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1.1.

Single application of OX7-Immunoliposomes loaded with low-dose MMF reduced mesangial cell proliferation and proteinuria in experimental mesangial proliferative glomerulonephritis

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Purpose: OX7-immunoliposomes (OX7-IL) represent an efficient vector for directed drug delivery to glomerular mesangial cells (MC; *Tuffin G, JASN, 2005*). We now evaluated mycophenolate mofetil (MMF)-containing OX7-IL in experimental mesangial proliferative glomerulonephritis. We incorporated low dose MMF in OX7-IL (1.37 ug/kg bw) using pH insensitve pegylated unilamellar IL. Anti-Thy1.1 nephritis was induced by a single iv. injection of OX7 antibodies (1 mg/kg bw) at day 0.
Methods and materials: Male Wistar rats were divided into five groups: Group A (n = 6): healthy rats, group B (n = 18): nephritic rats, group C (n = 18): nephritic rats treated with empty OX7-IL (1.8 umol lipids/ml with 5 umol/kg bw), group D (n = 18): nephritic rats treated with MMF-containing OX7-IL (MMF: 1.37 ug/kg bw), and group E (n = 18): nephritic rats treated with free MMF (MMF: 1.37 ug/kg bw). Treatments of groups C–E were administered by single iv injection (180 ul) at day +2. Nephrectomy of six animals per group was performed at days +5 and +9 (group A at day +9 only) after kidney perfusion with 1.5% paraformaldehyde/1.5% glutaraldehyde in 0.15M hepes buffer. Stereology using a physical dissector was applied to determine the number of MC per kidney. Albuminuria was analyzed by HPLC.
Results: MMF-loaded IL-OX7 of group D decreased MC proliferation, compared to other nephritic groups B and E ($p < 0.001$; Dunnett's multiple comparison).

	Group A	Group B	Group C	Group D	Group E
MC at day+5 (mean±SEM)		11'130'810 971'162	11'544'428 ± 1'248'668	9'016'643 ± 2112482	11'180'994 ± 532'446
MC at day+9 (mean±SEM)	5'953'618 ± 591'052	13'792'021 ± 1'039'931	11'993'675 ±277'958	10'251'246 ± 809'154	13'501'345 ± 498'092

MMF-loaded OX7-IL caused an almost complete abolition of albuminuria at d+9, expressed as µg albumin/µmol creatinine (mean ± SEM): Group D: 7.4 ± 4.4, group B: 252.2 ± 75.5, and group A: 0.8 ± 0.13 (C vs. B, $p < 0.002$; Dunnett's multiple comparison).
Conclusion: In conclusion, the directed one-shot delivery of low-dose MMF to MC represents a novel and efficient approach for the therapy of experimental mesangial proliferative glomerulonephritis. These results open up a new perspective of the treatment of glomerulonephritis in humans.

1.2.

Donor CD40 is required for alloreactive T cell cytotoxicity in the context of limited T cell help

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Purpose: Allo-reactive cytotoxic T lymphocytes (allo-CTLs) induce tubulointerstitial injury during kidney allograft rejection. Renal tubular epithelial cells (RTECs) do not express the costimulatory B7 molecules, but constitutively express CD40. The aim of this study was to investigate the role of donor CD40 in the interaction of allo-CTLs with RTEC, and in skin and kidney allograft rejection.
Methods and materials: Primary cultures of murine RTECs were prestimulated with IFN-β and IFN-γ to induce high surface expression of MHC class I and II. Responder T cells from CBA mice (H-2k; purified CD8+ T cells either with or without CD4 help) were restimulated *in vitro* for 5 days with either autologous, allogenic wild-type C57BL/6 (WT B6, H-2b) or allogenic CD40$^{-/-}$ (B6 background, H-2b) splenocytes and then tested against RTECs from WT B6 or CD40$^{-/-}$ mice using a standard cytotoxicity assay (51Cr release). Cytokine analysis of the coculture supernatants was performed with standard ELISA assays. Skin graft recipients were CBA mice, and donors were B6 WT or CD40$^{-/-}$ mice. At day 0 full- thickness tail skin was transplanted to the dorsal flank area of recipient mice. Graft rejection was defined as graft necrosis >90% of the graft. In certain groups CD4+ or CD8+ T cell depletion of recipient mice was performed by i.p. administration of a depleting monoclonal anti-CD4 (GK1.5) or anti-CD8 (YTS169) antibody on days –5, –1, and +9.
Results: CD8+ CTLs showed no cytolytic activity against allogenic B6 RTECs when restimulated in the absence of CD4+ T cell help. In contrast when CD4 help was present during restimulation, CD8+ CTLs killed WT and CD40-/- RTECs equally. However, when CD40 was missing both on the stimulating splenocytes and on the target RTECs, cytotoxicity of allo- CTLs was reduced. Cytotoxicity was alloantigen-specific, since no killing was detected by responders restimulated with autologous or third party splenocytes. We further analyzed cytokine production in these restimulation cocultures. When CD8+ CTLs were stimulated in the presence of CD4 help, a high allo-specific IFN-gamma and IL-10 production was detected, and this cytokine production was only slightly reduced in the absence of CD40 on stimulating cells. In contrast, the production of the proinflammatory cytokine IL-17, which was also detectable only in the presence of CD4+ T cells, was completely abolished when stimulators lacked CD40.
To evaluate the role of donor CD40 expression in vivo, we performed skin and kidney allografts from B6 donors (WT B6 or CD40$^{-/-}$) on fully MHC-mismatched CBA recipients. No difference in the time course of rejection between WT and CD40$^{-/-}$ grafts could be detected, unless CD4+ T cells were depleted. The depletion of CD8+ T cells did not have any effect. Similar experiments using CD40$^{-/-}$ donors for renal allografts are in progress.
Conclusion: CD40 is an important costimulatory molecule for the interaction between allo-CTLs and RTECs in situations, where CD4+ T cell help is limited. However, the main impact of CD40 seems to be on CD4+ T cells, where it is required for IL-17 production and mediates T cell help for full activation of allo-CTLs. Strategies to block or down-regulate CD40 might be therapeutically useful to prevent kidney allograft rejection.

1.3.

Combined bone marrow and kidney transplantation – a new mouse model to study allograft tolerance induced by mixed chimerism

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Purpose: Combined bone marrow (BM) and kidney transplantation has been the only successful approach to induce kidney allograft tolerance in humans. However, the precise mechanisms of tolerance induction in these patients – particularly in transient mixed chimeras – are not understood. This study aimed to establish a mouse model to evaluate kidney allograft tolerance induced by mixed chimerism.
Methods and materials: Three groups of orthotopic murine kidney transplantations were performed: (i) With non-life supporting transplants in two MHC-mismatched strain combinations (CBA/H-2k → B6/H-2b, B10.RIII/H-2r → B6) and syngeneic controls (n = 17 in total), the time points and scoring systems for histological analysis were determined. (ii) Then, B6 mice (n = 19) were conditioned (3Gy total body irradiation, 2 mg anti-CD154) and received BM from CBA donors to induce a state of mixed chimerism. Six weeks later, donor CBA or third party B10.RIII kidneys were transplanted and removed 2–3 weeks later for histology. (iii) Finally, B6 mice (n = 3) received BM transplantation and six weeks later a life-supporting allogeneic donor-type kidney allograft. As control an equal number of syngeneic transplants were performed. Kidney function was monitored by weekly urea measurements, and grafts were harvested for histology at week 6. Histological analysis was performed on paraffin sections using hematoxylin-eosin, PAS and immunohistochemical stainings.
Results: Acute kidney allograft rejection with vascular lesions (Banff II-III) was found in both strain combinations (n = 5–6/group) 2–3 weeks post-transplant. In contrast, stable mixed chimeras accepted fully mismatched donor-type kidney allografts (n = 6), whereas third party allografts in chimeric (n = 5) and donor-type allografts in non-chimeric (n = 5) recipients were acutely rejected. This demonstrated that conditioning was not generally immunosuppressive, but donor-specific allograft tolerance was induced. To demonstrate functional tolerance, life-supporting donor allografts were performed into mixed chimeras. All mice (n = 6) with initially successful grafts survived until week 6, and serum urea levels were identical between iso- and allografts.
Conclusion: We have successfully established a murine model for MHC-mismatched combined BM and kidney transplantation demonstrating histological and functional donor-specific tolerance. This model will now be used to study the mechanisms of kidney allograft tolerance in stable and transient mixed chimeras.

1.4.

Systematic analysis of a human renal glomerulus-specific gene expression library – REGGEL

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Purpose: Glomerular diseases account for the majority of cases with chronic renal failure. In the last decade several genes were identified with key relevance for glomerular function. Several of these genes show a preferential or specific mRNA expression in the renal glomerulus. To identify additional candidate genes involved in glomerular function in humans a human renal glomerulus-specific gene expression library (REGGEL) could be a useful research tool.
Methods and materials: Gene expression profiles from human glomeruli and tubulointerstitium obtained from transplant living donors (n = 4) using Affymetrix HG-U133A arrays were studied and compared. Database for Annotation, Visualization and Integrated Discovery (DAVID) was used for gene ontology analysis. Results were validated using qRT-PCR on an independent cohort as well as *in vitro*. Protein

levels were analyzed *in vitro* by Western Blot and immunofluorescence.
Results: Comparison of gene expression profiles from human glomeruli with the tubulointerstitial compartment resulted in 677 genes with prominent overrepresentation in the glomerulus. Genes with known glomerular overexpression served for validation and were all found in the novel REGGEL (e.g. WT1, NPHS1, NPHS2, SYNPO, DAG1, EHD3, PLA2R1, PLCE1, POD1, PODXL, PTPRO, TJP1, T1A-2). In addition a large number of genes not previously reported to be expressed in the glomerulus were identified. We verified the mRNA expression for several novel glomerulus-enriched genes by qRT-PCR. Gene ontology and pathway analysis identified biological processes previously not reported to be of relevance in glomeruli, among others axon guidance. This finding was further validated by assessing the mRNA and protein expression of the axon guidance molecules neuritin and roundabout receptor ROBO1 in additional renal biopsies and *in vitro*.
Conclusion: Identification of glomerular-specific genes and proteins as well as molecular mechanisms and gene networks may represent a promising approach to the understanding of development and function of the glomerulus and its derangement in common glomerular diseases.

1.5.

Aldosterone suppression in preeclampsia is due to impaired VEGF signaling in preeclampsia

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Purpose: Aldosterone production is low in preeclampsia despite compromised plasma volume. Since preeclampsia is characterized by excess circulating soluble VEGF receptor, sFlt1, we hypothesized that inhibition of VEGF signaling in the adrenal glands may lead to the suppressed aldosterone noted in these subjects.
Methods and materials: Primary HUVECs and the human adrenal cell line H295R were cultured. Sprague-Dawley rats were exposed to adenovirus-transfected mouse sFlt-1. Plasma volume was measured by injecting TR-albumin. Adrenals were removed for histological, immunofluorescence (CD31 and Kdr) and electron microscopically evaluation. sFlt-1 levels in rat plasma, and aldosterone concentration in rat plasma and urine as well as in cell culture supernatants were measured by ELISA. In H295R cells, aldosterone production was further determined by 3H-DOC/aldosterone conversion assays.
Results: Media, conditioned 24-hrs by VEGF-treated HUVECs, transferred to H295R cells increased angiotensinII-stimulated aldosterone production by 30 ± 6% ($p < 0.03$), as compared to a reduction of 50 ± 1% ($p < 0.0004$) in HUVECs not exposed to VEGF. Inhibition of VEGF by adenovirus-based sFlt-1 overexpression in HUVECs abolished the VEGF response. In vivo studies, suggested that sFlt1 overexpression not only decreased plasma volume, but also suppressed aldosterone levels ($r2 = 0.1367$; $p = 0.0406$). This was associated with a decrease in the capillary density in the zona glomerulosa of the adrenal glands. Electron microscopic studies suggest a profound reduction in endothelial fenestral density.
Conclusion: Aldosterone production in adrenal cells closely depends on intact VEGF signaling in the zona glomerulosa. Importantly, the low aldosterone availability further compromising already reduced plasma volume in preeclampsia might be the result of antiangiogenic factors rather then a physiological response.

