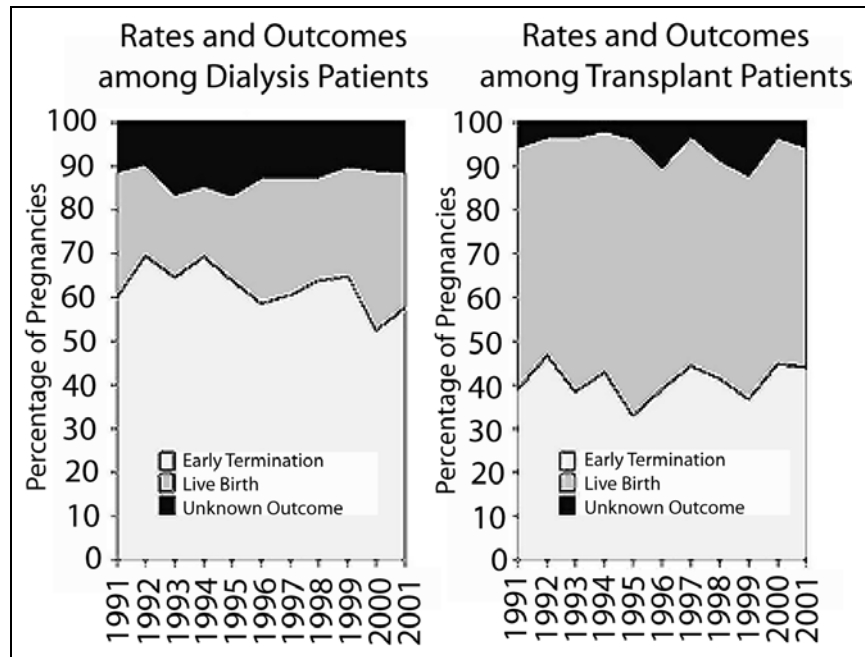
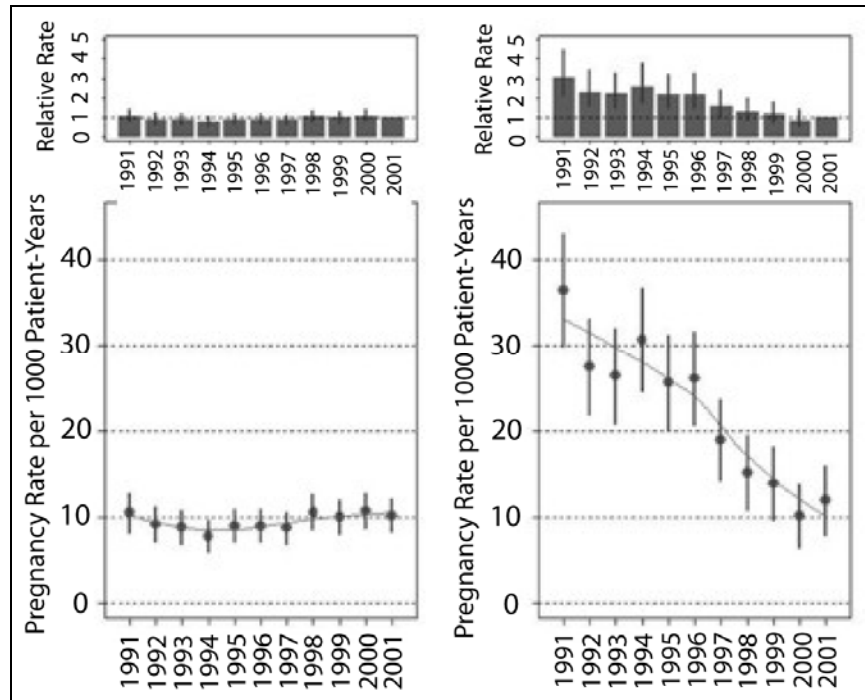


Pregnancy, Antepartum Complication, and Outcome Rates in the Dialysis and Renal Transplant Populations

