O., Magalhães G.L., Carvalho L.F., Filho G.F., Magacho E.J., Colugnati F., Bastos M.G.

ABSTRACT
Background: Death with a functioning graft is currently one of the main causes of kidney graft loss. A large proportion of cases is attributed to infectious complications that can be related to overimmunosuppression. We retrospectively studied 80 kidney transplant patients, grafted from January 2005 to December 2009, to assess the prevalence of excessive immunosuppression, and its possible correlation with infections and infection-related death.
Methods: Excessive immunosuppression was defined by a prescribed dosage above the expected to the time point or an elevated drug blood level according to the Kidney Disease: Improving Global Outcomes (2009) recommendations at 1, 3, 6, and 12 months, and then annually.
Results: Death with a functioning graft accounted for 76.5% of losses. Overall, 53.8% of deaths were from infections, and 38.5% from cardiovascular causes. Acute rejection episodes were noted in 8.8% of patients. Only 10% of patients had adequate immunosuppression throughout the follow-up. Seventy-two percent of patients showed adequate immunosuppression at least half of the 18 evaluated points, although 50% showed between 1 and 3 drugs administered above recommended dosages during the whole period. Infections were recorded in 78.8% patients, with a median of 3 episodes per patient. Any level of excessive immunosuppression was associated with infections (odds ratio, 11.2; $P < .001$), but not with death caused thereby.
Conclusion: Excessive immunosuppression among this cohort was associated with a greater incidence of infections, but not with death from this cause.

14. Fever of Unknown Origin (FUO) in a pediatric kidney transplant recipient: Questions and Answers.

Pediatr Nephrol. 2015;30(12):2109-13.

Nadeem S., Sukumaran L., Siegel D.A., Jernigan S.M., Greenbaum L.A.

Abstract not available

15. High incidence of malignancy in polyomavirus-associated nephropathy in renal transplant recipients.

Transplant Proc. 2010;42(3):817-8

Chen C.H., Wen M.C., Wang M., Lian J.D., Cheng C.H., Wu M.J., Yu T.M., Chuang Y.W., Chang D., Shu K.H.

ABSTRACT

Human polyomaviruses (PV), including JC and BK virus, have been reported to cause polyomavirus-associated nephropathy (PVAN), in renal transplant patients. PV infection has been demonstrated to be associated with malignancies in animals; however, the association between malignancy and viral infections in humans is not clear. We retrospectively reviewed our 864 (M:F=502:362) kidney transplant patients over the past 25 years. We identified PVAN in 6 patients (0.69%), including BK nephropathy (n=5) and JC nephropathy (n=1). Three patients (50%) improved after reducing the immunosuppression, but 3 (50%) progressed to graft loss despite this reduction. Malignancy occurred in 5 out of the 6 patients (83%; P<.0001 compared with patients without PVAN), including transitional cell carcinoma (n=2), renal cell carcinoma (n=1), squamous cell carcinoma of skin (n=1) and Kaposi sarcoma (n=1). We concluded that kidney transplant patients with PVAN are at a significantly greater risk to develop malignancy. Whether this is due to a direct effect of PV infection or the result of overimmunosuppression remains to be determined in a future study.

16. Hydronephrosis in pediatric kidney transplant: clinical relevance to graft outcome.

J Pediatr Urol. 2013;9(2):217-22.

Chu L., Jacobs B.L., Schwen Z., Schneck F.X.

ABSTRACT

Objective: To evaluate our pediatric renal transplant patient population at the Children's Hospital of Pittsburgh to better understand the clinical significance of hydronephrosis.

Materials and methods: We retrospectively reviewed records of patients who had received a renal transplant in 1998-2008. Exclusion criteria included multi-organ transplants and allograft failure within 3-months. We determined the incidence of hydronephrosis and compared serum creatinine, incidence of pyelonephritis, rejection and vesicoureteral reflux between the hydronephrotic and non-hydronephrotic cohorts. Data were analyzed using descriptive statistics, Student's t-test and Pearson Chi-Square test.

Results: 51 patients (35 male, 68.6%) were identified. The mean age at time of transplant was 8.7 ± 5.9 years and the mean follow-up period was 45.2 ± 45.4 months. Common causes of renal failure included posterior urethral valves, renal dysplasia, reflux and prune belly syndrome. Twenty-five (49%) patients developed hydronephrosis. This was associated with worsening renal function ($p = 0.008$). Hydronephrosis was also associated with pyelonephritis ($p = 0.03$) and male gender ($p = 0.004$). Age at transplant may be a predictor of pyelonephritis: median age of 10 patients with pyelonephritis was 4.6 years (range 0.6-19.9 years). Hydronephrotic cohort had increased rate of reflux and rejection; as not all patients underwent voiding cystourethrogram and/or allograft biopsy, this result was not significant.

Conclusions: Pediatric renal graft hydronephrosis was correlated with worsening renal function and increased incidence of pyelonephritis. More aggressive preoperative and postoperative urological testing and management should help preserve renal function.

17. Immunologic basis of graft rejection and tolerance following transplantation of liver or other solid organs.

Gastroenterology. 2011;140(1):51-64.

Sánchez-Fueyo A., Strom T.B.

ABSTRACT

Transplantation of organs between genetically different individuals of the same species causes a T cell-mediated immune response that, if left unchecked, results in rejection and graft destruction. The potency of the alloimmune response is determined by the antigenic disparity that usually exists between donors and recipients and by intragraft expression of proinflammatory cytokines in the early period after transplantation. Studies in animal models have identified many molecules that, when targeted, inhibit T-cell activation. In addition, some of these studies have shown that certain immunologic interventions induce transplantation tolerance, a state in which the allograft is specifically accepted without the need for chronic immunosuppression. Tolerance is an important aspect of liver transplantation, because livers have a unique microenvironment that promotes tolerance rather than immunity. In contrast to the progress achieved in inducing tolerance in animal models, patients who receive transplanted organs still require nonspecific immunosuppressant drugs. The development of calcineurin inhibitors has reduced the acute rejection rate and improved short-term, but not long-term, graft survival. However, long-term use of immunosuppressive drugs leads to nephrotoxicity and metabolic disorders, as well as manifestations of overimmunosuppression such as opportunistic infections and cancers. The status of pharmacologic immunosuppression in the clinic is therefore not ideal. We review recently developed therapeutic strategies to promote tolerance to transplanted livers and other organs and diagnostic tools that might be used to identify patients most likely to accept or reject allografts.

18. Immunological monitoring of calcineurin inhibitors for predicting cytomegalovirus infection in kidney transplant recipients.

Transplantation. 2008;86(8):1060-7.

Couzi L., Thiébaut R., Carron J.C., Moreau J.F., Merville P., Taupin J.L.