1.6.

Role of the naïve and memory CD4+ T-cell repertoire in transplantation

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Purpose: The exact role of individual T cell-subsets in the development of rejection is not clearly defined. Given their distinct phenotypes, effector functions and trafficking patterns, naïve (CD45RBhiCD44lo) and memory (CD45RBloCD44hi) T cells may play distinct roles in anti-donor immunity after transplantation. Furthermore, only the CD4+CD45RBlo population contains CD4+CD25+ T cells, a subset with suppressive functions playing a major role in the maintenance of peripheral tolerance. The aim of this work was to study the contribution of these individual subsets in alloresponses via the direct and indirect pathways using a murine experimental model.
Methods and materials: Purified naïve or memory CD4+ T cells were adoptively transferred into lymphopenic mice undergoing a skin allograft. Donor to recipient MHC combinations were chosen in order to study the direct and the indirect pathways of allorecognition separately. Graft survival and *in vivo* expansion, effector function and trafficking of the transferred T cells was assessed at different time points after transplantation.
Results: We found that the cross-reactive CD4+CD45RBlo memory T-cell pool was heterogeneous and contained cells with regulatory potentials, both in the CD4+CD25+ and CD4+CD25-populations. CD4+ T cells capable of inducing strong primary alloreactive responses *in vitro* and rejection of a first allograft *in vivo* were mainly contained within the CD45RBhi naïve CD4+ T-cell compartment. CD4+CD45RBlo T cells proliferated less abundantly to allogeneic stimulation than their naïve counterparts both *in vitro* and *in vivo,* and allowed prolonged allograft survival even after the depletion of the CD4+CD25+ subset. Interestingly, CD4+CD25-CD45RBlo T cells were capable of prolonging allograft survival, mainly when the indirect pathway was the only mechanism of allorecognition. The indirect pathway response, which was shown to drive true chronic rejection and contribute to chronic allograft dysfunction, was predominantly mediated by naïve CD4+ T cells.
Conclusion: This work provides new insights into the mechanisms that drive allograft rejection and should help develop new clinical immunosuppressive protocols. In particular, our results highlight the importance of selectively targeting individual T-cell subsets to prevent graft rejection but at the same time maintain immune protective responses to common pathogens.

Oral Presentations – General Nephrology

2.1.

Fibrillary glomerulonephritis – outcome with and without immunosuppressive treatment

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Purpose: Fibrillary glomerulonephritis is a rare disease diagnosed in about 0.5–1% of all native kidney biopsies. A diagnosis is made by electron microscopy. The disease is characterized by randomly arranged fibrillary deposits with a diameter of 12 to 20 nm in the mesangial and glomerular basement membrane in contrast to immunotactoid glomerulopathy (diameter 20–40 nm). Congo red staining is negative. Most of the patients present with nephrotic proteinuria. There is no proven effective treatment available. According to the literature, the outcome is poor. In a previous study with 3 patients, we observed a favourable course when an early steroid treatment was begun. None of the three patients reached end stage renal disease (ESRD). Therefore, we decided to assess the long term follow up of all the patients with fibrillary glomerulonephritis diagnosed since 1992 at our centre of reference for renal pathology in Basel.
Methods and materials: All native renal biopsies examined in the institute of renal pathology at the University of Basel were evaluated for fibrillary glomerulonephritis from 1992 until 2008. 20 patients were found from ten different hospitals in the region. We mailed questionnaires to the centres to ask for follow up data. Primary end point was ESRD or death of any cause. Secondary end points were reduction of proteinuria lower than 1 gram/day and improvement of eGFR.
Results: 20 patients were included. Four patients had to be ruled out because of missing follow up data in three cases, and diagnosis post-mortem in one case. Patients characteristics are shown in table 1. Follow up data are shown in table 2.The mean follow up was 21.7 month (1-115.1). Six patients died (37.5%), three without having ESRD, two died on hemodialysis, and one died in uremia at the age of 84 years without renal replacement therapy. Six patients (37.5%) reached ESRD, five of them went on hemodialysis. 13 (81.3%) patient received an immunosuppressive therapy with steroids, five of them in combination with cyclophosphamide. In the treatment group patients tended to be younger, proteinuria was lower and eGFR higher than in the group without immunosuppressive treatment. There was no statistically significant difference concerning ESRD in the treatment group versus the group without immunosuppressive treatment (table 2). In relation to the histological pattern membranous glomerulonephritis (MGN) had a better outcome as compared to membranoproliferative glomerulonephritis (MPGN), and mesangial proliferative/ sclerosing glomerulonephritis (MES) (table 3).

Table 1
Patient characteristics at time of biopsy; n = 16

Age (years)	59.9 (33–84.4)
Female	7 (43.8%)
Clearance MDRD (ml/min)	44.9 (5.7–103.3)
Clearance <60 ml/min	10 (63%)
Proteinuria g/day	7.9 (0.5–18.4)
nephrotic syndrome	11 (68.8%)
concommitant diseases:	
– Hypertension	7 (43.8%)
– Diabetes	1 (6.3%)
– Lymphoproliferative disease	3 (18.8%)
– rheumatoid disease	2 (12.5%)
Kidney biopsy:	
– Lymphoproliferative disease	3 (18.8%)
– crescents in biopsy	8 (50.0%)
– MPGN	9 (56.2%)
– MES	5 (31.3%)
– MGN	2 (12.5)%

MPGN: membranoproliferative glomerulonephritis; MES: mesangial proliferative/sclerosing GN; MGN: membranous glomerulonephritis;

Table 2
Outcome with and without immunosuppressive therapy

	with therapy (n = 13)	without therapy (n = 3)
Age (years)	58.7 (33–84.4)	65.0 (54.4–78.8)
Female	5 (38.5%)	2 (66.7%)
Clearance MDRD (ml/min)	53.5 (5.7–103.3)	34.5 (23–45.1)
Clearanace <60 ml/min	7 (53.8%)	3 (100%)
Proteinuria g/day	7.8 (0.5–18.4)	12 (0.88–15)
nephrotic syndrome	9 (69.2%)	2 (66.7%)
outcome:		
– deaths	4 (30.8%)	2 (66.7%)
– ESRD	5 (38.5%)	1 (33.3%)
– dialysis	4 (30.8%)	1 (33.4%)
– Proteinuria <1 g/day	7 (53.8%)	1 (33.4%)
– improvement of eGFR	2 (15.4%)	0 (0%)
Biopsy:		
– crescents in biopsy	8 (61.5%)	0 (0%)
– MPGN	9 (69.2%)	0 (0%)
– MES	2 (15.4%)	3 (100%)
– MGN	2 (15.4%)	0 (0%)

Table 3

	Mean eGFR ml/min (range)	Mean Proteinuria g/day (range)	Crescents	ESRD
MPGN (n = 9)	53.5 (5.7–103.3)	7.8 (0.5–12.75)	7 (77.8%)	3 (33.3%)
MES (n = 5)	28.6 (23–45.1)	7.98 (0.88–15)	1 (20%)	3 (60%)
MGN (n = 2)	80.5 (67.8-93.2)	9.87 (1.34–18.4)	0 (0%)	0 (0%)

Conclusion: Fibrillary glomerulonephritis is a heterogeneous disease associated with significant risk of ESRD and mortality. Current treatment modalities are insufficient. The course of the disease may be influenced by the histological type of the glomerulonephritis. Randomized prospective trials are crucial to validate different treatment strategies.

2.2.

Passive smoking increases blood pressure in pre-school children

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Purpose: Passive smoking is associated with early arterial damage, arterial stiffening and increased arterial pressure in adults. Parents smoking at home are mostly responsible for children's exposure to tobacco smoke. The influence of passive smoking on blood pressure in childhood has not been studied so far. We aimed to analyze the influence of passive smoking on blood pressure in a large cohort of pre-school children.
Methods and materials: As part of a screening project, blood pressure, BMI and fat mass were determined in 4237 pre-school children (5.7 ± 0.4 years) and other potential preventable risk factors (e.g. parental smoking habits) were documented.
Results: Smoking was reported by 28.5% of the fathers and 20.7% of the mothers, by both parents in 11.9%. Significantly higher systolic (+1.0, 95% confidence interval +0.5 to +1.5 mm Hg, p <0.0001) and diastolic (+0.5, 95% confidence interval +0.03 to +0.9 mm Hg, p <0.02) blood pressure values were observed in children of smoking parents. In a multivariate analysis passive smoking independently influenced systolic blood pressure (p = 0.0004), increasing the risk to have a systolic blood pressure level of more than one standard deviation above the mean by 28% (95% confidence interval 10% to 50%).
Conclusion: Already in pre-school children, environmental factors like passive smoking or dietary habits play a crucial role in determining blood pressure level. Because blood pressure increase related to passive smoking may be only partially reversible after cessation of the exposure, the present data strongly emphasize the importance of implementing smoke-free environments for children at home and in public places.

2.3.

Effect of sodium loading/depletion on renal oxygenation in young normo- and hypertensive men measured with bold-MRI

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Purpose: To measure renal tissue oxygenation in young normo-and hypertensive volunteers under conditions of salt loading and depletion using blood oxygen level dependent magnetic resonance imaging (BOLD-MRI).
Methods and materials: Ten normotensive (NT) male volunteers (age 26.5 ± 7.4 y) and eight non-treated, hypertensive (HT) male subjects (age 28.8 ± 5.7 y) were studied after one week on a high salt (HS) regimen and again after one week on a low sodium diet (LS).
On the 8th day, BOLD-MRI was performed under standard hydration conditions. BOLD-MRI is a non-invasive method that uses deoxy-hemoglobin as an endogenous contrast agent.
Deoxyhemoglobin is a paramagnetic molecule that induces magnetic field perturbations, thus leading to a faster signal attenuation in gradient echo T2*-weighted sequences. Acquisition of MRI images with increasing echo times allows computation of their regression with the logarithm of the signal. This slope is an estimate of the relaxivity R2*, defined as 1/T2*, and related to the concentration of deoxyhemoglobin. Hence, high local R2* value corresponds to high local deoxyhemoglobin concentration and thus to low local pO_2 level. In our study, four coronal slices were selected in each kidney, and combination sequence was used to acquire T2* weighted images. We measured the mean R2* (1/T2*) to determine cortical and medullar oxygenation.
Results: Baseline characteristics and their changes are shown in the table. The mean cortical R2* was not different under conditions of HS or LS (17.8 ± 1.3 vs. 18.2 ± 0.6 respectively in NT group, p = 0.27; 17.4 ± 0.6 vs 17.8 ± 0.9 in HT group, p = 0.16). However, the mean medullary R2* was significantly lower under LS conditions in both groups (31.3 ± 0.6 vs 28.1 ± 0.8 in NT group, p <0.05; 30.3 ± 0.8 vs 27.9 ± 1.5 in HT group, p <0.05), corresponding to higher medullary oxygenation as compared to HS conditions, without significant changes in hemoglobin or hematocrit values. The salt induced changes in medullary oxygenation were comparable in the two groups (ANOVA, p = 0.1).