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Literature concerning pregnancy in the end-stage renal disease population is scarce. Okundaye et al (AJKD, 31; 5: 766-773) surveyed 930 United States (US) dialysis units serving 6230 women aged 14 to 44 years, and reported that 2.2% of these patients became pregnant from 1992 to 1995. However, this survey included only 40% of US dialysis units. We calculated pregnancy, antepartum complication, and outcomes rates from US Medicare claims data. We analyzed both period-prevalent dialysis and transplant patients from 1991 to 2001. For each year, female patients were prevalent at least 90 days before December 31 of the previous year; were alive on December 31 of the previous year; were between 14 and 44 years of age on January 1; carried Medicare as primary payer and Medicare Part B coverage throughout the one-year follow-up period; and survived throughout the one-year follow-up period. Only transplant patients within 3 years of most recent graft were included. Pregnancy was identified by the presence of at least 1 Medicare Part A Inpatient or at least 3 Medicare Part A Outpatient or Part B pregnancy-associated claims. Antepartum complications (hemorrhage, infection, pre-eclampsia, and early labor) and outcomes (ectopic pregnancy, induced abortion, spontaneous abortion, vaginal delivery, and cesarean section delivery) were also identified.

The age-adjusted pregnancy rate among dialysis patients has been stable at roughly 10 pregnancies per 1000 patient-years (ppK). In contrast, the age-adjusted pregnancy rate among transplant patients has fallen steadily, from 36.4 ppK (95% CI: 29.8-43.1, Relative



Rate = 3.05, $p < 0.01$), to 26.1 ppK in 1996 (95% CI: 20.6-31.6, Relative Rate = 2.19, $p < 0.01$), to 11.9 ppK in 2001. The decline in transplant pregnancy rates to levels comparable to dialysis pregnancy rates warrants further investigation. In particular, toxicity from intensive immunosuppression must be evaluated. Pregnancy outcomes also vary by modality. Among dialysis pa-

tients, between 23 and 37 percent of pregnancies annually have resulted in a live birth since 1996. However, among transplant patients, between 50 and 53 percent of pregnancies annually have resulted in a live birth since 1996.

The Influence of Sex Hormone Levels on the Bone Mineral Density more than 6 Years after Renal Transplantation

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Renal transplantation leads to an accelerated bone loss early after transplantation in the majority of patients. Data on the bone mass development in ultra long-term renal transplant recipients is limited. Especially the influence of circulating sex hormones and gender on the bone mineral density (BMD) in long-term renal transplant recipients needs further investigation. We performed a retrospective analysis of the lumbar BMD between 6 and 20 years after renal transplantation.

In 67 patients (47 ± 12 years, 38 male) with a minimum interval of 72 months after transplantation lumbar BMD measurements (method: Dual Energy X-Ray Absorptiometry) were performed (= complete cohort). 31 patients (= longitudinal cohort) underwent serial BMD measurements (number of DEXA scans 3 to 10, median 5; mean follow-up 39 ± 18 months, start at 86 ± 22 months). All patients received prednisolone. Sixteen percent of patients were treated with bone-stabilizing agents (oral calcitriol and/or calcium).

Complete cohort: The BMD was significantly reduced in comparison to young healthy (mean T-score -1.33 ± 1.40) and age-matched controls (mean Z-score -0.91 ± 1.45) at 88 ± 31 months. Osteopenia or osteoporosis were present in two thirds of patients. In the *longitudinal cohort* a mean annual lumbar BMD loss of $-0.6 \pm 1.9\%$ was detectable equivalent to a -0.03 ± 0.15 reduction of Z-scores per year. **Impact of hormonal status:** In the complete cohort postmenopausality was associated with significantly lower BMD levels compared to men ($p=0.0441$). Women and men within the lowest tertile of sex hormone levels (LH, FSH, DHEAS, testosterone, progesterone, estradiol) did not exhibit significant dif-

ferences in terms of lumbar BMD compared to those in the highest tertile. The mean annual bone loss was statistically indistinguishable between men and women. There was no significant correlation of sex hormone levels and the BMD in men and premenopausal women. In postmenopausal women, however, low estradiol and high LH levels correlated with the extent of annual BMD loss ($p<0.05$).