ABSTRACT

Background: The short-term results of kidney transplantation are mainly attributed to the use of calcineurin inhibitors (CNI). However, opportunistic infections and cytomegalovirus (CMV) infections remain frequent and occur in the case of overimmunosuppression. Measurement of the biological effects of CNI could provide clues to identify overimmunosuppressed kidney transplant recipients (KTR) who would subsequently develop CMV infection.

Methods: Forty-one KTR given cyclosporine (n=18) or tacrolimus (n=23) were followed up every week during 1 month, then every month during 11 months, by measuring the patient's whole blood ability to inhibit interleukin-2 (IL-2) gene transcription and by measuring the patient's intracellular T-cell IL-2, interferon-gamma (IFN-gamma), and tumor necrosis factor-alpha (TNF-alpha) production in response to polyclonal activation.

Results: Cytomegalovirus infection or disease occurred in 19 patients and was significantly associated with CMV serological status D+R- and D+R+ (HR=19.6 and 6.6, respectively, P=0.0001). Immunosuppressive treatment was associated with a long-lasting decrease of all cytokines produced by the patient's T-cells. However, none of these assays taken separately at any of the time points of the follow-up allowed to predict the occurrence of a subsequent CMV infection. We only observed a weak association between cumulative low levels of the percentage of TNF-alpha producing CD8+ T cells before CMV infection and its occurrence just afterwards (HR=1.39 for 1000 unit lower, P=0.04). However, this association did not remain significant after adjustment for CMV serological status.

Conclusions: This study suggests that immunological monitoring is not better than CNI whole blood levels for diagnosis of overimmunosuppression-induced CMV infection in KTR.

19. Immunosuppression reduction for BK virus nephropathy: a case for caution.
Transpl Infect Dis. 2007;9(3):244-8.
Womer K.L., Guerra G., Dibadj K., Huang Y., Kazory A., Kaplan B., Srinivas T.R.

ABSTRACT
BK virus nephropathy (BKVN) is increasingly recognized as a major cause of renal allograft failure. Recent reports demonstrate that prompt reduction of immunosuppression upon detection of persistent viremia can be associated with resolution of viremia, with minimal risk of acute rejection (AR). However, these experiences in general have occurred in centers with low baseline risks of AR. It is possible that a finer balance between overimmunosuppression and the risk of AR may exist in centers that routinely transplant patients with higher risk of AR. Thus the risk/benefit of this strategy may be altered in these centers. We report a case of antibody-mediated rejection that followed reduction of immunosuppression for BKVN diagnosed more than 3 months after the onset of viremia. This rejection episode resulted in a greater decrease in graft function than the initial BKVN episode. Issues relevant to the management of these patients are discussed, including the need for improved immune monitoring assays to determine more accurately the balance between infection and rejection.

20. Immunosuppressive minimization with mTOR inhibitors and belatacept.

Transpl Int. 2015;28(8):921-7

Diekmann F.

ABSTRACT

BK virus nephropathy (BKVN) is increasingly recognized as a major cause of renal allograft failure. Recent reports demonstrate that prompt reduction of immunosuppression upon detection of persistent viremia can be associated with resolution of viremia, with minimal risk of acute rejection (AR). However, these experiences in general have occurred in centers with low baseline risks of AR. It is possible that a finer balance between over immunosuppression and the risk of AR may exist in centers that routinely transplant patients with higher risk of AR. Thus the risk/benefit of this strategy may be altered in these centers. We report a case of antibody-mediated rejection that followed reduction of immunosuppression for BKVN diagnosed more than 3 months after the onset of viremia. This rejection episode resulted in a greater decrease in graft function than the initial BKVN episode. Issues relevant to the management of these patients are discussed, including the need for improved immune monitoring assays to determine more accurately the balance between infection and rejection.

21. Impact of prophylactic versus preemptive valganciclovir on long-term renal allograft outcomes.

Transplantation. 2010;90(4):412-8.

Spinner M.L, Saab G., Casabar E., Bowman L.J., Storch G.A., Brennan D.C.

ABSTRACT

Background: Both prophylactic and preemptive oral valganciclovir therapy are effective for the management of cytomegalovirus (CMV) postrenal transplantation in the short term. The long-term effect of either strategy is less well defined.

Methods: We analyzed the data on 115 adult recipients previously enrolled in a prospective randomized controlled trial of prophylaxis versus preemptive therapy for CMV. The primary outcome was a composite of freedom from acute rejection, graft loss, or death. Secondary outcomes included individual primary outcomes, posttransplant cardiovascular events, new-onset diabetes mellitus after transplantation, achievement of goal blood pressure, change in body mass index, interstitial fibrosis/tubular atrophy, and change in renal function. The analysis period was a minimum of 48-month posttransplant or a date of death or graft loss, whichever was earlier.

Results: The primary outcome was similar between groups (83% prophylactic vs. 81% preemptive, P=0.754). The secondary outcomes showed similarities between the prophylactic and preemptive groups. Four patients in the prophylactic group (8%) compared with none in the preemptive group (0%) died with a functioning graft, P=0.043.

Conclusions: Within the limitations of sample size, our data suggest that either strategy for the management of CMV immediately after transplantation seems effective for patient and graft survival in the long term. CMV management is one of the many therapeutic strategies incorporated into a renal transplantation protocol, which often differs among institutions, and the decision as to which approach to use remains center- and resource-specific. The increased incidence of death in the prophylactic group requires further investigation.

22. Influenza A H1N1/2009 infection in pediatric solid organ transplant recipients.
Transplant Infectious Disease. 2012;14(6):584-588
Gavaldà J., Cabral E., Alonso E., Perez-Romero P., Pérez A., Quintero J., Campins M., Vilalta R., Alonso A., Len O., Navarro M., Nieto J., Jara P., Charco R., Pahissa A., Cordero E.

ABSTRACT
Aim and method: The aim of this study was to describe the clinical characteristics and outcome of pandemic influenza A H1N1/2009 (pH1N1) infection, in a retrospective cohort of pediatric patients with kidney and/or liver transplant and confirmed pH1N1 infection from June to December 2009, diagnosed in 2 Spanish teaching hospitals.
Results: Forty-nine patients were included. Pneumonia was diagnosed in 4 patients (8.2%), and 3 of them required respiratory support. There were no related deaths.
Conclusion: Antiviral treatment within 48 h was associated with a lower likelihood of pneumonia (0/38, 0%) than treatment started after 48 h (4/11, 36.3%) ($P < 0.01$).

23. Initiation of a screening protocol for polyoma virus results in a decreased rate of opportunistic non-BK viral disease after renal transplantation.

Transpl Infect Dis. 2011;13(1):1-8.

Koleilat I., Kushnir L., Gallichio M., Conti D.J.