Normotensive group (N = 10)	Baseline (±SD)	High Salt	Low Salt	p-value
Body Weight (kg)	77.9±12.8	78.4±13.1	77.4±13.2	0.072
SBP (mm Hg)	124.6±8.0	121.9±5.6	118.8±4.9	0.093
DBP (mm Hg)	66.7±7.0	66.7±7.8	65.4±4.9	0.45
24h urinary volume (ml)		2442±903	1780±683	0.047
24h urinary sodium (mmol)		328±96	20.2±14	<0.005
Hypertensive group (N = 8)				
Body Weight (kg)	80.8±17.6	81.8±17.4	80.9±17.8	0.045
SBP (mm Hg)	141.8±6.7	140.9±9.6	136.3±8.5	0.026
DBP (mm Hg)	91.9±4.5	85.0±11.9	83.6±12.3	0.39
24h urinary volume (ml)		2036±952	1718±826	0.45
24h urinary sodium (mmol)		239±126	76.8±87	<0.005

Conclusion: Dietary sodium restriction leads to increased renal medullary oxygenation compared to high sodium intake in normo- and hypertensive subjects. This observation may in part explain the potential renal benefits of a low sodium intake.

2.4.

Is it appropriate to index glomerular filtration rate for body surface area

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Purpose: Obesity is an established independent risk factor for chronic kidney disease. Thus, measurement of glomerular filtration rate (GFR) is important in this population. Traditionally, GFR has been indexed for body surface area (BSA), but this indexation may not be appropriate in obese individuals. Therefore, the objective of the study was to compare absolute GFR with GFR indexed for BSA and with GFR indexed for height.

Methods and materials: The study was conducted in 66 families from the Seychelles islands that included several members with hypertension. GFR and effective renal plasma flow (ERPF) were measured using inulin and PAH clearances, respectively. Antihypertensive treatment, if used, was withheld 2 weeks before conducting the clearances. Participants with diabetes mellitus were excluded from the analysis. BSA was calculated using the Dubois formula. We assessed trend across BMI categories using a non parametric test.
Results: Participants included 174 women and 127 men. The prevalence of hypertension was 61%, of which 68% were treated. The table shows that absolute GFR, GFR indexed for height, ERPF, filtration fraction were significantly higher across BMI categories. When GFR was indexed for BSA, the association between GFR and BMI categories was lost.

Table 1
Renal hemodynamic variables by BMI categories

	BMI <25 kg/m²	BMI 25–29 kg/m²	BMI ≥30 kg/m²	P trend
N	97	108	96	
Age (years)	42(36;51)	45.5(37;53)	45.5(38;54.5)	<0.05
BMI (kg/m²)	22.4(20.8;23.6)	27.3(26.2;28.3)	33.3(31.3;36)	<0.001
GFR (ml/min)	99(82;117)	110(94;128)	117(99;151)	<0.001
GFR (ml/min/ 1.73 m²)	100(89;118)	103(91;119)	105(87;125)	0.32
GFR (ml/min/m)	100(87;114)	112(98;129)	124(105;149)	<0.001
ERPF (ml/min)	424(331;521)	462(370;539)	477(372;578)	0.01
Filtration fraction	0.23(0.21;0.26)	0.24(0.22;0.27)	0.25(0.24;0.28)	<0.001

Conclusion: Indexing GFR for BSA in overweight and obese individuals leads to a substantial underestimation of GFR. Filtration fraction, which does not depend on BSA, is higher in obese individuals, which suggests glomerular hyperfiltration. Indexing GFR for BSA therefore would mask the underlying glomerular hyperfiltration. As the number of nephrons does not increase with weight gain, absolute GFR represents a better marker of single nephron GFR and is more appropriate.

2.5.

Anti-VEGF treatment accelerates progression of polycystic kidney disease in the Han:SPRD rat

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Purpose: Polycystic kidney disease (PKD) is characterized by the development of innumerable cysts, which lead to progressive kidney enlargement, and subsequent loss of renal function. The formation of cysts is associated with new vessel formation and enhanced expression of vascular endothelial growth factor (VEGF) and VEGF receptors, suggesting that angiogenesis is an important factor in cystogenesis. Here we examined the effect of anti-VEGF antibody treatment on the cystic kidney disease progression in a rat model for PKD.
Methods and materials: Four-week-old male heterozygous cystic (Cy/+) and wild-type normal (+/+) Han:SPRD rats were administered the anti-VEGF antibody B20.4.1 (5 mg/kg) or control IgG twice a week intraperitoneally for a total of 5 weeks. BUN and serum creatinine were monitored throughout the study to assess renal function. At week 10, the rats were sacrificed and kidney weights were measured to calculate the 2 kidney/total body weight (2K/TBW) ratio. Furthermore, histological changes and cyst volume density (CVD) were determined in both groups.
Results: A 5-week treatment with B20.4.1 caused an increase in total kidney weight by 57% and a >2 fold increase in the 2K/TBW ratio. CVD increased in Cy/+ by 97 % in the anti-VEGF treated group in comparison to the control group. Compared to IgG treated Cy/+, anti-VEGF treatment worsened the decline of renal function, as serum creatinine and BUN were 84% and 85% higher, respectively. Anti-VEGF treatment increased markedly the urinary protein excretion and reduced body weight in +/+ and Cy/+ rats. Fragmentocytes were not detected in the peripheral blood smear.
Conclusion: Anti-VEGF treatment caused an unexpected acceleration of cystic kidney disease progression in the Han:SPRD rat model. The augmented urinary protein excretion reflects glomerular damage caused by the inhibition of VEGF-mediated glomerular homeostasis.

2.6.

Isolated postural proteinuria associated with left renal vein entrapment: Results of a 6- or-more-year follow-up evaluation

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Purpose: Imaging studies, mostly renal ultrasonic imaging and Doppler flow scanning, demonstrate entrapment of the left renal vein in the fork between the aorta and the proximal superior mesenteric artery in most subjects with fixed and reproducible isolated postural proteinuria, a benign condition that resolves spontaneously. It has been therefore postulated that partial obstruction to the flow in the left renal vein in the upright position is a major cause of this form of proteinuria.
Methods and materials: To further address the role of left renal vein entrapment, we reassessed 13 subjects (8 female and 5 male subjects aged between 12 and 24, median 20 years) with postural proteinuria associated with anterior left renal vein entrapment ≥6 years after the initial diagnosis.
Results: Blood pressure, renal function, microscopic urine sediment analysis and supine protein excretion ratio were normal in the subjects. Upright protein excretion was normal in 9 and still pathologically increased in the remaining 4 subjects. Renal ultrasonic imaging and Doppler flow scanning failed to demonstrate left renal vein entrapment in the 9 subjects without persisting postural proteinuria and in 1 subject with persisting postural proteinuria. Persisting left renal vein entrapment was noted in the remaining 3 subjects with persisting postural proteinuria.
Conclusion: The present analysis provides substantial further support for entrapment of the left renal vein by the aorta and the superior mesenteric artery as a common cause of isolated postural proteinuria.

Oral Presentations – Transplantation

3.1.

Preformed donor-specific antibodies with a high strength are the best predictor for antibody-mediated kidney rejection

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Purpose: Detection of donor-specific anti-HLA antibodies (DSA) with single antigen beads (SAB) has markedly improved the assessment of sensitized renal allograft recipients. However, the relevance of preformed DSA by SAB to predict posttransplant outcome remains controversial. Luminex cross-match (LXM) testing is a new technique to measure sensitization against a given donor and may help to identify relevant DSA prior to transplantation. The aim of this study was to assess sensitivity, specificity and positive and negative predictive values (PPV, NPV) of pretransplant LXM, FACS cross-match (FXM) and DSA strength by SAB for renal allograft rejection within the first year post-transplant.
Methods and materials: All recipients of a living donor kidney in Zurich and Geneva between 2005 and 2007 were screened for the presence of HLA antibodies by Luminex or ELISA. In positive patients, FXM and LXM were performed retrospectively and the specificity and strength (mean fluorescence intensity, MFI) of anti-HLA antibodies were determined by SAB. The tests were then correlated with occurence of antibody-mediated rejection (AMR) and allograft outcome in the first year post-transplant.
Results: The main findings are the following: (i) pretransplant DSA against class I (DSA-I), but not against class II, are predictive for AMR; (ii) with increasing strength of DSA-I, the sensitivity is decreasing and the specificity is increasing; ROC-curve analysis yielded a maximum accuracy at 900 MFI (iii) the LXM for class I (LXM-I), but not for class II, provides a higher accuracy than the FXM and B-cell CXM (in the context of a negative T-CXM), and the specificity of all XMs is greatly increased in combination with DSA-I values above 900 MFI. For T-cell mediated rejection (TMR), none of the tests was predictive. In detail, our results are as follows: DSA-I (measured by SAB) with 900 MFI or more predict an AMR with a sensitivity of 75% and a specificity of 90%. DSA-I with 5,200 MFI or more result in a sensitivity of 50% and a specificity of 100%. The LXM-I has a sensitivity of 57% and a specificity of 85%. A positive LXM-I and concomitant DSA >900 MFI deliver a sensitivity of 57% and a specificity of 96%, leading to a PPV of 80% and a NPV of 90% for AMR in our sensitized population. The mean decline of creatinine clearance (estimated by Cockroft-Gault) after one year was 11 ml/min (14%) in all patients, and in patients with AMR 24 ml/min (26%; p = 0.027), in patients with TMR 13 ml/min and in patients without any rejection episode 7 ml/min. Patients with DSA-I >900 MFI had a significantly higher GFR decline of 21 ml/min (23%; p = 0.025).

Conclusion: The best prediction of AMR and consecutively graft function in a T-CXM negative population is delivered by the SAB test alone or by SAB in combination with the LXM. Both, the SAB test and the LXM, are only valid for HLA class I. The decision to transplant or not should not be based solely on a binary XM result, but the clinician should use SPA assays, that provide greater sensitivity for detecting DSA and a semiquantitative analysis to enhance the interpretation of XM results. These tests together with patient's clinical data must be integrated into the decision algorithms for performing a given transplant or not and for guiding immunosuppressive treatment and strategies for desensitization.

3.2.

Outcome of kidney grafts from pediatric donors younger than three years

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Purpose: Renal transplantation from pediatric donors younger than three years is compromised by a high risk for early vascular and urological complications limiting their wide use for adult allograft recipients. The aim of this single-centre retrospective study was to analyze transplantation-related complications, graft function and survival from pediatric donors <3 years of age.
Methods and materials: All transplantations from donors <3 years performed within the last five years were included in the analysis.
Results: Sixteen of 171 deceased donor renal transplantations (9.4%) performed within the last five years were from donors <3 years of age. Donors had a median age of 16 mo (range: 5–34 mo), recipients of 52 years (range: 22–72 yrs). Thirteen were solitary renal allograft and three en-bloc. Two of 16 patients (13%) lost their graft in the early postoperative period. One as a result of arterial thrombosis (en-bloc allograft from 9 month old donor) and one with early humoral rejection and subsequent vascular thrombosis. Two more patients required additional surgery in the early postoperative period. After a median follow-up time of 26 months (range: 9–66 mo), 14 of 16 patients have a well functioning graft with a median serum creatinine of 84 mmol/l (range: 30–160 mmol/l) and a median estimated CrCl by using the Cockroft-Gault formula of 80.5 ml/min (range: 33–160 ml/min), respectively.
Conclusion: Renal transplantation from donors <3 years of age has an acceptable early loss and complication rate (i.e. 13% each) with excellent intermediate-term allograft function. To reduce early graft lost it is important to avoid immunological risks and apply appropriate surgical technics for en-bloc transplantation.

3.3.