Our data confirm a significantly reduced lumbar bone density in the very late period after renal transplantation. The lumbar BMD decreased by $-0.6 \pm 1.9\%$ per year later than 72 months posttransplant. In postmenopausal long-term renal transplant recipients low estradiol levels were associated with an accelerated bone loss. In male transplant recipients low testosterone levels did not influence lumbar bone density.

A Simplified Strategy for Clinical Management of Late Cytomegalovirus (CMV) Infection after Oral Ganciclovir Prophylaxis in de novo Renal Recipients

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Late cytomegalovirus disease after ganciclovir prophylaxis occurs in 5-21% of renal recipients within the first year posttransplantation. Identifying patients at risk for late disease is clinically difficult, costly and cumbersome as follow-up intervals lengthen.

We performed a prospective 1-year study to assess a minimum post-prophylaxis CMV-DNA-PCR monitoring frequency for identifying patients at risk for late CMV disease.

Fifty-four *de novo* recipients were prospectively followed by quantitative CMV PCR monitoring (Amplicor CMVtest, Roche Diagnostics; LLQ: 500 copies/mL blood) during (week 2), at the end (on the last day of 12 weeks ganciclovir prophylaxis) and again two weeks after conclusion of oral ganciclovir prophylaxis. Oral ganciclovir

was administered in a dose of 1000 mg t.i.d, adjusted to renal graft function and discontinued on the last day of week 12 as per protocol. Patients were assessed weekly for clinical signs of CMV syndrome or tissue-invasive CMV disease until week 14 posttransplantation; bi-weekly until 6 months and monthly until 1 year (according to the criteria for CMV syndrome and disease outlined by Paya C et al: *Am J Transplant* 2004; 4: 611-20).

Recipients (13 D+/R-; 14 D+/R+; 27 D-/R+) received tacrolimus in combination with either mycophenolate mofetil ($n=47$) or sirolimus ($n=7$) and corticosteroids as maintenance therapy. Six (11%) patients (4 D+/R-; 2 D-/R+) developed a positive CMV PCR by week 12, at the end of ganciclovir prophylaxis. Two additional patients (D+/R-) became PCR positive 2 weeks after completion of ganciclovir prophylaxis. In total 8 recipients (14.8%) had detectable viral replication (mean viral load: 4.27 ± 0.68 log copies/mL) by week 14. None of these patients had a prior positive CMV PCR. Of these 8 recipients, 1 patient developed breakthrough CMV syndrome during ganciclovir prophylaxis (in week 8) and 2 of the 7 remaining PCR positive recipients (28.6%) developed gastrointestinal (biopsy-proven) CMV disease, 2 weeks after becoming PCR positive. All CMV infections responded to intravenous ganciclovir treatment. Of the 45 recipients who did not become CMV PCR positive by week 14 posttransplantation, only one patient (2.2%) developed (biopsy-proven) CMV disease (gastrointestinal and pulmonary) at 25 weeks; the other 44 recipients remained free of disease during 12 months clinical follow-up. This method of minimal CMV monitoring (at the end of week 12 and on week 14) had a high specificity (88%) and negative predictive value (97.8%) for late CMV disease but a weaker sensitivity (66%) and poor positive predictive value (25%).

Limited quantitative CMV PCR monitoring, at the end of 3 months oral ganciclovir prophylaxis and again 2 weeks after conclusion of prophylaxis, enables clinicians to identify renal recipients at risk for developing late CMV disease. For these latter patients, close clinical follow-up is warranted and allows substantial cost savings compared to generalized and prolonged use of PCR monitoring.

The Donors Perspective: A Comparative Analysis of Satisfaction after Open vs. Laparoscopic Living Donor Nephrectomy

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Living donor kidney transplantation offers an excellent recipient outcome with low donor risk. Although technically demanding, the laparoscopic donor nephrectomy is gaining wide popularity, as donor morbidity is lower and graft function is equal. However, the most important outcome parameter, donor satisfaction, has not been studied in detail. The aim of this study was to compare donor satisfaction between those treated with the laparoscopic vs. open techniques.