ABSTRACT

BK virus nephropathy (BKVN) is increasingly recognized as a major cause of renal allograft failure. Recent reports demonstrate that prompt reduction of immunosuppression upon detection of persistent viremia can be associated with resolution of viremia, with minimal risk of acute rejection (AR). However, these experiences in general have occurred in centers with low baseline risks of AR. It is possible that a finer balance between overimmunosuppression and the risk of AR may exist in centers that routinely transplant patients with higher risk of AR. Thus the risk/benefit of this strategy may be altered in these centers. We report a case of antibody-mediated rejection that followed reduction of immunosuppression for BKVN diagnosed more than 3 months after the onset of viremia. This rejection episode resulted in a greater decrease in graft function than the initial BKVN episode. Issues relevant to the management of these patients are discussed, including the need for improved immune monitoring assays to determine more accurately the balance between infection and rejection.

24. Intracellular ATP concentrations of CD4 cells in kidney transplant patients with and without infection.

Clin Transplant. 2008;22(1):55-60. Koleilat I., Kushnir L., Gallichio M., Conti D.J. Sánchez-Velasco P., Rodrigo E., Valero R., Ruiz J.C., Fernández-Fresnedo G., López-Hoyos M., Piñera C., Palomar R., Leyva-Cobián F., Arias M.

ABSTRACT

In the field of organ transplantation, overimmunosuppression is associated with severe side effects, such as infection, drug toxicity, and cancer, whereas underimmunosuppression is associated with acute rejection. Intracellular adenosine triphosphate (iATP) concentration following CD4 cell activation provides an assessment of cellular immune function to help monitor the immune status of immunosuppressed patients. This assay has shown to be the first post-transplant test related not only to the risk of acute rejection but also with the appearance of infection. The aim of our study was to compare the iATP concentrations of CD4 cells between healthy adults and kidney transplant recipients from a European population, analyzing the differences according to transplant clinical status. Samples from 81 kidney transplant patients who were admitted to our hospital over a nine-month period were drawn. T-cell activation was measured by determining the increase of iATP from CD4 cells. Results were compared with patient clinical status (rejection, infection, and stability). Three patients suffered an acute rejection episode and they were not included in the analysis (mean iATP concentration 247 +/- 87 ng/mL). iATP concentrations differed significantly between stable and infected patients (313 +/- 193 vs. 197 +/- 114 ng/mL; p = 0.008). iATP concentration values were not related to the length of admission, age, peak and current panel reactive antibodies, mismatches, leukocytes, weight, creatinine, days after transplantation and blood levels of cyclosporin, tacrolimus, and sirolimus. This assay measures global immune responses of CD4 T cells from a whole-blood sample, allowing for the assessment of the impact of immuno- suppressive drugs and of the patient's underlying clinical conditions. This assay identifies transplant patients at risk for infection or rejection, providing information which can guide immunosuppressive therapy.

25. Issues in solid-organ transplantation in children: translational research from bench to bedside.

Clinics (Sao Paulo). 2014; 69(Suppl 1): 55–72.

Lipshultz S.E., Chandar J.J., Rusconi P.G., Fornoni A., Abitbol C.L., Burke G.W., Zilleruelo G.E., Pham S.M., Perez E.E., Karnik R., Hunter J.A., Dauphin D.D., Wilkinson J.D.

ABSTRACT

In this review, we identify important challenges facing physicians responsible for renal and cardiac transplantation in children based on a review of the contemporary medical literature. Regarding pediatric renal transplantation, we discuss the challenge of antibody-mediated rejection, focusing on both acute and chronic antibody-mediated rejection. We review new diagnostic approaches to antibody-mediated rejection, such as panel-reactive antibodies, donor-specific cross-matching, antibody assays, risk assessment and diagnosis of antibody-mediated rejection, the pathology of antibody-mediated rejection, the issue of ABO incompatibility in renal transplantation, new therapies for antibody-mediated rejection, inhibiting of residual antibodies, the suppression or depletion of B-cells, genetic approaches to treating acute antibody-mediated rejection, and identifying future translational research directions in kidney transplantation in children. Regarding pediatric cardiac transplantation, we discuss the mechanisms of cardiac transplant rejection, including the role of endomyocardial biopsy in detecting graft rejection and the role of biomarkers in detecting cardiac graft rejection, including biomarkers of inflammation, cardiomyocyte injury, or stress. We review cardiac allograft vasculopathy. We also address the role of genetic analyses, including genome-wide association studies, gene expression profiling using entities such as AlloMap®, and adenosine triphosphate release as a measure of immune function using the Cylex® ImmuKnow™ cell function assay. Finally, we identify future translational research directions in heart transplantation in children.

26. JAK3 inhibition: what potential for the future?
Transplant Res. 2013; 2(Suppl 1): S6.
Legendre C.

ABSTRACT
JAK3 inhibition with the CP-690,550 compound has an immunosuppressive potency in murine models, nonhuman primates and humans. This drug blocks STAT5 activation in most T-cell subpopulations but less effectively in T-regulator cells. In low to moderate risk human kidney transplant recipients, combined with mycophenolate mofetil, steroids and an induction with basiliximab, CP-690,550 proved as effective as calcineurin inhibitors with regard to prevention of acute rejection but better than calcineurin inhibitors with regard to preservation of kidney function and histology. However, at the same time, an increased incidence of overimmunosuppression consequences (cytomegalovirus, BK virus and lymphoproliferation) was observed and led to discontinuation of this specific drug development in kidney transplantation.

27. Late Persistent Positive EBV Viral Load and Risk of Solid Cancer in Kidney Transplant Patients
Transplantation.2017;101(6): 1473–1478
Bamoulid J., Courivaud C., Coaquette A., Crépin T., Clémence C., Gaiffe E., Roubiou C., Rebibou J.M., Ducloux D.

ABSTRACT
Background: Recent studies reported that posttransplant Epstein-Barr virus (EBV) replication is frequent and indicates overimmunosuppression. We hypothesized that long-term EBV replication may identify overimmunosuppressed patients at higher risk of cancer.
Methods: We analyzed a prospective cohort of renal transplant recipients having routine EBV PCR surveillance. All cancers (except EBV-related neoplasia) were recorded.
Results: Mean follow up was 94 + 23 months. Samples (8412) were available in 669 patients. Three hundred eighty-eight of the 669 patients (58%) had at least 1 positive viremia during follow-up.Epstein-Barr virus D+/R- patients (P = 0.046) as well as those having received antithymocyte globulin (P < 0.001) were more likely to develop persistent EBV viremia. Eighty-six patients (12.9%) developed a cancer during follow-up. The cumulated incidence of cancer was higher in patients with persistent high EBV replication (22.4% vs 10.2%, P = 0.005). The effect of persistent EBV infection remained significant even after adjustment for all confounding factors (hazard ratio, 1.69; 95% confidence interval, 1.10-2.61; P = 0.018). Age, history of antithymocyte globulin use, smoking, and history of cancer were also associated with cancer occurrence.
Conclusions: Persistent high EBV viral load is associated with the occurrence of solid cancer. In this setting, more intensive screening and/or minimization of immunosuppressive treatment are probably required.

28. Long-term remission of recurrent severe anemia as a result of parvovirus B19 infection in a pediatric renal transplant recipient.