Short-course thymoglobulin induction and steroid-free immunosuppressive regimen in renal transplantation

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Purpose: Optimal induction and maintenance immunosuppressive therapies in renal transplantation are still a matter of debate.Chronic corticosteroid usage is a major cause of morbidity but steroid-free immunosuppression (SF) can result in unacceptably high rates of acute rejection and even graft loss.
Methods and materials: We have conducted a prospective open-labelled clinical trial in the Geneva-Lausanne Transplant Network from March 2005 to May 2008. 20 low immunological risk (<20% PRA, no DSA) adult recipients of a primary kidney allograft received a 4-day course of thymoglobulin (1.5 mg/kg/d) with methylprednisolone and maintenance based immunosuppression of tacrolimus and enteric-coated mycophenolic acid (MPA). The control arm consisted of 16 matched recipients treated with basiliximab induction, tacrolimus, mycophenolate mofetil and corticosteroids. Primary endpoints were the percentage of recipients not taking steroids and the percentage of rejection-free recipients at 12 months.Secondary end points were allograft survival at 12 months and significant thymoglobulin and/or other drugs side effects.
Results: In the SF group, 85% of the kidney recipients remained steroid-free at 12 months. The 3 cases of steroids introduction were due to one acute tubulo-interstitial rejection occurring at day 11, one tacrolimus withdrawal due to thrombotic microangiopathy and one MPA withdrawal because of multiple sinusitis and CMV reactivations. No BK viremia was detected nor CMV disease. The 6 CMV negative patients who received a positive CMV allograft had a symptomatic primoinfection after their 6-month course valgancyclovir prophylaxis. In the steroid-based group, 3 acute rejection episodes (acute humoral rejection, acute tubulointerstitial Banff IA and vascular Banff IIA) occurred in 2 recipients, 3 BK virus nephropathies were diagnosed between 45 and 135 days post transplant No side effects were associated with thymoglobulin infusion.In the SF group, 4 recipients presented severe leukopenia or agranulocytosis and one recipient had febrile hepatitis leading to transient MPA withdrawal. Discontinuation of MPA was needed in 2 patients for recurrent sinusitis and CMV reactivations. Patient and graft survival was 100% in both groups at 12 month follow-up.
Conclusion: Steroid-free with short-course thymoglobulin induction therapy was a safe protocol in low-risk renal transplant recipients. Lower rates of acute rejection and BK virus infections episodes were seen compared to the steroid-based control group. A longer follow-up will be needed to determine whether this SF immunosuppressive regimen will result in higher graft and patient survival.

3.4.

Bcl-2 inhibition – a new concept to prevent rejection of solid organ allografts

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Purpose: ABT-737 is a small molecule inhibitor of antiapoptotic Bcl-2 proteins. It has shown proapoptotic activity against lymphomas, pancreatic cancer and small cell lung cancer and a beneficial effect on multiple animal models of autoimmunity. The safety profile of ABT-737 – and of the orally bioavailable counterpart ABT-263 – has been excellent in phase I clinical studies (moderate lymphopenia and thrombocytopenia). The modulation of lymphocyte apoptosis, which plays a pivotal role for the regulation and termination of any immune response, represents a novel approach to prevent rejection after solid organ transplantation. This study evaluated for the first time the effect of ABT-737 on allogeneic T cell responses in vitro and in vivo.
Methods and materials: In a first set of experiments the immunosuppressive potency of ABT-737 was tested in mixed lymphocyte reactions (MLR) in vitro and compared with established immunosuppressive drugs (cyclosporine, mycophenolic acid, everolimus and dexamethasone). To analyze alloantigen-specific responses, the BM3.3 T cell receptor (TCR) transgenic mouse (background CBA / H-2k) was used. The BM3.3 mouse expresses on CD8 T cells a transgenic TCR specific for the MHC class I molecule Kb (expressed on B6 mice), which can be stained with the monoclonal anti-idiotypic antibody Ti98. In these MLR cultures T cell activation (determined by CD25 surface expression), proliferation (determined by CFSE dilution) and apoptosis (determined by Annexin V staining) were analyzed by FACS during the different phases of T cell activation and differentiation. Furthermore cytokines production was measured by ELISA. In a second set of experiments, the effect of ABT-737 on different immune cells was tested in vivo after 5 days of daily i.p. injections of 50 mg/kg ABT-737. In order to check the selectivity of ABT-737 on alloantigen-specific T cells in vivo, we generated syngeneic bone marrow chimeras expressing the BM3.3 TCR only on a fraction of the total CD8 T cell population. These syn-chimeras were injected with ABT-737 or vehicle daily for 5 days after alloantigen-specific priming. Survival of BM3.3 cells was measured over the time.
Results: ABT-737 inhibits T cell activation, proliferation and cytokine production in the setting of an allogeneic stimulation in vitro. The comparison of ABT-737 with established immunosuppressive drugs gives interesting information about the involved immunosuppressive mechanisms: according to the three signal model of T cell activation, ABT-737 interferes neither with the signal 1-dependent initial T cell activation (as shown by cyclosporine) nor with the signal 3-determined induction of proliferation (as shown by mTOR inhibitors and mycophenolic acid). ABT-737 induces apoptosis of lymphocytes and its potency changes dramatically during the course of the immune response: alloreactive cells are very sensitive to ABT-737 before activation, become resistant after activation and become sensitive again during proliferation. ABT-737 induces lymphopenia in vivo: a significant absolute reduction of total lymphocyte numbers (B and T cells), but not of CD11b positive cells was observed in the spleen, and a significant reduction of relative T cell numbers in peripheral blood. When testing the effect of ABT-737 on alloantigen-specific T cells using the mentioned syn-chimeric mice, we found – similar to the in vitro experiments – that alloreactive T cells are ABT-737 relatively resistant during the full activation phase after priming. No significant side effects of this compound were observed.
Conclusion: ABT-737 efficiently suppresses allogeneic reactions in vitro. Its apoptosis induction effect seems to be selective on different cell populations in vivo and changes during the course of alloantigen-specific reactions in vitro and in vivo. Our preliminary data support the potential role of Bcl-2-inhibition as a new concept for induction therapy or maintenance immunosuppression after organ transplantation. Further experiments using a skin graft model are in progress.

3.5.

Non-invasive functional renal hemodynamic measurements by color-coded duplex ultrasound: A paired kidney analysis

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Purpose: Donor-related factors have a direct impact on renal hemodynamic and renal function in kidney transplants. We investigated if different non-invasive color-coded duplex ultrasound techniques used at present to estimate renal allograft blood flow are appropriate to detect a donor-related influence on transplant hemodynamics.
Methods and materials: 26 consecutive pairs of kidneys transplanted from the same donor to two different recipients were studied on average 2.8 years (range 0.7–5.5) after transplantation under standardized conditions. During the same ultrasound examination, we evaluated the mean renal resistance index of three different segmental arteries (RI) (see Bergmann et al. 2009) and the dynamic tissue perfusion intensity (PI) of sub-segmental cortical vessels by recording sonographic videos. For the latter purpose, PI was calculated by an innovative software algorithm using the color pixel video information of a predefined cortical region (see Scholbach et al. Transplantation 2005).
Results: Donor age was 53.9 years (mean; range 17–78), 48% were male. Recipient age at examination was 53.4 years (range 30–77). 50% were male. CIT was 10 hours (range 3 to 20), 86%were first transplants. RI was correlated with pulse pressure ($r = 0.64$; $p < 0.001$), recipient age ($r = 0.42$; $p < 0.03$) but not with transplant function expressed as estimated glomerular filtration rate (eGFR) or with PI. The results of a variance analysis between and within pairs of recipients are displayed in table 1. Renal transplant function of the recipient was dependent on donor-derived factors. We observed a donor-derived influence on cortical PI ($p = 0.03$), which was not seen for RI.

	mean square within pairs	mean square between pairs	r donor-derived	*p*
eGFR	328	800	0.42	***0.01***
S-Urea	21	50	0.39	***0.02***
tissue	0.15	0.32	0.35	***0.03***
perfusion intensity (PI)				
BMI	15	29	0.32	***0.04***
Transplant length	0.9	1.6	0.29	*0.06*
Resistance index (RI)	0.004	0.004	0.11	*0.3*
systolic blood pressure	345	322	–0.03	*0.6*

Conclusion: Intrinsic donor derived factors determine renal transplant function and renal hemodynamics, reflected by PI of cortical blood flow but not by RI of segmental arteries. Dynamic tissue perfusion intensity (PI) measured by color-coded duplex ultrasound is a promising new method to study non-invasively cortical blood flow in renal allografts.

3.6.

Extracellular matrix-related transcripts including MMP7 & TIMP1 are molecular markers of renal allograft acute rejection

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Purpose: Definition of acute renal allograft rejection (AR) markers is of diagnostic and therapeutic interest. Features of T cell-mediated AR are tubule-interstitial and vascular inflammation associated with excessive extracellular matrix (ECM) remodelling, regulated by metzincins, including matrix metalloproteases (MMP) and tissue inhibitors of metalloproteases (TIMP). Our study focused on microarray analyses of metzincins (METS) and metzincins and related genes (MARGS) in biopsies of renal transplant patients to identify molecular markers of AR.
Methods and materials: We investigated renal transplant biopsies either with AR (n = 10), borderline AR (n = 4), AR+IF/TA (n = 7) or normal histology (n = 20) by Affymetrix genechips. A selection of candidate genes was examined in more detail on mRNA and protein level by qRT-PCR of microdissected glomeruli and tubules and immunhistochemistry respectively. Furthermore, patient serum was analyzed by ELISA.
Results: Subsets of METS and MARGS icluding MMP-7 and TIMP-1, differentiated AR from borderline AR, AR+IF/TA and normal histology in a principal component analysis, revealed subcluster formation in AR+IF/TA cases and separated borderline patients. Furthermore, METS and MARGS expression correlated to histological Banff t- and i-scores. We established 2 AR classifier in our dataset, either based on METS (including MMP-7, TIMP-1) or on MARGS and confirmed their performance in 3 publicly available data-sets. Thirteen MARGS were significantly enriched in the AR patients of all 4 datasets including MMP-7, -9, TIMP-1, -2, thrombospondin-2 and fibrillin-1. Microarray results were confirmed for MMP-7, -9 and THBS-2 by RT-PCR of microdissected glomeruli / tubules and for MMP-2, -9 and TIMP-1 by immunohistochemistry. TIMP-1 and THBS-2 were also enriched in AR patient serum.
Conclusion: METS and MARGS were differentially regulated in AR. Especially MMP-7 and TIMP-1 represent molecular markers and potential therapeutic targets.

Oral Presentations – Dialysis

4.1.

Prolonged catheter survival in patients with acute kidney insufficiency on continuous renal replacement therapy using a less thrombogenic micropatterned polymer modification

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Purpose: Continuous renal replacement therapy (CRRT) has been increasingly used in critically ill patients with acute kidney insufficiency (AKI). One of the major properties that likely influence the catheter lifespan includes its inner surface specificity. We hypothesized that the improvement of blood-surface interaction by a reactive polymer film coating might reduce thrombogenic events in the vascular access device and subsequently lead to prolonged catheter survival in the clinical setting.
Methods and materials: We therefore compared, in a randomized single-blinded study, the clinical application of two temporary catheters (TCs): one standard double lumen catheter (sDLC – GamCath® (Gambro-Lund/Sweden)) and one surface modified catheter i.e. micropatterned structure in a polymer system (smDLC – GamCath Dolphin® Protect) with identical geometry and flow design. Anticoagulation and platelet anti-aggregation were allowed. Efficacy endpoints were defined as the ability to complete 72-h CRRT without interruption due to TCs dysfunction and ability to achieve blood flow rates of ≥150 mL/min. Safety endpoints were defined as the occurrence of infection or bleeding.
Results: We evaluated 236 critically ill patients with AKI on CRRT (CVVHDF) with mean ± SD age of 56.5 ± 18.3 y. Total ultrafiltrate was 18.4 ± 6.7 liters, for 3.2 ± 2.5 liters/d. The clinical investigation revealed that the number of hours before TCs removal according to clinical requirements was significantly higher with smDLC as compared with sDLC (116 ± 38 vs. 92 ± 27 hours; $p = 0.004$). The blood flow rate was 221 ± 29 mL/min vs. 187 ± 36 mL/min for smDLC and sDLC; $p = 0.01$. TC malfunction occurred in 11% and 24% for smDLC and sDLC; $p = 0.001$. Thrombosis of smDLC and sDLC was observed in 3.2 (2.7 episodes per 1,000 UCT days) vs. 7.1% (4.2 episodes per 1,000 UCT days); $p = 0.001$. There was a significant difference in local infection rate as observed ($p = 0.002$).
Conclusion: Micropatterned surface coating with a polyurethane polymer significantly increased TC survival with lower dysfunction rate and better bacteriological barrier than sDLC in critically ill patients with AKI necessitating CRRT.