Methods: All living donors between 01/1977 and 10/2003 were included. Donor procedures were performed by flank incision before 05/2000 and strictly by hand-assisted laparoscopic technique thereafter. Somatic data was acquired from our database and from the Swiss Organ Live Donor Registry. Complications were graded by a five-point therapy-based system. To evaluate donor satisfaction, a previously validated questionnaire, consisting of 69 questions regarding emotional and somatic aspects related to the period before kidney donation, after the operation and today was sent to all donors. Kidney donors living outside Switzerland (n=25) or without a traceable address (n=10) were excluded from the survey.

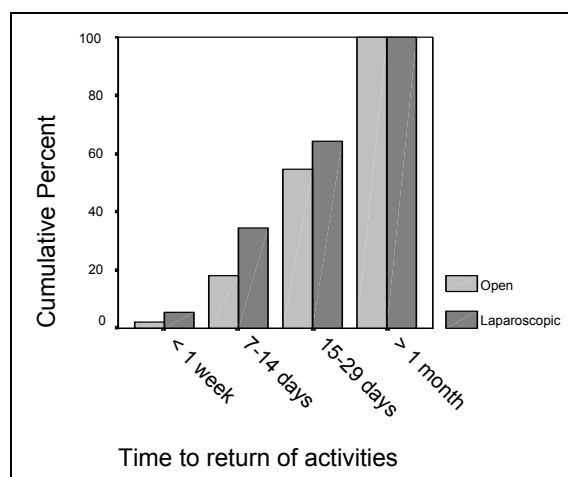
Results: 165 donors were included (with 71 open and 94 laparoscopic accesses). Baseline characteristics of both cohorts were comparable regarding sex, BMI, blood group. Laparoscopic donors were significantly older (49 vs. 45 years, p=0.012) and displayed several

trends: they were less frequently first degree relatives, had undergone previous abdominal surgery more often and were more frequently taking medication. No deaths and one intra-operative complication (colon perforation by laparoscopic access) occurred. Postoperative complications were mostly mild without differences between techniques. Hospitalisation was significantly shorter for the laparoscopic procedure (median 6 vs. 8 days, p<0.001).

Out of 130 questionnaires sent, 111 were returned (85%). Almost all donors in both groups reported that they volunteered to the donation without pressure and had not been concerned about living with one kidney. The type of the surgical procedure and worries about the scar were not important in their decision to donate. The cohort of laparoscopic donors reported less postoperative pain (p=0.020), less pain after one week (p=0.003) and a quicker return to

normal activities (p=0.047). They were also more satisfied with medical care (p=0.003) and emotional support (p=0.029). After the procedure 92% of all donors had no concerns about living with one kidney and 97% agreed with the statement "I would do it again".

Conclusion: Our analysis underscores that excellent results can be achieved by living donor kidney transplantation. Even though baseline characteristics were somewhat less favourable in the laparoscopic cohort, complications were infrequent and mild. Furthermore laparoscopy resulted in significantly less pain, shorter hospitalisation and quicker return to activity, as well higher short-term satisfaction. In the long run almost all donors were very satisfied and would do it again, regardless of the technique. Due to significant somatic and psychological short-term benefits, laparoscopy should be the technique of choice for living kidney donation.



Heart Transplantation in Patients with Marfan's Syndrome

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Objectives: Due to the risk of vascular complications the indication for heart transplantation in patients with Marfan's syndrome and end stage heart disease remains controversial. We analysed the results of such patients who underwent heart transplantation at our institution.

Material and Methods: Seven patients with Marfan's syndrome (median age 38, range 22-56 years) underwent HTx between April 1986 and August 2004. The primary vascular manifestation of Marfan's syndrome was type-A aortic dissection in 3 and ascending aortic aneurysm in 4 patients. All patients had cardiovascular operations prior to transplantation (ascending aortic replacement (n = 7), mitral valve replacement or repair (n = 3), thoracoabdominal aortic replacement (n=2), fenestration of type-B dissection (n=1). All had refractory heart failure (NYHA IV) before transplantation. Two patients underwent transplantation after VAD support.