Pediatr Transplant. 2011;15(4):E76-9.

Shen Q., Xu H., Cao Q., Zhou L.J., Xu J., Fang X.Y., Ge J.

ABSTRACT

We studied a case of recurrent PV-B19-associated anemia in a renal transplant child with long-term remission induced by baseline immunosuppression adjusted and intensive IVIG therapy. This was a 15-yr-old boy. Seven wk after transplantation, he experienced acute rejection, which was treated with high-dose steroids, ATG, and plasmapheresis. Ten wk after transplantation (three wk after rejection), his hemoglobin dropped to 54 g/L and serum PV-B19 PCR was positive. After therapy with IVIG and conversion from mycophenolate mofetil to rapamycin, anemia resolved. But the patient had fever on the fourth day of IVIG with mild pulmonary edema and rise in serum creatinine. Two months after the first course of IVIG, anemia recurred and a second course of IVIG (preadministration methylprednisolone) was given, which was followed by the resolution of anemia without side effect and recurrence two months later again. Baseline immunosuppression was adjusted with dual immunosuppression and low doses including prednisolone and tacrolimus. At the same time, monthly course of IVIG was repeated four times. Within the next 23 months, anemia did not recur and renal function remained stable. In conclusion, PV-B19-associated anemia can be recurrent in immunocompromised children and baseline immunosuppression should be carefully adjusted to control PV-B19 infection.

29. Long-term side effects of treatment with mTOR inhibitors in children after renal transplantation.

Pediatr Nephrol. 2013;28(8):1293-8.

Kranz B., Wingen A.M., Vester U., König J., Hoyer P.F.

ABSTRACT

Background: mTOR inhibitors (mTORI) have emerged as alternative and additive immunosuppressive agents in pediatric renal transplantation (pRTx). Their immunosuppressive, anti-proliferative, and anti-neoplastic mechanisms have been described to be effective, whereas some side effects are alarming. In particular, growth and pubertal development are of concern. The aim of this study was to look for long-term side effects of mTORI therapy in pRTx.

Patients and methods: The retrospective analysis focused on side effects, growth, and pubertal development under mTORI therapy in 31 children. Eighteen children were routinely monitored for estradiol, testosterone, LH, and FSH levels.

Results: The occurrence of bacterial infections, lymphoceles, myelosuppression, and the course of overall linear growth was comparable with other pediatric renal transplant cohorts. According to the clinical puberty status, all but one patient showed normal age-related development in parallel to normal serum hormone levels. Only one patient experienced cytomegaly virus infection under mTORI, no post-transplant lymphoproliferative disorders (PTLD) occurred.

Conclusions: Long-term mTORI therapy is safe in pRTx. No negative impact on growth and pubertal development was observed.

30. Noninvasive immune monitoring assessed by flow cytometry and real time RT-PCR in urine of renal transplantation recipients.

Transpl Immunol. 2006 Aug;16(2):73-80.

Galante N.Z., Câmara N.O., Kallas E.G., Salomão R., Pacheco-Silva A., Medina-Pestana J.O.

ABSTRACT

Background: Monitoring recipient's alloreactivity has shown to be critical for limiting overimmunosuppression besides allowing preemptive treatment of acute rejection (AR).

Methods: Flow cytometry and real time RT-PCR were performed in urine of kidney transplant recipients with AR (n = 13) and compared with pyelonephritis (n = 10), chronic allograft nephropathy (n = 13), acute tubular necrosis (n = 13) and stable graft function (n = 11). Expression of CD3, CD4, CD8, HLA-DR, Fas-L, ICAM-1 and CD25 were assessed using flow cytometry. mRNA of perforin, granzyme B and Fas-L were quantified by real time RT-PCR.

Results: Frequencies of CD3+, HLA-DR+, Fas-L+, ICAM-1+ and CD25+ cells were significantly higher in AR group ($p < 0.05$). ROC curves showed sensitivity from 70% to 91% and specificity from 30% to 100%, whereas the highest sensitivity and specificity was 91% and 100% respectively, for Fas-L+ cells. Levels of mRNA of perforin, granzyme B and Fas-L were significantly augmented in AR, while the sensitivity and specificity ranged from 85% to 88% and from 55% to 100%, respectively.

Conclusions: Analyses of immune activation markers by flow cytometry and real time RT-PCR are equally useful for noninvasive monitoring kidney allografts.

31. Oseltamivir-resistant 2009 H1N1 influenza pneumonia during therapy in a renal transplant recipient.

Pediatrick Transplantation. 2006 Aug;16(2):73-80.

Shetty A.K., Ross G.A., Pranikoff T., Gubareva L.V., Sechrist C., Guirand D.M., Abramson J., Lin J.J.

ABSTRACT

The emergence of oseltamivir-resistant 2009 H1N1 influenza virus (conferred by the H275Y substitution in NA) during therapy or prophylaxis in immunocompromised patients is a serious concern. The optimal therapy for immunosuppressed patients with oseltamivir-resistant 2009 H1N1 influenza virus is unknown and few options exist. We report a 10-yr-old recipient of kidney transplant who was hospitalized with oseltamivir-resistant 2009 H1N1 influenza pneumonia complicated by severe respiratory failure, ARDS, and renal failure requiring institution of ECMO and CRRT. On presentation, treatment with oseltamivir (second course) and broad-spectrum antibiotics was initiated. Immunosuppressive agents were stopped on hospital day (d) 2. On hospital d 7, given his critical status, immunocompromised state, and difficulty in obtaining intravenous zanamivir, after obtaining ethical approval and parental consent, he was treated with intravenous peramivir (through an Emergency Investigational New Drug Application) for two wk. He tolerated the regimen well and his clinical status improved gradually. Several factors may have contributed to virus clearance and survival including recovery of the immune system, aggressive critical care support, and administration of peramivir. Ongoing surveillance is essential to monitor how oseltamivir-resistant H275Y mutant viruses may evolve in the future.

32. Peripherally circulating CD4⁺ FOXP3⁺ CXCR3⁺ T regulatory cells correlate with renal allograft function.

Scand J Immunol. 2012;76(3):320-8.

Hoerning A., Köhler S., Jun C., Tebbe B., Fu J., Menke J., Wilde B., Dolff S., Feldkamp T., Briscoe D.M., Kribben A., Hoyer P.F., Witzke O.