4.2.

S. aureus infections in hemodialysis patients: role of hygiene measures

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Purpose: Patients with end-stage renal disease have an increased risk for *Staphylococcus aureus* (SA) nasal carriage. Nasal carriage is a recognized risk factor for the development of an endogenous SA-infection and SA-bacteremia. It is also known that health care workers can transmit SA to patients, especially through hand contact. There are different approaches to the avoidance of SA-infections in hemodialysis patients. We investigated whether the rates of non-bacteremic SA-infections and SA-bacteriemias could be reduced through hygiene measures alone in the hemodialysis unit.
Methods and materials: From 2000 to 2008, a yearly swab test for

the nasal carriage of SA was taken from all hemodialysis patients. No eradication therapy was undertaken in any SA carrier. As from the beginning of 2004, we intensified hygiene measures (hand-disinfection, sterile gloves and masks for puncture procedure and citrate lock-solution for catheters) on the unit. The incidence of SA-infections and SA-bacteremias for the periods before and after instoring these hygiene measures was evaluated.
Results: The rate of SA nasal carriage ranged from 24.3% in 2000 to 34.1% in 2004 and 17.9% in 2008.

The table shows the rate of SA infections/bacteremias:

	2000–2003 (n = 133)	2004–2008 (n = 167)	P-value
Patient-months (pts-mo)	3222	4530	
SA-Infections per 100 pts-mo	0.962 (31/32.2)	0.508 (23/45.3)	0.025+
SA-bacteremias per 100 pts-mo	0.186 (6/32.2)	0.088 (4/45.3)	0.336*

+ Chi-square test, * Fisher's exact test

Conclusion: SA-infections and -bacteremias decreased after intensifying the hygiene measures. Thus, hygiene measures alone can diminish SA-infections and -bacteremias in patients undergoing hemodialysis.

4.3.

Which clinical and biochemical factors affect quality of life in maintenance hemodialysis patients?

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Purpose: Hemodialysis (HD) treatment is associated with high morbidity and mortality, thus, quality of life (QoL) is invariably low in this population. However, the factors which determine QoL and there interrelation are incompletely understood. The aim of this study was to assess the characteristics of a Swiss HD cohort with regard to both their physical and mental QoL.
Methods and materials: The study population consists of a total of 122 patients participating in the *monitor!* trial, a prospective dynamic hemodialysis cohort study assessing a wide range of clinical, laboratory and anthropometrical parameters. A baseline assessment including the assessment of the physical and mental QoL, applying the respective SF-12 instruments (KDQOL-SFTM) was performed at time of inclusion into the *monitor!* cohort, which continuously occurred between summer of 2006 and winter of 2008. Medical charts of all study participants were reviewed in July 2009 including living status and hospital days since inclusion into the cohort. Patients were stratified by the median of the physical and mental composite of the SF-12 QoL instrument at time of inclusion into the study and analyzed for their clinical and biological baseline characteristics as well as for living status and cumulative length of hospital stay during follow-up.
Results: Results are given as mean ± SDV for subgroups stratified by the median of either the physical or mental composite of the SF-36 QoL questionnaire.

	QoL Physical Composite			QoL Mental Composite		
	Low	High	P	Low	High	P
N	66	66	–	65	67	–
Age, yr	69.4±11	63.5±15	**0.012**	68.2±13	64.7±14	0.139
Alive, %	73.8	82.5	0.287	80.0	76.2	0.672
Hospital days, n	15±20	9.4±21	0.123	13.1±19	11.3±22	0.606
Dry weight, kg	69.7±14	76.7±17	**0.031**	70.1±13	75.5±17	**0.037**
Lean body mass, kg	44.7±9	51.5±9	**0.002**	46.5±8	49.9±9	0.077
Body mineral mass, gr	1858±649	2226±690	**0.012**	2018±508	2078±862	0.684
3 min walk, m	172±86	198±56	0.053	170±69	201±73	**0.018**
24-h step count, n	4767±5743	8522±8822	0.017	4939±6551	8269±8273	**0.035**
Hb, g/dl	12.3±3	12.7±1	0.352	12.5±3	12.5±1	0.885
Phosphate, mM/L	1.62±0.4	1.72±0.4	0.172	1.67±0.4	1.68±0.4	0.872
PTH, ng/L	270±265	278±248	0.869	291±264	257±248	0.444
25-OH Vit. D, µg/L	17.1±12	25.0±21	0.026	17.5±11	24.0±20	0.063
Albumin, g/L	40.3±4	41.3±3	0.130	40.4±4	41.2±4	0.273
CRP, mg/L	8.1±9	5.5±6	0.053	7.9±9	5.8±6	0.125
IL-6, ng/L (<3.3)	10.8±13	6.2±5	**0.007**	10.3±13	6.7±5	**0.033**
Cupper, µmol/L (12–24)	17.6±4	15.4±3	**0.000**	17.4±3.9	15.6±3	**0.005**
Selenium, µmol/L (0.89–1.9)	0.64±0.2	0.76±0.3	**0.009**	0.64±0.2	0.76±0.3	**0.009**
NT-pro-BNP, ng/L (<400)	14564±17720	9557±15200	0.092	12645±16293	11622±17078	0.726
QoL, *physical composite* (>50)	14.2±14	45.2±7	**0.000**	18.3±19	40.7±11	**0.000**
QoL, *mental composite* (>50)	25.4±26	52.9±9	**0.000**	20.7±21	57.1±5	**0.000**

Bivariate correlation analysis revealed significant associations between both physical and mental QoL with age (neg.), lean body mass, mineral mass, endurance (3 min walk, step count), 25-OH-Vit. D, selenium and cupper. In addition physical and mental QoL are highly correlated to each other.
Conclusion: Higher body weight and whole body mineral content are significantly associated with better physical QoL. This may result in better endurance, as reflected by higher step count. In addition, patients with better physical QoL have significantly higher serum 25-OH-Vit. D concentrations, which may be causally interrelated and be a factor for higher bone mineral mass in this group. Trace elements, such as selenium, may be associated with physical QoL, and seem to be rather low in the analyzed population of maintenance HD patients. Mental QoL is clearly associated with factors determining physical status and capacity. Not surprisingly, physical and mental QoL are highly correlated with each other. Further analysis of these data will have to assess causal interrelationship between aspects of quality of live and biological parameters in this HD cohort, including social factors.

4.4.

Hemoglobin levels and development of ESA dose in hemodialysis patients after conversion to C.E.R.A. A multicenter observational study

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Purpose: In December 2007 C.E.R.A. (Methoxy-polyethylenglycol epoetin beta) was introduced to the Swiss market. C.E.R.A. allows to treat patients on hemodialysis in a monthly interval. In the EIRA study (**E**xtended Dosing **I**ntervalls in Therapy of **R**enal **A**nemia) we analyzed data of dialysis patients treated with erythropoesis stimulating agents (ESA) over a period of 12 months to gain knowledge about treatment patterns and efficacy as well as cost effectiveness in Swiss patients.
Methods and materials: Multi centre, prospective observational study performed in 34 Swiss dialysis centers. Patients demographics, hemoglobin values, iron parameters, CRP and kt/V values were collected in three questionnaires at baseline, month 6 and 12 for patients that were treated with an application interval of ESA of at least 4 weeks duration. Iron status, course of hemoglobin values and the development of ESA dose as well as development of treatment cost according to Swiss list prices were evaluated. Here we present the intermediate analysis at month 6.
Results: Over a recruitement period of 6 months 205 patients were included into the study. Patients sex was 58% male and 42% female. Mean Age of patients was 65.2 years (range 25–95). 185 (90%) patients were treated with hemodialysis and 20 patients (10%) with peritoneal dialysis. In the month before data collection started 137 patients were treated with epoetin beta, 25 with epoetin alfa, 34 with darbepoetin alfa and 5 with C.E.R.A.. 4 Patients were ESA naive. At month 6 184 patients remained in the study. Four patients remained on darbepoetin alfa at month 6, all others were switched to C.E.R.A. at baseline. The mean hemoglobin value of patients was stable throughout the observation period (11.7 at baseline vs. 11.61 month 6; p = 0.95). Before conversion mean doses of epoetin alfa and beta combined were 39151 ± 29912 IU/month and for darbepoetin 207 ± 165 µg/month. In patients treated with C.E.R.A. doses remained stable during the 6 month observation period (163 µg month 1 vs. 160 µg month 6). In patients switched from other ESA monthly average cost of ESA treatment declined from CHF 759 to CHF 650 under C.E.R.A. (p = 0.04). In 148 patients complete data on iron status at BL and month 6 was available. While ferritin levels did not significantly differ between BL and month 6 (376 ng/ml vs. 444 ng/ml; p = 0.1), transferrin saturation was significantly higher at month 6 (26% vs 29%; p = 0.01). The number of patients that did not reach one of the K-DOQI criteria for iron metabolism (Ferritin >200 ng/ml and Transferrin saturation >20%) was 46% at BL and increased to 33% at month 6.
Conclusion: Patients switched to C.E.R.A. from treatment with either darbepoetin alfa or epoetin alfa/beta maintained stable hemoglobin values in the first 6 month after conversion. After the switch cost of ESA treatment decreased by 14%. Analysis of iron parameters revealed room for improvement in iron replacement therapy that might further decrease cost of treatment.

4.5.

The DIA-PAIN Study: cause, severity and management of pain and correlated symptoms in chronic dialysis patients

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Purpose: Although dialysis sustains life, underlying systemic diseases and painful syndromes persist. Little is known about the epidemiological characteristics of pain and their correlated symptoms

in chronic dialysis patients. In addition, objective data about the appropriate management of pain in this population are missing. The aim of the study is to analyze the incidence, causes, severity of pain and the strategy of pain management in long-term dialysis patients. The secondary aim of the study is to measure the incidence and severity of pain-correlated symptoms and the overall impact of the burden of symptoms in the patient's daily life.
Methods and materials: All patients on haemo- or peritoneal-dialysis, treated in study-affiliated nephrology units in Southern Switzerland and able to converse and complete a questionnaire in Italian, gave consent to be included in an observational, prospective, cohort, multicentre study. Ethics approval was obtained by a local committee. A chart review was conducted by the investigators of each nephrology unit to collect demographic and clinical data. Patients were interviewed in a multidimensional approach, evaluating pain and pain-related symptoms using a detailed questionnaire based on the *"Brief Pain Inventory"* (BPI) and the *"Edmonton Symptom Assessment System" (ESAS)* duly modified for patients in chronic dialysis. Activities in daily life were assessed. The interviews were conducted in hospital or the home setting, face-to-face by a trained study nurse from the Palliative Care Service.
Results: From October 2008 to January 2009, 168 patients were tested for eligibility. 123 were interviewed. Data were analyzed by the Institute of Communication and Health (ARCHE). Incidence of pain was 66%. Intensity, type, localization and treatment of pain and pain-associated symptoms were represented. Strong interference with daily activities has been demonstrated and some major risk factors in the development of pain during dialysis therapy has been identified.
Conclusion: The severity of symptoms in dialysis patients is equal in magnitude to that of many populations of cancer patients and patients with HIV. Pain assessment and management according to the WHO guidelines is mostly inadequate, leading to undertreatment of patients. Identification of risk factors and instauration of adequate algorithms of analgesic prescription should be a major target of nephrology units in improving symptom management in chronic dialysis patients.