Results: There were no perioperative deaths. Two patients died of causes unrelated to Marfan's disease (pneumonia on day 27, n = 1; stroke on day 102, n = 1). One patient died due to type-B dissection 3.8 years after transplantation. Two patients underwent thoracoabdominal aortic replacement for chronic dissection 14 and 20 months post-transplantation, respectively. The Kaplan-Meier survival rate was 71% at 1 year and 54% at 10 years.

Conclusions: Heart transplantation in patients with Marfan's syndrome can be performed with good long-term survival, similar to that of patients without Marfan's syndrome. Close follow-up and timely operation of aortic pathologies is mandatory. Reluctance to place these patients on a heart transplant waiting list appears not to be justified.

Reduction of Long-term Malignoma Incidence by Single Dose ATG-induction after Heart Transplantation: A two Center Study

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Objectives: To compare effectiveness and safety profile of a single dose versus a multiple (5-7x)-dose ATG-induction after heart transplantation used in two different centers using a retrospective analysis in comparable cohorts.

Material and Methods: 2 groups of heart recipients were included. In Gr. I patients (n = 84, age 53 ± 13) transplanted 01/92 - 12/98 received 5.8 ± 0.8 doses of rATG, in Gr. II patients (n = 104, age 52 ± 12) transplanted 05/95 - 12/00 received a single dose rATG. All pat. were maintained with CyA, azathioprin/MMF, steroids and received CMV IgG prophylaxis as well as preemptive i. v. ganciclovir treatment. Surveillance was achieved by regular endomyocardial biopsing and echocardiography, coronary angiography performed at 1 year post HTx, thereafter when indicated.

Results: Follow-up in Gr. I was 8.4 ± 3.6, in Gr. II 6.7 ± 2.4 years. Freedom from acute rejection (AR) at 1 month/1 year was 14.3/23.8 % in Gr. I vs. 13.5/34.6% in Gr. II respectively (p=n.s.). Death due to AR occurred in 5/84 patients in Gr. I and in 1/104 in Gr. II. Survival at 1 month, 1 and 5 years was 83.4, 72.6 and 63.1 % in Gr. I vs. 87.2, 81.5 and 75.1 % in Gr. II, respectively (p = n. s.). Freedom from graft vasculopathy at 6 years was 77.4% in Gr. I vs. 85.6% in Gr. II (p=n.s.). Incidence of malignancy at 1 and 6 years was 3.6 and 10.7 % in Gr. I vs. 0 and 3.8% in Gr. II. (p ≤ 0.05 at 6 years). No further malignoma was diagnosed in either group beyond 6 years post HTx.

Conclusions: Overall incidence of AR and survival is similar in both groups.

Incidence of malignancy, however, is significantly lower at a followup of up to 9 years in those patients that received only a single dose of ATG.

Immunomonitoring after Human Heart Transplantation

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Introduction: The aim of this study was to analyse cytokine and costimulatory-molecule expression profiles in human heart transplants undergoing rejection episodes. We therefore analysed gene expression profiles that may help to diagnose phases of rejection earlier and also provide information about the cause.

Material and Methods: A timecourse of intragraft mRNA expression of TNF- α , IFN- γ , IL-6 and CTLA-4 was analysed in 31 cardiac biopsies obtained from 4 heart transplant recipients with episodes of acute rejection (ISHLT scores 1A to 4). In addition mRNA expression of Fas-ligand, granzyme B and perforin was determined. Gene expression was analysed using real-time RT-PCR and correlated with ISHLT-histology-score. All patients received the same standard immunosuppression. The patients' clinical outcome was followed up for 12 months.