ABSTRACT

Peripheral immunoregulation depends on T regulatory cell trafficking into the allograft to modulate the local alloresponse. Little is known about the relevance of trafficking receptors for Tregs after solid organ transplantation in humans. In this study, expression of the peripheral chemokine receptors CXCR3 and CCR5 on CD4⁺ FOXP3⁺ Treg cells was analysed and correlated with allograft function in renal transplant recipients. Flow cytometry analysis of peripheral blood mononuclear cells of 54 renal transplant recipients receiving a calcineurin inhibitor-based immunosuppression was performed for CD4, CD25, FOXP3, CXCR3 and CCR5 within the first 18 months post-transplantation. Correlation analysis of chemokine receptor expression and glomerular filtration rate as calculated by MDRD (eGFR) was performed. Expression of the peripheral homing receptors CXCR3 ($r = 0.44$, $P < 0.05$) and CCR5 ($r = 0.45$, $P < 0.05$) on FOXP3⁺ Tregs correlated with renal allograft function (eGFR) in patients receiving tacrolimus ($n = 28$), but not cyclosporine A (CsA) ($n = 26$). CsA but not tacrolimus reduced surface expression of CXCR3 on FOXP3⁺ Tregs in renal transplant recipients as correlated to trough levels ($r = -0.42$, $P < 0.05$). In contrast to CD4⁺ CXCR3⁺ CD25(lo) T cells, flow-sorted CD4⁺ CXCR3⁺ CD25(hi) Tregs isolated from healthy individuals did not produce IFNγ or IL-17 ex vivo and expressed high levels of GARP mRNA both at baseline as well as after TCR activation indicating functional regulatory activity. Expression of the peripheral trafficking receptors CXCR3 and CCR5 on FOXP3⁺ Tregs is associated with renal allograft function. These results suggest that Treg trafficking may also depend on the interaction of CXCR3 or CCR5 and their respective ligands.

33. Pneumocystis jirovecii multilocus genotyping profiles in Northern Ireland.
J Med Microbiol. Aug;62(Pt 8):1170-4.
Curran T., McCaughey C., Coyle P.V.

ABSTRACT
Pneumocystis jirovecii causes pneumonia, a severe opportunistic infection in immunosuppressed patients that has both person-to-person airborne transmission and environmental transmission as important routes of infection. An increasing incidence of P. jirovecii in Northern Ireland prompted a detailed epidemiological and molecular review that included enhanced surveillance on all lower respiratory specimens. Genotyping of these P. jirovecii positive specimens was undertaken using multiple locus sequence typing (MLST) targeting known variable regions of the P. jirovecii genome. Multiple circulating types were found among all patient risk categories. However, a predominance of one MLST type was found in a P. jirovecii outbreak amongst the renal transplant population. Our results demonstrate the diversity of P. jirovecii strains amongst the local immunosuppressed cohort and highlight the importance of genotyping in the investigation of common sources of P. jirovecii amongst immunosuppressed patients.

34. Risk factors for BK virus infection in the era of therapeutic drug monitoring.
Transplantation. 2013;95(12):1498-505.
Borni-Duval C., Caillard S., Olagne J., Perrin P., Braun-Parvez L., Heibel F., Moulin B.

ABSTRACT
Background: Overimmunosuppression is a widely recognized risk factor for BK virus (BKV) infection, particularly with the combination of tacrolimus, mycophenolate mofetil (MMF), and steroids. Nevertheless, the exact impact of exposure to tacrolimus and MMF is not well understood.
Methods: We examined 240 kidney recipients between 2006 and 2008. BKV was monitored every 2 months in the urine or blood. A kidney biopsy was performed when viremia exceeded 10 copies/mL.
Results: Ninety-five (40%) patients had sustained viruria, 48 (20%) sustained viremia, and 17 (7%) biopsy-proven polyomavirus-associated nephropathy. The mean time-to-occurrence was 7.6, 7.9, and 9.7 months for viruria, viremia, and polyomavirus-associated nephropathy. Risk factors associated with BKV infection in univariate analyses were retransplantation, panel-reactive antibody more than 0%, cytomegalovirus D+/R-, cold ischemia time, delayed graft function, induction with antithymocyte globulins, acute rejection before month 3 (M3), tacrolimus trough levels more than 10 ng/mL, and M3 AUC0-12 hr more than 50 hr mg/L. Multivariate analyses showed that cytomegalovirus D+/R- (adjusted hazard ratio [AHR], 2.03; P=0.05), acute rejection (AHR, 5.4; P<0.001), and mycophenolic acid AUC0-12 hr more than 50 hr mg/L (AHR, 3.6; P=0.001) were risk factors for BKV.
Conclusions: This study identified a link between a state of increased immunosuppression and BKV infection, especially in patients with higher MMF exposure and elevated tacrolimus trough levels at M3.

35. Risk Stratification for Rejection and Infection after Kidney Transplantation

Clin J Am Soc Nephrol. 2015; 10(12): 2213–2220.

Cippà P.E., Schiesser M., Ekberg H., van Gelder T., Mueller N.J., Cao C.A., T. Fehr, Bernasconi C.

ABSTRACT

Background and objectives: Definition of individual risk profile is the first step to implement strategies to keep the delicate balance between under- and overimmunosuppression after kidney transplantation.

Design, setting, participants, & measurements: We used data from the Efficacy Limiting Toxicity Elimination Symphony Study (1190 patients between 2002 and 2004) to model risk of rejection and infection in the first year after kidney transplantation. External validation was performed in a study population from the Fixed-Dose Concentration-Controlled Trial (630 patients between 2003 and 2006).

Results: Despite different temporal dynamics, rejections and severe infections had similar overall incidences in the first year after transplantation (23.4% and 25.5%, respectively), and infections were the principal cause of death (43.2% of all deaths). Recipient older age, deceased donor, higher number of HLA mismatches, and high risk for cytomegalovirus disease were associated with infection; deceased donor, higher number of HLA mismatches, and immunosuppressive therapy including cyclosporin A (compared with tacrolimus), with rejection. These factors were integrated into a two–dimensional risk stratification model, which defined four risk groups: low risk for infection and rejection (30.8%), isolated risk for rejection (36.1%), isolated risk for infection (7.0%), and high risk for infection and rejection (26.1%). In internal validation, this model significantly discriminated the subgroups in terms of composite end point (low risk for infection/rejection, 24.4%; isolated risk for rejection and isolated risk for infection, 31.3%; high risk for infection/rejection, 54.4%; $P<0.001$), rejection episodes (isolated risk for infection and low risk for infection/rejection, 13.0%; isolated risk for rejection and high risk for infection/rejection, 24.2%; $P=0.001$), and infection episodes (low risk for infection/rejection and isolated risk for rejection, 12.0%; isolated risk for infection and high risk for infection/rejection, 37.6%; $P<0.001$). External validation confirmed the applicability of the model to an independent cohort.

Conclusions: We propose a two–dimensional risk stratification model able to disentangle the individual risk for rejection and infection in the first year after kidney transplantation. This concept can be applied to implement a personalized immunosuppressive and antimicrobial treatment approach.

36. Subclinical Epstein-Barr virus viremia among adult renal transplant recipients: incidence and consequences.

Am J Transplant. 2013;13(3):656-62.

Bamoulid J., Courivaud C., Coaquette A., Chalopin J.M., Gaiffe E., Saas P., Ducloux D.