4.6.

Increasing B-Type natriuretic peptide levels predict mortality in unselected hemodialysis patients – the cardiorenal syndrome type IV

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Purpose: Cardiac disease is the major cause of death in patients undergoing chronic hemodialysis. Recent studies have found B-type natriuretic peptide (BNP) levels to accurately mirror the cardiovascular burden of dialysis patients. However, the prognostic potential of BNP measurements in dialysis patients remains unknown.
Methods and materials: Enrolment included 113 chronic dialysis patients who were prospectively followed-up. BNP levels were measured at baseline and six monthly thereafter. The potential of baseline BNP and annual BNP changes to predict all-cause and cardiac mortality were assessed as endpoints.
Results: Median follow-up was 735 [354–1459] days. 35 (31%) patients died, 17 (15%) of them from cardiac causes. Baseline BNP levels were similar among survivors and non-survivors and failed to predict all-cause and cardiac death. Cardiac death was preceded by a marked increase in BNP levels. In survivors BNP levels remained stable (median change preceding cardiac death: +175% [+20 ± 384%] vs. –14% [–35 ± 35%] in survivors over the 18 months preceding either death or the end of follow-up, p <0.001). Hence, annual BNP changes adequately predicted all-cause and cardiac death in the subsequent year (AUCall-cause = 0.70 [SD 0.05, 95%CI (0.60–0.81)]; AUCcardiac = 0.82 [SD 0.04, 95%CI (0.73–0.90)]. A BNP increase of 40% provided the best cut-off level. Multivariate Cox-regression analysis confirmed that annual increases over 40% powerfully predicted all-cause (OR 6.77(95%CI 1.44–31.82), p = 0.015) and cardiac (OR 6.84 (95% CI 1.48–31.72), p = 0.014) mortality within the consequent year.
Conclusion: Annual BNP increases above 40% strongly predicted all-cause and cardiac death in the subsequent year. Hence, serially measuring BNP levels may present a novel tool for risk stratification and treatment guidance of ESRD patients on chronic dialysis.

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Recombinant human erythropoietin prior to cardiac surgery: does it prevent acute kidney injury?

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Purpose: Recombinant erythropoietin has pleiotropic actions and has been found to be nephroprotective in animal models submitted to ongoing renal ischemic injuries. We implemented a pilot study aiming to assess the effect of two single doses of a-epoetin on renal function in patients having cardiac surgery.
Methods and materials: From June 08 to June 09, 80 patients having cardiac surgery were randomised to receive either 40000 IU a-Epoetin (n = 20) or 20000 IU a-epoetin (n = 20) or a normal saline injection after cardio-pulmonary bypass. To assess acute kidney injury, renal function was measured by serum creatinine and cystatin C and acute tubular injury was evaluated by urinary NGAL. Serum creatinine, cystatine C and urinary NGAL were measured prior to the injection and at 48 hours. This trial is registered at ClinicalTrials.gov, No NCT00676234
Results: Patient groups did not differ in terms of age, gender, comorbidities and baseline renal function. Mean baseline cystatine C was 1.22 (+0.36), 1.31(+0.37), 1,26 (+0.37) mg/l for control, 20000 and 40000 IU a-Epoetin groups respectively (ns). Mean baseline urinary NGAL were 21 (6-52), 41(17-61) and 9 (1-51) ng/ml for control, 20000 and 40000 IU a- Epoetin groups respectively (ns). At day 2, urinary NGAL were 29 (13-52), 16 (2-41) and 26 (3-59) ng/ml for control, 20000 and 40000 IU a-Epoetin groups respectively (ns). At day 2, 4 patients in the control group, 3 and 5 in the 20000 and 40000 IU a-Epoetin groups respectively, transiently decrease their renal function but there was no significant changes between the groups.
Conclusion: A single administration of either 20000 or 40000 IU a-Epoetin after cardiac surgery does change significantly at 48 hours neither urinary excretion of NGAL nor renal function decrease in patients with no baseline renal impairment. More studies are needed to better define whether recombinant erythropoietin has a protective effect in patients prone to AKI.

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Dietary fibre intake and the risk of CaOx stone formation

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Purpose: Insufficient intake of dietary fibre is currently regarded as a habit which might aggravate the risk of renal stone formation (RSF) by means of increased intestinal-hyperabsorption of Ca and hypercalciuria, or through insufficient K+ and alkali intakes resulting in hypocitraturia. On the other hand, whether high or even excessive dietary fibre intake holds a protective role or is a risk factor of RSF in itself is a matter for debate, since it has been suggested that a high fibre intake may limit the intestinal absorption of water by trapping water in the cellulose structure of the fibres.
Methods and materials: To address this issue, 84 consecutive idiopathic calcium stone formers (ICSF) investigated at our renal stone clinic were divided into 3 groups according to the mean daily intake of dietary fibre (DF) recorded over a 7-day survey by the patients on their free choice diet.
Results: The following differences were statistically significant

	Total fluid intake	Beverage intake	U-Volume	K-intake	U-K
	(l/d)	(l/d)	(l/24 h)	(g/d)	(mEq/24 h)
group 1: DF <15 g/d (n = 33)	2.71±0.18	2.14±0.17	1.75±0.14	2.16±0.09	65±3
group 2: 15 ≤ DF <22 g/d (n = 37)	2.85±0.16	2.16±0.15	2.09±0.14	2.74±0.08	68±3
group 3: DF ≥22 g/d (n = 14)	3.61±0.26	2.63±0.26	2.38±0.18	3.29±0.15	75±4
p<	<0.005(1v3) <0.01(2v3)	NS	<0.05(1v2) <0.005(1v3)	<0.0001 (1v2,1v3)	<0.05 (1v3)

The probability of CaOx stone formation (Psf CaOx) was >0.9 in 39% of the patients in group 1, 24% in group 2, and 29% in group 3.
Conclusion: At low fibre intake (<15 g/d), there is an increased risk of CaOx stone formation. With increasing DF intake over the range 15–32 g/d, urinary volume does not decrease; this is in agreement with a previous study on this topic over that particular range. From a previous work we know, however, that at higher intakes of fibre, urine volume would decrease and cause an increase in the Psf CaOx. Therefore DF intakes up to ca 30 g/d can be regarded as safe.

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Glomerular hyperfiltration and increased proximal sodium reabsorption in subjects with type 2 diabetes or impaired fasting glucose in a population of the African region

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Purpose: Glomerular hyperfiltration (GHF) is a well recognized early renal alteration in diabetic patients. The prevalence of GHF is largely unknown in populations in the African region with respect to normal fasting glucose (NFG), impaired fasting glucose (IFG) and type 2 diabetes (DM). This study assessed the prevalence of GHF in African subjects with and without type 2 diabetes who participated in a prospective family-based hypertension study.
Methods and materials: The cross sectional study was conducted in the Seychelles islands among members of families including at least one member with hypertension. Glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and renal sodium handling were measured using inulin-, PAH- and endogenous lithium clearances, respectively.
Results: The baseline characteristics of the 363 participants (mean age 44.7 years) are shown in the table. 6.6% had IFG, 9.9% had DM and 63.3% had hypertension. The prevalence of GHF, defined as a GFR >140 ml/min, was 17.2%, 29.2% and 52.8% in NFG, IFG and DM, respectively (P trend <0.001). Compared to NFG, the adjusted odds ratio for GHF was 1.99 (95% CI 0.73-5.44) for IFG and 5.88 (2.39–14.45) for DM. Lithium clearance and fractional excretion of lithium were lower in DM and IFG than NFG (P <0.001).

Covariable	Normal fasting glucose	Impaired fasting glucose	Diabetes	P
N	303	24	36	
Age (years)	44 (37; 53)	47 (39; 55)	49 (40.5; 62.5)	0.007
Sex (% female)	56	48	42	0.017
BMI (kg/m^2)	27.4 (23.8; 31.1)	28.5 (25.7; 31.7)	28.9 (25.8; 32.4)	0.205
Alcohol (g/day)	0 (0; 7)	0 (0; 13)	0 (0; 16)	0.045
Smoking (%)	13	8	8	0.925
Office MAP (mm Hg)	99 (90; 109)	105 (98; 113)	105 (99; 116)	<0.001
Serum potassium (mmol/L)	3.7 (3.6; 3.9)	3.7 (3.5; 4)	3.8 (3.7; 4)	0.139
PRA (ng/ml/h)	0.34 (0.15; 0.63)	0.44 (0.28; 0.61)	0.40 (0.13; 0.55)	0.740
Plasma aldosterone (pg/ml)	53 (43; 66)	58 (43; 80)	59 (46; 79)	0.159
Urinary sodium (mmol/24 h)	102 (67; 134)	86 (60; 127)	110 (77; 159)	0.177
Urinary potassium (mmol/24h)	41 (31; 51)	42 (30; 55)	51 (39; 72)	0.001
Urine volume (l/24h)	1.8 (1.2; 2.3)	2.0 (1.1; 2.7)	1.9 (1.3; 2.7)	0.193

Conclusion: In this population of African descent, subjects with impaired fasting glucose or type 2 diabetes had a high prevalence of GHF and enhanced proximal sodium reabsorption. These findings provide further insight on the elevated incidence of nephropathy reported among African diabetic individuals.

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Impact of specialised renal care in patients with chronic kidney disease stage 4–5: the implicate study

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Purpose: Chronic kidney disease (CKD) prevalence, and subsequent end stage renal disease (ESRD) is on the rise, particularly in patients older than 65 years. Despite constant improvements of renal replacement therapies (RRT), the morbidity and mortality of these patients remain high, There is therefore a need for the development and implementation of new strategies through collaboration between primary care physicians (PCP) and nephrologists. However, prior to the increase of medical resources devoted to renal care, assessment of the impact of specialised care in renal patients should be thoroughly evaluated.
Methods and materials: We started in July 2009 a prospective randomised trial studying patients with stage 3 to 5 CKD in order to determine the impact of specialised care by nephrologists compared to guidelines-directed management by PCP on: a) prognosis (clinical outcome), b) planning of RRT (urgent versus planned initiation RRT) and c) patient satisfaction. Patients with CKD stage 3, 4 and 5 (CCl <40 ml/min according to abbreviated MDRD formula) aged 18–80 years old and enrolled during a hospitalization will be randomised in two arms: – combined management PCP – nephrologists or management by PCPs only, with the help of written instructions. We are planning to enrol 400 patients during a 30 months period. Our primary (composite) endpoint will be: death, and hospitalisation during the 24 months after inclusion. Our secondary endpoints will be: initiation of urgent RRT, decline of renal residual function at 2 years, decline of quality of life. This trial is registered at ClinicalTrials.gov, No NCT00929760
Results: Interim results are awaited at the end of 2010.
Conclusion: Patients with CKD experience high morbidity and mortality, particularly when RRT has to be initiated urgently. Adequate management of patients with CKD stage 3–5 should improve survival of these patients but also decrease complications and cost of urgent initiation of RRT

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Telemetric blood pressure monitoring in hypertensive patients with renal insufficiency