Results: Unexpectedly, there was no strong up-regulation of IFN- γ during episodes of acute rejection. IL-6 and TNF- α was increased during phases of rejection in one patient. However, interestingly expression of CTLA4, a negative regulator of T-cell activation, was markedly increased during the onset of all rejection episodes in all patients. All patients recovered from their rejection episodes and there was no fatality. The patient who showed increased IL-6 and TNF- α expression during the rejection episode has mean-

while a slightly reduced transplant function while all other patients have normal graft function.

Conclusions: Intragraft cytokine expression showed inter-individual differences despite comparable histological grading. Up-regulation of CTLA-41g mRNA was found consistently before and during the onset of all rejection episodes and might be a promising marker to detect pending acute rejections in the clinical setting.

HLA-DR Matching Improves Survival after Heart Transplantation – Is it Time to Change Allocation Policies?

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Objectives: HLA matching has improved outcome in kidney transplantation but is not considered in current allocation policies in heart transplantation. This study analyses the impact of HLA matching on long-term outcome after heart transplantation.

Material and Methods: The records of 240 consecutive heart transplant recipients (1995-2003, mean age 51.8±11.7 years, mean follow-up 5.9±1.8 years) were analyzed retrospectively. According to the renal allocation policy HLA mismatches (MM) on the loci HLA-A, HLA-B and HLA-DR were calculated, resulting in 0 to 6 MM. Patients with primary graft failure were excluded from statistical analysis.

Results: Survival analysis revealed a statistically significant impact of HLA-DR MM on survival. 5-year survival in patients without HLA-DR MM (n=9) was 100%. in patients with one HLA-DR MM (n=102) 82% and 75 % in patients with two HLA-DR MM (n = 104; log rank 1 MM vs 2MM: p=0.05). Freedom from cardiac allograft vasculopathy after 5 years was 89% in HLA-DR identical recipients (n=9), 61% in patients with one HLA-DR MM (n=93)

and 54% in patients with two HLA-DR MM (n = 92; log rank 1 MM vs. 2MM: p = 0.09). Conventional matching with 6 mismatches over the 3 major HLA loci revealed that the relative risk for adverse outcome increases with the numbers of MM

Conclusions: HLA-DR matching had a significant impact on survival after HTx in our centre. In our efforts to achieve the best comparative use of scarce donor organs the inclusion of HLA-DR matching into allocation policies might improve long-term outcome after HTx

Impact of Donor-transmitted Coronary Atherosclerosis on Outcome after Heart Transplantation

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Background: Due to the shortage of donor hearts the criteria for organ acceptability have been considerably extended. Therefore, the probability of transmission of atherosclerotic lesions by means of transplantation has increased. The purpose of this study was to evaluate the impact of preexisting coronary atherosclerosis (CAS) on the outcome of transplantation.

Material and Methods: Between 4/1986 and 12/2000 1253 patients underwent heart transplantation at our institution. In 1168 of these patients the coronary arteries were investigated by angiography (n=950) or autopsy (n=218) within 6 months after transplantation. Focal and noncircumferential atherosclerosis with 50 % stenosis in proximal segments was regarded as native and transmitted CAS rather than transplant vasculopathy. Hazard function and Kaplan-Meier analysis were used.

Results: In 82 patients CAS was diagnosed by angiography (n=49) or autopsy (n=33) (CAS group) and in 1086 patients no CAS was found (NCAS group). Early after HTx the instantaneous risk to die was threefold higher in the CAS group (0.17 vs. 0.05); however, beyond the first year the annual decrease in the CAS and NCAS groups was comparable (4.2%/year vs. 5.4%/year, p>0.05). Furthermore, incidence of graft vessel disease (GVD) and health-related quality of life (SF-36 questionnaire) were comparable (p>0.05). Only biopsy-proven micro-GVD, i.e. severe proliferative vascular wall thickening, was found more often in the CAS group after 5 years (83.8% vs. 74.9%, p=0.005) but this was without further clinical implications.

Conclusions: Transmitted CAS impairs the short-term but not the long-term outcome after HTx. Nevertheless, coronary angiography of donor hearts should be performed liberally, i.e. in donors 40 years old.