ABSTRACT

The natural history and clinical significance of posttransplant Epstein-Barr virus (EBV) infection remain largely unknown. The aims of this study are to describe the incidence, risk factors and consequences of EBV infection after kidney transplantation. A total of 383 consecutive patients having received a kidney transplant between January 2002 and December 2010 were included. EBV polymerase chain reaction (PCR) was performed every 2 weeks for 3 months, and every 4 weeks for the next 9 months. A total of 155 of the 383 patients (40%) had at least one positive viremia during the first year posttransplant. The median time to viremia was day 31 posttransplant (14-329). A total of 73 (47%) had EBV viremia > 10(3) log and 23 (15%) had positive viremia for more than 6 months. EBV D+/R- patients (12/18 (67%) versus 143/365 (39%), p = 0.02) and those having received antithymocyte globulins (ATG) (54% vs. 35%; p<0.001) were more likely to develop EBV infection. EBV infection (hazard ratio [HR], 3.03; 95% confidence interval [CI], 1.72-8.29; p = 0.01) was associated with the occurrence of opportunistic infections. A positive EBV PCR during the first 6 months posttransplant was associated with graft loss (HR, 3.04; 95% CI, 1.36-6.79; p = 0.014). EBV reactivation is frequent after transplantation and reflects overimmunosuppression. Prospective studies should examine the association between EBV and graft loss.

37. The Effect of Later Change or Modulation of Immunosuppression on Long-Term Renal Transplant Results

Transplantation Proceedings, 42, 4037–4039 (2010).

Lee J.J., Kim M.S., Kim Y.S., et al.

ABSTRACT

Proper maintenance of immunosuppression is required to achieve long-term graft survival. The aim of this study was to evaluate the effect of change or modulation of an immunosuppressive regimen (IR) on graft survival during the posttransplant period in patients undergoing kidney transplantation. A total of 1164 patients who underwent kidney transplantation between January 1997 and December 2008 at Yonsei University Health System were enrolled. All patients initially received calcineurin inhibitor (CNI)- based double or triple IR (DIR and TIR, respectively). The causes of IR changes or modulation were reviewed retrospectively. Graft survival rate was compared according to types of maintenance immunosuppression (DIR versus TIR). Initially, DIR and TIR were adopted in 201 (17.3%) and 963 (82.7%) recipients, respectively. In 77 DIR recipients (38.8%) and 271 TIR recipients (28.1%), IRs were changed. Among recipients of an initial DIR, the most frequent reasons for IR change were acute rejection (50%) within 6 months of transplantation and chronic allograft dysfunction (70%) after 6 months. In TIR recipients, the reasons for IR change included drug toxicity or drug-related side effects (34.3%) within 6 months of transplantation and complications related to overimmunosuppression (39.3%) after 6 months. The group in which the IR was changed from the initial DIR to the later TIR had a statistically superior graft survival rate compared to the group that did not have a change in the initial DIR (P = .032). In contrast, TIR recipients without change had better graft survival rate than recipients with initial TIR change to later DIR (P < .001). Change or modulation of immunosuppression from initial DIR to later TIR could affect long-term graft survival.

38. The need for minimization strategies: current problems of immunosuppression
Transplant International 28 (2015) 891–900.
Bamoulid J., Staeck O., Halleck F., et al.

SUMMARY
New immunosuppressants and the better use of immunosuppressant combination therapy have led to significant improvements in renal allograft outcomes over the last decades. Yet, despite dramatic reduction in rejection rates and improvement in 1-year graft survival, long-term graft attrition rates remained rather constant. Current immunosuppressant combinations are frequently leading to overimmunosuppression and are increasing cardiovascular risk. Importantly, calcineurin inhibitors are nephrotoxic, contribute to cardiovascular risk and chronic allograft dysfunction. Furthermore, immunosuppressant-associated toxicities aggravate immune-mediated nephron injury and side effects lead to nonadherence, an identified important reason for late acute and chronic antibodymediated rejections. The frequent development of a chronic humoral response indicates rather insufficient immunosuppression of current combinations than simple under-immunosuppression. While there is no evidence that increasing immunosuppressive doses will improve outcomes or reduce de novo HLA-antibody formation, there is clear evidence that adequate minimization strategies will reduce side effect burden. Because of low rejection risk, but frequent side effects, drug minimization is particularly relevant for the many maintenance patients. In summary, new therapeutic strategies need to be developed from adequately powered clinical trials for reduction of the many side effects of immunosuppressants. Such evidence-based and time-dependent immunosuppressive minimization strategies are needed to achieve better long-term outcomes in the future.

39. Urinary tract infection following kidney transplantation: frequency, risk factors and graft function

Pediatr Nephrol (2012) 27:651–657.

Esezobor C. I., Nourse P. and Gajjar P.

ABSTRACT

The aim of this study was to determine the proportion of children who develop urinary tract infection (UTI) after kidney transplantation (KTx) and to identify the factors associated with UTI and its impact on graft function. To this end, we undertook a chart review of children who underwent KTx at Red Cross Children's Hospital between January 2003 and December 2009 and were followed-up for at least 6 months after transplantation. Sixty-two children (53.2% males) were followed-up for a mean (standard deviation) period of 36.9 (19.7) months. Mean age at transplantation was 10.0 (4.6) years. Twenty-five (40.3%) children had 89 UTI episodes during the study period, equivalent to 0.94 UTI episodes per one patient year of follow-up. Acute pyelonephritis occurred in 17 (27.4%) children; another 17 (27.4%) had multiple post-KTx UTI. *Klebsiella* (40.0%) and *Escherichia* (28.0%) were the commonest organisms. Those with post-KTx UTI were, at transplantation, younger (8.3 vs. 11.2 years; p= 0.017), had lower urinary tract abnormality (LUTA) (13 vs. 1; p=0.000) and had pre-KTx UTI (13 vs. 5; p=0.001). Multivariate analysis revealed that only age <5 years at transplantation and LUTA remained significant and that UTI KTx was not associated with worsening graft function. UTI is common after post-KTx. Among our patient cohort, younger age and LUTA were risk factors, but UTI did not affect graft function.

40. Urinary tract infections in pediatric renal transplant recipients – a two center risk factors study

Pediatr Transplantation 2009: 13: 881–886.

Feber J, Spatenka J, Seeman T, Matousovic K, Zeman L, Dusek J, Morávek J, Janda J, Barrowman NJ, Guerra L, Leonard M. Urinary tract infections in pediatric renal transplant recipients – a two center risk factors study.