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Purpose: Despite the wide choice of treatments available for the management of hypertensive patients, less than 30% of hypertensives have a normalized blood pressure (BP) and results are even worst for hypertensive patients with diabetes or renal diseases. Since morbidity and mortality derived from hypertension are strongly linked to the level of BP, the need to improve the quality of BP control is crucial. The goal of the present study was to investigate the clinical interest of a telemonitoring system to improve BP control in patients with chronic kidney diseases.
Methods and materials: Male and female hypertensive patients with renal insufficiency (Stage III or IV) and proteinuria having not achieved a normalized BP (<130/80 mm Hg) or experiencing adverse drug reactions (ADRs) requiring a modification of their antihypertensive treatment were enrolled in this telemetric BP monitoring program. A validated, automated self-measurement BP and heart rate (HR) monitoring device (Stabil-O-Graph; Stolberg, Germany [2]) and a balance were provided to each patient in combination with a modem to transfer the measured parameters to a central database. Participating physicians had a password protected access to all data of their patients. Patients were instructed how to use the Stabil-O-Graph, the balance and the modem (visit 1) and used the telemetric devices for approximately one month prior (visit 2) to the anticipated treatment modification. After treatment modification due to insufficient BP control and/or ADRs (add-on of lercanidipine or substitution of an antihypertensive drug by lercanidipine) the patients' BP, HR and weight were monitored by the telemetric device for 1 month (visit 3) and a subsequent follow up period of 3 months (visit 4). The system featured setting alerts for non-compliance on agreed measuring intervals, exceeding maximum and/or increased mean values.
Results: The telemetric system was used easily at home after instruction by the physician or a nurse and generated ambulant profiles of BP, PR and weight. Physicians' access to patient profiles was easy and quick and weekly/monthly generated reports allowed monitoring the outcome of any treatment modification. Setting the appropriate alerts needed some experience, and each of the patients required his/her individual alert profile. The majority of patients were comfortable using the systematic BP monitoring and confident being supervised by his/her physician, and the overall compliance was high. Preliminary results of first 24 patients showed a marked decrease of baseline systolic BP (149.0 ± 13.6 mm Hg) and diastolic BP (88.3 ± 10.8 mm Hg) of 11.6 and 7.0 mm Hg to a SBP and DBP of 137.4 ± 13.6 and 81.3 ± 9.2 mm Hg at visit 4 (p <0.05).
Conclusion: The current experience, although uncontrolled, indicated that telemetric systems may be useful for individual management of hypertensive patients and monitoring modifications of treatment regimens. Patients' confidence in the treatment regimen and compliance were positively affected resulting in a significant reduction of BP and increasing the chance to reach the BP targets recommended by international guidelines.

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Fetal exposure to angiotensin receptor blockers: outcome of two cases

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Purpose: The activity of the renin-angiotensin system plays an important role throughout embryologic development, especially for the maturation of the kidneys. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are contraindicated in pregnant woman because of serious and deleterious effects on fetal development including oligohydramnion, pulmonary hypoplasia, hypocalvaria, renal dysplasia, fetal death, postnatal renal failure and hypotension. There is a wide spectrum of manifestations ranging from fetal or early neonatal death to minor problems during the neonatal period associated with a possible favourable outcome.
Methods and materials: We describe two cases of fetal exposure to angiotensin receptor blockers in order to better understand the neonatal and childhood outcome.
Results: *Case A*: At 31 weeks of gestation a male boy was delivered by cesarian section because of maternal infection and anhydramnion.

During the whole pregnancy the 39-year old mother received candesartan cilexetil 16 mg daily for mild essential hypertension. Immediately after birth the child developed respiratory distress, arterial hypotension (requiring dopamine and epinephrin), oliguria (serum creatinine up to 281 µmol/l and urea up to 15.6 mmol/l) and a pathologically increased urinary protein to creatinine ratio of 739 mg/mmol. The physical examination disclosed limb contractures, skull hypoplasia with microcephaly and underdeveloped calvarian bones. The boy is currently 34 month of age with slightly elevated blood pressure values and normal kidney function. Renal ultrasound demonstrates small and hyperechogenic kidneys with loss of corticomedullary differentiation. His cognitive and especially his linguistic development is moderately retarded. *Case B*: At 35 weeks of gestation a 34-year old woman who received valsartan during the whole pregnancy delivered a boy, which presented an oligohydramnion. The newborn showed limb contractures, narrow chest and skull bone hypoplasia as well as neonatal arterial hypotension, anuria and enlarged hyperechogenic kidneys. Creatinine and urea increased up to 245 µmol/l and 11.1 mmol/l, respectively. Renal replacement therapy could be avoided and creatinine normalised within 14 days. At the age of 7 months, arterial hypertension was observed, requiring treatment with the calcium channel blocker amlodipine. Currently the boy is 12 month old, he has a well-controlled arterial hypertension with amlodipine 0.2 mg/kg, the kidney function is normal.
Conclusion: There are significant fetal risks associated with the use of ACEI and ARB at all stages of pregnancy. Long-term follow up of fetal exposure to ACEI/ARB revealed an impairment of renal function, development of arterial hypertension and neurocognitive deficits. Thus, careful and regular monitoring is mandatory in children with fetal exposition to angiotensin receptor blockers; women of childbearing age using ACEI or ARB should be advised about the fetal toxicity of these antihypertensive medications and switched to other drugs before or immediately after the conception.

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Elevated FGF-23 levels in patients with early stage ADPKD and normal GFR

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Purpose: Autosomal dominant polycystic kidney disease (ADPKD) is as a hereditary disorder which is characterized by progressive cyst formation, leading to chronic renal failure (CRF). Parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) are phosphaturic hormones that that play an important role in maintaining phosphate homeostasis in CRF. The purpose of the present investigation was to correlate PTH and FGF-23 levels with parameters of calcium and phosphate metabolism in ADPKD patients with normal or mildly impaired renal function (CKD stage 1-2).
Methods and materials: Intact PTH, FGF-23 (c-term form), calcium, phosphate and the urinary excretion of calcium and phosphate were determined in 100 ADPKD patients (mean age 31 years, 36% females) with preserved GFR (estimated creatinine clearance 119 ± 27 ml/min).
Results: Sixteen % of the patients had elevated PTH levels (mean 48.9 ± 1.6 pg/ml). Conversely, the mean FGF-23 levels were significantly above the normal range in 99% of the patients (mean 163 ± 33 RU/ml, normal range 0 to 125R RU/ml). Serum calcium (2.3 ± 0.3 mmol/l) and phosphate (0.9 ± 0.1 mmol/l) levels were in the normal range. The fractional excretion of calcium (0.7 ± 1.0%) and phosphate (14.6 ± 12.2%) were normal. FGF-23 levels were significantly associated with PTH (univariate correlation r = 0.221, p = 0.027). In the multivariate linear regression model, higher FGF-23 levels were significantly associated with higher PTH levels (Beta = 0.629, p = 0.010) independently of age, eCrCl, calcium, phosphate, and fractional excretion of calcium and phosphate.
Conclusion: We conclude that FGF-23 but not PTH levels are elevated in early stage ADPKD. The rise in FGF-23 levels might be an early predictor of abnormalities in the mineral metabolism of ADPKD patients with normal PTH levels and normal kidney function.

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Hemolytic-uremic syndrome in children living in Switzerland: a nationwide surveillance from 1997 to 2003

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Purpose: Hemolytic-uremic syndrome – characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal impairment – is a leading cause of acute renal failure in childhood. In its typical presentation, it is preceded by an episode of diarrhea mostly due to Shiga-like toxin-producing *Escherichia coli*. Multiple studies indicate important geographical variation in relation to clinical, epidemiological, and microbiological features. Beside some single centre studies, nationwide data on childhood hemolytic-uremic syndrome in Switzerland are not available.
Methods and materials: A prospective, national surveillance through the Swiss Pediatric Surveillance Unit from April 1997 through March 2003.
Results: One hundred-fourteen cases (median age 20.5, range 0–161 months; 50% boys) were reported by 38 pediatric units (annual incidence 1.42 per 105 children aged 16 years or less). Shiga-like toxin-producing E. coli were isolated in 60% of tested stool specimens, serotype O157:H7 in eight of them. Sixteen children presented with only minimal renal involvement, including three with the primary site of infection within the urinary tract. Twelve patients presented with atypical hemolytic-uremic syndrome, six of them due to infection with *Streptococcus pneumoniae*. Overall mortality was 5.3% (6/114), including two children with atypical hemolytic-uremic syndrome due to *Streptococcus pneumoniae*. The severity of thrombocytopenia significantly correlated with mortality.
Conclusion: Hemolytic-uremic syndrome is not rare in Switzerland, predominantly affecting children less than five years of age. Contrasting other countries, E. coli O157:H7 play only a minor role in the etiology. Incomplete manifestation with minor renal involvement is not uncommon and in some cases the primary site of the infection is located in the urinary tract. Severe thrombocytopenia seems to be associated with a bad outcome. The highest mortality (33%) is observed in *Streptococcus pneumoniae*-associated atypical hemolytic-uremic syndrome. Robust clinical, epidemiological and bacteriological data have been established through this prospective cross-sectional study using a national surveillance unit.

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NGAL and Cystatin C predict acute kidney injury in patients with acute decompensated heart failure

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Purpose: Acute kidney injury, defined as acute changes in serum creatinine, is associated with increased resource utilization and mortality in patients with acute decompensated heart failure. Unfortunately, serum creatinine increases lack behind the triggering kidney insult. Serum levels of neutrophil gelatinase-associated lipocalin (NGAL) and Cystatin C appear to be a novel specific biomarker for the early identification of acute kidney injury. The utility of serum NGAL and Cystatin C levels in acute decompensated heart failure is presently unknown.
Methods and materials: Enrolment included 87 consecutive ADHF patients presenting to the emergency department of the University Hospital Basel. NGAL and Cystatin C samples were collected at baseline and every six hours until 48 after admission. Serum creatinine values were collected at baseline, daily for four days following admission and at discharge. Acute kidney injury was defined as an absolute difference of at least 0.3 mg/dl between peak and admission creatinine values. The potential of admission and serial biomarker sampling to predict AKI were assessed as endpoints.
Results: Acute kidney injury occurred in 17 (20%) patients during the first three days and in 30 (35%) patients throughout the entire hospitalisation. Patients experiencing acute kidney injury were more likely to be diabetic and suffer from chronic kidney disease. Baseline NGAL and Cystatin C levels were similar among AKI and non-AKI patients and failed to predict in-hospital acute kidney injury. In contrast, NGAL and Cystatin C samples drawn 12 hours before the defining creatinine increase adequately predicted the occurrence of AKI compared to all biomarker samples drawn in non-AKI patients (AUCNGAL: 0.85 [SD 0.04, 95%CI (0.78–0.92)]; AUCCystatin 0.85 [SD 0.03, 95%CI (0.78–0.91)]. A NGAL level of 98.6 mg/l and Cystatin C level of 1.65 mg/l provided the best cut-off levels with sensitivities of 100% and specificities of 60% respectively. Multivariate Cox-regression analysis confirmed categorical and continuous NGAL (OR 1.01 (95%CI 1.01–1.02), p <0.001) and Cystatin C(OR 3.86 (95%CI 1.93–7.72), p <0.001) levels to independently predict AKI.
Conclusion: Serial NGAL and Cystatin C sampling powerfully predicts the occurrence of acute kidney injury in patients with acute decompensated heart failure.