ABSTRACT

UTI are common in renal Tx recipients and may significantly impact on the graft function. The aim of our study was to evaluate the prevalence, risk factors, and significance of UTI in Tx children. We performed a retrospective cross-sectional study of 76 Tx patients, median age at Tx was 13.4 yr. Twenty-one of 76 (28%) patients developed at least one UTI during the mean follow-up time of 3.3 ± 2.0 yr post-Tx. The first UTI occurred at a median of 160 days post-Tx. The RR of having UTI was significantly higher in patients with the primary diagnosis of obstructive uropathy (RR = 2.6, 95th CI = 1.1–6.0, p = 0.032), history of PN pre Tx (RR = 2.7, 95th CI = 1.3– 5.4, p = 0.009) and pre Tx VUR (RR = 2.2, 95th CI = 1.1–4.5, p = 0.045). These three factors also significantly decreased the infection- free survival time to the first UTI. Most UTI caused reversible acute allograft dysfunction, but the long-term graft function could not be reliably assessed with SCr. In conclusion, UTI occurred in 28% of pediatric Tx recipients, mostly during the first year post-Tx despite antibiotic prophylaxis. The diagnosis of obstructive uropathy, history of UTI and VUR prior to Tx were significant risk factors.

41. Use of antibody induction in pediatric renal transplantation

Curr Opin Organ Transplant 13:495–499.

Pescovitz M. D.

ABSTRACT

Purpose of review: The present review provides an update on the recent literature documenting the use of antibody induction in pediatric transplantation.

Recent findings: The use of antibody induction has been increasing as it has been considered to be an important component of steroid-avoidance protocols following pediatric renal transplantation. According to registry data, anti-interleukin-2R monoclonal antibodies are the predominant agents being used, with slightly more patients receiving basiliximab than daclizumab. Using antibody induction, steroid avoidance is possible while maintaining rejection rates of less than 10%. Preliminary data are appearing, in which both steroid elimination and calcineurin reduction are possible. Concerns, however, are being raised about the risk of overimmunosuppression, in particular increased rates of polyoma virus and lymphoma.

Summary: Antibody induction is firmly entrenched within the pediatric renal transplant community. There is an ongoing evolution of the types of antibodies being used. The ultimate answer for efficacy and safety will require larger samples and prospective studies.

42. The ABC of pneumococcal infections and vaccination in patients with chronic kidney disease
Clin Kidney J (2015) 8: 318–324.
Vandecasteele S. J., Ombelet S., Blumental S. and Peetermans W. E.

ABSTRACT
Background: In the general population, pneumococcal polysaccharide vaccines (PPV) decrease the incidence of invasive pneumococcal disease (IPD) whereas the impact on the prevention of noninvasive pneumococcal disease is less clear. As compared with PPV, pneumococcal conjugate vaccines (PCV) provoke a higher, longer-lasting immune response resulting in a 45% decreased incidence in vaccine-type pneumonia, and a 75% decrease in vaccine-type IPD.
Methods: Literature review on pneumococcal vaccination in end-stage renal disease.
Results: As compared with the general population, patients with chronic kidney disease (CKD) suffer increased mortality and morbidity from pneumococcal disease (PD), being up to 10-fold for those treated with dialysis. Numerous, usually small and methodological heterogeneous studies demonstrate that PPV provokes a serological response in dialysis patients, kidney transplant recipients, children with nephrotic syndrome and CKD patients receiving immunosuppressive medication. This response is of less intensity and duration than in healthy controls. Similar observations were made for the PCV. The protective value of these vaccine-elicited anti-pneumococcal antibodies in the CKD population remains to be substantiated. For patients treated with dialysis, epidemiological data demonstrate a correlation-which does not equal causality-between pneumococcal vaccination status and a slightly decreased total mortality. Clinical outcome data on the effectiveness of pneumococcal vaccination in the prevention of morbidity and mortality in the CKD population are lacking.
Conclusions: Awaiting better evidence, pneumococcal vaccination should be advocated in all patients with CKD, as early in their disease course as possible. The ACIP schedule recommends a PCV-13 prime vaccination followed by a PPV-23 repeated vaccine at least 8 weeks later in pneumococcal non-vaccinated patients, and a PCV-13 vaccine at least 1 year after the latest PPV vaccine in previously vaccinated patients. In the UK, vaccination with PPV-23 only is recommended. There exist no good data supporting re-vaccination after 5 years in the dialysis population.

43. Biomarkers of Over-Immunosuppression

Clinical pharmacology & Therapeutics, volume 90 number 2, august 2011

Budde K, Matz M, Dürr M and Glander P.

SUMMARY

An important goal in transplantation is to tailor immunosuppression to the individual needs of the patient, avoiding both rejection and over-immunosuppression. Opportunistic infections and malignancies remain a significant cause of death after transplantation and are obvious consequences of over-immunosuppression. Currently, monitoring of immunosuppression is conducted mainly on the basis of pharmacokinetic characteristics, which do not necessarily predict clinical outcome in the individual. This review focuses on the potential of using biomarkers as a monitoring tool to prevent over-immunosuppression after transplantation.

44. A Markov Chain Model to Evaluate the Effect of CYP3A5 and ABCB1 Polymorphisms on Adverse Events Associated with Tacrolimus in Pediatric Renal Transplantation

The AAPS Journal, Vol. 15, No. 4, October 2013

Sy S. K. B., Heuberger J., Shilbayeh S. et al.

ABSTRACT

The SNP A6986G of the CYP3A5 gene (*3) results in a non-functional protein due to a splicing defect whereas the C3435T was associated with variable expression of the ABCB1 gene, due to protein instability. Part of the large interindividual variability in tacrolimus efficacy and toxicity can be accounted for by these genetic factors. Seventy-two individuals were examined for A6986G and C3435T polymorphism using a PCR-RFLP-based technique to estimate genotype and allele frequencies in the Jordanian population. The association of age, hematocrit, platelet count, CYP3A5, and ABCB1 polymorphisms with tacrolimus dose- and body-weight-normalized levels in the subset of 38 pediatric renal transplant patients was evaluated. A Markov model was used to evaluate the time-dependent probability of an adverse event occurrence by CYP3A5 phenotypes and ABCB1 genotypes. The time dependent probability of adverse event was about double in CYP3A5 non-expressors compared to the expressors for the first 12 months of therapy. The CYP3A5 non-expressors had higher corresponding normalized tacrolimus levels compared to the expressors in the first 3 months. The correlation trend between probability of adverse events and normalized tacrolimus concentrations for the two CYP3A5 phenotypes persisted for the first 9 months of therapy. The differences among ABCB1 genotypes in terms of adverse events and normalized tacrolimus levels were only observed in the first 3 months of therapy. The information on CYP3A5 genotypes and tacrolimus dose requirement is important in designing effective programs toward management of tacrolimus side effects particularly for the initial dose when tacrolimus blood levels are not available for therapeutic drug monitoring.

45. Therapeutic drug monitoring in pediatric renal transplantation

Pediatr Nephrol (2015) 30:253–265

Lutz T. Weber

ABSTRACT

Finding the balance between clinical efficacy and toxicity of immunosuppressive drugs is a challenge in renal transplantation (RTx), but especially in pediatric RTx patients. Due to the expected longer life-span of pediatric transplant patients and the long-term consequences of drug-induced infectious, malignant and cardiovascular adverse effects, protocols which minimize immunosuppressive therapy make conceptual sense. In this context, therapeutic drug monitoring is a tool which provides support for the individualization of therapy. It has, however, limitations, and specific data in the pediatric cohort are comparatively sparse. There is large heterogeneity among the studies conducted to date in terms of methods, follow-up, endpoints, immunosuppressive regimens and patients. In addition, data from adult studies are not readily transferrable to the pediatric situation. This educational review gives a concise overview on aspects of therapeutic drug monitoring in pediatric RTx.

46. Barcelona Consensus on Biomarker-Based Immunosuppressive Drugs Management in Solid Organ Transplantation

Ther Drug Monit, Volume 38, Number 2S, April 2016

Brunet M., Shipkova M., van Gelder T. et al.

ABSTRACT

With current treatment regimens, a relatively high proportion of transplant recipients experience underimmunosuppression or overimmunosuppression. Recently, several promising biomarkers have been identified for determining patient alloreactivity, which help in assessing the risk of rejection and personal response to the drug; others correlate with graft dysfunction and clinical outcome, offering a realistic opportunity for personalized immunosuppression.

This consensus document aims to help tailor immunosuppression to the needs of the individual patient. It examines current knowledge on biomarkers associated with patient risk stratification and immunosuppression requirements that have been generally accepted as promising. It is based on a comprehensive review of the literature and the expert opinion of the Biomarker Working Group of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology. The quality of evidence was systematically weighted, and the strength of recommendations was rated according to the GRADE system. Three types of biomarkers are discussed: (1) those associated with the risk of rejection (alloreactivity/tolerance), (2) those reflecting individual response to immunosuppressants, and (3) those associated with graft dysfunction. Analytical aspects of biomarker measurement and novel pharmacokinetic–pharmacodynamic models accessible to the transplant community are also addressed. Conventional pharmacokinetic biomarkers may be used in combination with those discussed in this article to achieve better outcomes and improve long-term graft survival. Our group of experts has made recommendations for the most appropriate analysis of a proposed panel of preliminary biomarkers, most of which are currently under clinical evaluation in ongoing multicentre clinical trials. A section of Next Steps was also included, in which the Expert Committee is committed to sharing this knowledge with the Transplant Community in the form of triennial updates.

47. BK Virus Infection in Pediatric Renal Transplantation

Transplantation Proceedings, 47, 62-66 (2015)

Zarauza Santoveña A., García Meseguer C., Martínez Mejía S. et al.

ABSTRACT

Background: Polyomavirus BK (BKV) is a common complication after renal transplantation and an important cause of graft loss. The purpose of this study was to determine the incidence of BKV infection (viremia) in our population and to describe clinical features, global outcomes, and potential correlations with clinical or epidemiologic factors.

Methods: This retrospective single-center study included 84 pediatric recipients of kidney transplantation from January 2006 to September 2012. BKV infection screening consisted of periodic determination of decoy cells in urine samples, confirmed by means of quantitative polymerase chain reaction test in blood.

Results: Twenty-two patients (26%) developed BKV viremia. BKV replication appeared early after renal transplantation (median, 2 months). One-third of patients remained asymptomatic, and 27% presented elevated serum creatinine. Immunosuppression was reduced in 90% of patients, and 83% achieved clearance of viremia within 6 months. There was only 1 case of histologically confirmed BKV nephropathy, which evolved to graft loss despite leflunomide, intravenous immunoglobulins, and mycophenolate discontinuation. Risk of BKV viremia was associated with younger age at transplantation (5.9 y vs 10.9 years; $P = .001$) and cadaveric donor (relative risk, 3.2; $P < .05$). BKV infection did not affect short-term renal function and graft survival.

Conclusions: BKV viremia is very common in the pediatric renal transplant population, especially in younger children and in those receiving a kidney from cadaveric donors. It develops in the 1st months after transplantation. Reduction of immunosuppression seems to be a good therapeutic option, with high rates of clearance of the infection, although the only patient with confirmed BKV nephropathy had poor outcome.

48. Chronic Hepatitis E Resolved by Reduced Immunosuppression in Pediatric Kidney Transplant Patients

PEDIATRICS Volume 135, number 4, April 2015

Bouts A.H.M., Schriemer P. J. et al.

ABSTRACT

At present, transient asymptomatic hepatitis E virus (HEV) infection is common among healthy adults in Western Europe, as reported by blood transfusion services. In immune-suppressed patients HEV infection is often without clinical symptoms, but without therapeutic intervention it may become chronic and lead to cirrhosis. This report describes the course of chronic HEV infection after kidney transplantation in 2 children, who cleared the virus after reduction in immunosuppressive therapy. If aminotransferase levels continue to be moderately elevated after transplantation, HEV infection should be excluded.

49. Effect of Immunosuppressive Therapy on Cardiovascular Risk Factor Prevalence in Kidney-Transplanted Children: Comparative Study

Transplantation Proceedings, 48, 639-642 (2016)

García-Bello J.A., Romo-Del Río E.G., Mendoza-Gómez E. et al.

ABSTRACT

Background: Cardiovascular disease (CVD) is the second major cause of death in kidney-transplanted children. Cardiovascular risk factors (CVRF) prevalence after transplant may increase. The effect of immunosuppressive therapy has not been fully studied in children. The objective of the study was to measure and compare CVRF prevalence in kidney-transplanted children, depending of immunosuppressive therapy.

Methods: The study was an observational, transversal, retrospective, comparative study of pediatric patients transplanted at UMAE Hospital General Centro Medico La Raza. All patients were treated with prednisone and mycophenolic acid and any of cyclosporine, tacrolimus, or sirolimus. Demographic, clinical, and biochemical variables and immunosuppressive therapy were evaluated. We used analysis of variance, χ^2, and Fisher tests with the SPSS 18.0 statistical program.

Results: One hundred fifteen patients were studied. Sixty-five (56.5%) were male, and median age was 18.5 ±2.3 years. Seventy-eight (67.2%) were transplanted from a living related donor. Prevalence of anemia and nephrotic proteinuria was significantly less in patients treated with tacrolimus. Those treated with cyclosporine had a significantly greater prevalence of increased LDL-cholesterol, increased serum phosphorus, and increased calcium-phosphorus. Those treated with tacrolimus had lower, not significant, prevalence of hypertension, hyperuricemia, hypoalbuminemia, hypercholesterolemia, hypertriglyceridemia, and low serum HDL-cholesterol than those treated with sirolimus and cyclosporine. In multivariate analysis, patients treated with cyclosporine had significantly more probability of increased phosphorus (OR, 10.65; 95% CI, 2.75-41.16, P = .001) and calcium-phosphorus (OR, 37.94; 95% CI, 3.45-416.17, P = .003) than those treated with tacrolimus.

Conclusions: Patients treated with tacrolimus had less prevalence of CVRF than those treated with cyclosporine or sirolimus. Tacrolimus is the best immunosuppressive option to diminish CVRF in children after kidney transplantation.