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Acute Postinfectious Glomerulonephritis (APGN) versus Membrano-proliferative Glomerulonephritis Type I (MPGN-I) – Differentiation may be challenging

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Purpose: Differentiation between APGN and MPGN-I is important, particularly since APGN in paediatric patients is usually a self-limited disease. Renal biopsy in paediatric APGN is only performed in atypical cases. However, clinical and histological findings of both diseases sometimes overlap. In cases of endocapillary proliferative glomerulonephritides (GN) with subepithelial deposits (humps) – more typical for APGN - and concurrent subendothelial deposits – more

typical for MPGN-I, the differentiation may be impossible. The aim of the present study is to review 5 patients from Yerevan and 2 in Zurich with ambiguous initial findings.
Methods and materials: From Jan 2001 until June 2009 biopsies of native kidneys were performed in 248 (paediatric and adult) patients in Yerevan and in 254 paediatric patients in Zurich. Evaluation of Armenian patients was done by light microscopy (LM) in Yerevan and in Zurich by LM, electron microscopy and immuno-histochemistry (last 25 samples). During these 8½ years 14 patients (9 Yerevan; 5 Zurich) had histological diagnoses of APGN, and 12 (8 Yerevan; 4 Zurich) had MPGN-I, apart from the patients with overlapping features reported here.
Results: Five patients from Yerevan and 2 from Zurich had endocapillary proliferative GN showing overlapping histological features of both APGN and MPGN-I (humps and subendothelial deposits). All Armenian patients were male, aged 15–17 years except one (26 y.); those from Zurich were female, aged 11 and 12 yrs. Biopsies were performed within 2 months after initial presentation because of sustained nephritic symptoms, reduced renal function (4 of 7) and/or the nephrotic syndrome (5 of 7). Six patients had low C3 levels, two had repeat biopsies: One boy had advanced crescentic GN without deposits and one girl now showed MPGN-I in contrast to presumed APGN at first biopsy. All patients received ACE inhibitors, 6 had prednisolone and 1 cyclosporin A. At follow-up (½ to 4 years) one developed ESRF, one CKD IV, 4 had proteinuria and 1 was in full remission.
Conclusion: MPGN-I may occasionally present clinically as APGN. The course in 5 patients was compatible with MPGN-I. Histologically it may be difficult to differentiate between early MPGN-I and APGN in some cases of endocapillary proliferative GN. In these situations a close follow-up is required and occasionally a second biopsy, especially in patients with initial diagnosis of APGN with continuing clinical features or persistently low C3.

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Body composition monitoring by bioimpedance spectroscopy in children

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Purpose: Bioimpedance spectroscopy permits to quantitate the hydration status, lean and adipose tissue components. We used a novel bioimpedance spectroscopy device to assess body composition in children undergoing peritoneal dialysis (PD, n = 24, mean age 11.4), hemodialysis (HD, n = 24, mean age 16), after kidney transplantation (TPL, n = 40, mean age 15.4) or with chronic kindey disease (CNI, n = 44, mean age 15).
Methods and materials: Body composition was assessed using a bioimpedance spectroscopy device (BCM-Monitor, FMC). In children on HD, the measurement was performed before and 30 min after dialysis. Lean and fat mass were expressed by the Lean Tissue Index (LTI) and the Fat Tissue Index (FTI), and the hydration status as "fluid excess" relative to the fluid content of healthy children. Reference data were obtained in 607 healthy children and adolescents.
Results: Mean LTI was 12.6 ± 2.4 kg/m² for CNI, 12.6 ± 2.5 kg/m² for TPL, 13.2 ± 2.5 kg/m² for HD and 12.8 ± 2.4 kg/m² for PD children. Mean FTI was 5.6 ± 3.3 kg/m² for CNI, 7.3 ± 4.6 kg/m² for TPL, 6.1 ± 4.7 kg/m² for HD and 6.8 ± 4.4 kg/m² for PD children. The highest prevalence of children with insufficient amount of lean tissue and excessive amount of fat tissue was present in the group of transplanted children when compared to healthy children. FTI, but not LTI, displayed a strong linear relationship with BMI (r2 = 0.64, p <0.0001). Fluid excess was –0.2 ± 0.9 l (–1.5 ± 4.7% of body weight) in the PD patients and +1.0 ± 1.0 l (2.4 ± 2.3% of body weight) before HD sessions in the HD group. The measured difference in fluid excess before and after the hemodialysis session showed a strong linear correlation with the decrease in body weight during dialysis (r2 = 0.67, p <0.0001).
Conclusion: While a normal state of hydration was usually present, reduced lean tissue mass was detected in children with chronic kidney disease, in children undergoing dialysis and particularly in children after kidney transplantation. Bioimpedance spectroscopy using appropriate pediatric reference data may be a useful tool to identify subtle disorders of nutrition and fluid status in children on dialysis.

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Hypoventilation – a risk factor for modern version of Milk Alkali Syndrome

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Purpose: Milk alkali syndrome is a cause of hypercalcaemia, renal failure and alkalosis. It was originally described in patients ingesting large amounts of calcium containing milk for the treatment of peptic ulcer disease. Modern day version of the milk alkali syndrome is seen in patients with excessive intake of calcium carbonate containing antacid or calcium-supplementation for osteoporosis prophylaxis.
Methods and materials: n.a.
Results: We report a case of a 67-year-old woman who was admitted to our hospital due to progressive somnolence, nausea and vomiting, after dose elevation of an intrathecal morphine pump. After initial administration of naloxon consciousness did not improve. Blood tests showed severe hypercalcaemia (total calcium 4·68 mmol/l) and renal insufficiency with an estimated GFR by MDRD formula of 53 ml/min/1.75 m². Arterial blood gas analysis revealed primary respiratory acidosis (pH 7·32) with severe hypocapnia (pCO_2 10·8 kPa) and concomitant metabolic alkalosis (HCO_3 41 mmol/l). After treatment with sodium chloride 0.9% infusion, intravenous furosemide, and subcutaneous calcitonin, calcium normalized slowly and neurological symptoms disappeared. No evidence for malignancy associated hypercalcaemia, hyperparathyreoidism or hypervitaminosis D was found. Although the patient was treated with calcium sparing thiazide diuretics and calcium-supplementation for osteoporosis since two years, her serum calcium concentration remained normal until a few months before admission. Therefore an additional trigger emerged: Based on a known chronic hypoventilation syndrome, dose elevation of morphine, increased the compensatory renal bicarbonate generation which acted as a source for alkali, resulting in milk alkali syndrome with severe hypercalcaemia.
Conclusion: In contrast to the published historical and the modern version of the syndrome where ingested carbonate is the source of alkali, an equally important source of alkali in our case was the chronic compensatory elevation of bicarbonate due to hypoventilation which exacerbated after elevation of morphine administration.

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Prevalence of chronic kidney disease in Switzerland – Methodological aspects

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Purpose: Chronic kidney disease (CKD) is a progressive, irreversible loss of renal function over a period of months or years. CKD is associated with premature mortality, decreased quality of life, and increased health-care expenditures. The most common risk factors are cardiovascular disease (CVD), type 2 diabetes mellitus, hypertension, obesity, family history of CKD, and age above 60 years. Actually, prevalence data on the different CKD stages in Switzerland, in Europe and worldwide, defined by creatinine-based estimates of the glomerular filtration rate (GFR), are particularly limited. Early stages of CKD often remain unreported until they reach the most severe stage. Therefore, most information is available for end-stage renal disease (stage 5), which requires renal replacement therapy (dialysis or transplantation). The aims of the study are to evaluate the prevalence of CKD and CKD stages in the Swiss population, to evaluate the socioeconomic impact of CKD in Switzerland, to model future prevalence trends and relative costs, and to compare study results with data of cantonal laboratories.
Methods and materials: We will perform a multicenter, point-prevalence (cross-sectional) study in the cantons of Basel, Bern, Genève, Luzern, Ticino, Vaud and Zurich. In each canton 10–20 general practices will be recruited. All patients visiting the selected centres during defined days will be asked to participate to the study. The number of recruitment days depends on the achievement of the desired sample size. The target is to recruit 1000 to 2500 adult patients (≥18 years old). Emergency patients will be excluded for ethical reasons. The following variables will be collected: – Socio-demographic status (age, gender, BMI, work status) – Clinical status and laboratory parameters (blood pressure, plasma creatinine, albuminuria, plasma calcium and phosphate, parathyroid hormone, cystatin C, smoking status) – Co-morbidities (congestive heart failure, myocardial infarction, peripheral vascular disease, etc.)
– Family history
– Reason for visiting the practice
– Is the patient fasting at the time of the blood withdrawal?
– Diagnosis
– Has the patient been hospitalised in the past 12 months? Why?
– Which laboratory parameters would you, in any case measure, even in the absence of this study?
The biological samples will be stored in a biobank for eventual further analyse (e.g. to analyse cardiovascular biomarkers related to CKD).
Results: All patients who have completed the study without major protocol violations will be included in the analysis. All collected variables will be descriptively analysed. The prevalence of CKD stages will be firstly analysed in our study population. Correlations between socio-demographic/clinical status and CKD prevalence will be investigated. Subgroup and/or percentile analyses will be performed for the different CKD stages, for the plasma creatinine and for the creatinine-based estimates of the GFR. The estimated GFR (eGFR) will be calculated with established equations, as for example the Modification of Diet in Renal Disease study group (MDRD) formula, the Mayo Clinic quadratic equation, or the CKD equation. Secondly, we will calculate the prevalence at the national level, according to the Swiss age and gender distribution, to the frequency of physician visits

per year for different age classes, and to the frequency of laboratory analyses (for the collected parameters) in Switzerland. The third analysis phase consists in the development of several models to estimate the trends of CKD prevalence in Switzerland, taking into account future demographic changes (i.e. ageing of the Swiss population). Fourthly we will calculate the burden of CKD in our study population and at national level. The basic costs for the different CKD stages will be extrapolated from national and international literature. Future costs trends will be modelled taking into account future demographic changes and diseases prevalence changes. To predict the resource utilisation we will use an adapted version of the Charlson co-morbidity index. Additionally we will compare our data to those of some cantonal laboratories.
Conclusion: Assessment of renal function provides important prognostic information, since reduced GFRs are associated with increased risk for the development of end-stage renal disease, for cardiovascular disease and for premature mortality. Knowing the disease distribution in the Swiss population will provide fundamental information for developing mostly effective screening and preventing programs. The current and future socioeconomic impact of CKD in Switzerland will be evaluated. The increasing epidemic significance of CKD will soon necessitate the introduction of new screening/preventing approaches and guidelines. Through modelling of possible future scenarios, in particular related to the constant ageing of the population, it is possible to estimate if and when screening/preventing programs will become necessary to avoid an exponential growth of CKD-related health care costs.

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Hypernatremia in the emergency department: epidemiological and clinical features

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Purpose: Hypernatremia is a frequent finding in hospital settings, but published data is scarce. The aim of this study was to determine epidemiological and clinical features of patients with hypernatremia that was found at the time of presentation to the emergency department (ED).
Methods and materials: Between Jan 1st and Dec 31st 2007 38.932 patients consulted the ED of the University Hospital Basel (USB). All 11.106 patients with an Emergency Severity Index (ESI) of 1 to 3, and 3097 patients with ESI 4 (i.e. 14.203 patients in total) had a blood sample drawn at the time of presentation. Retrospectively, we identified all patients initially presenting with Hypernatremia defined by sodium concentration higher than 145 mmol/l and studied their medical records. Age, sex, season, complaints, final diagnosis, outcome, concomitant circumstances and the cause of hypernatremia were analyzed.
Results: 265 out of 14203 patients (incidence 1.87%; 61.29 ± 23.27 years of age; 52.4% male) presented with hypernatremia (147.98 ± 3.16 mmol/l): 56 (21.2%) in spring, 61 (23%) in summer, 68 (25.6%) in autumn and 80 (30.2%) in winter. Mortality during hospitalization was 7.55% (n = 20). The main complaints at the time of admission were: disturbance of vigilance 108 (40.75%), pain 37 (13.96%), and dyspnea 27 (10.19%). 26 patients (9.81%) were admitted due to trauma. Disorders of the central nervous system were most frequently observed (135; 50.94%; e.g. toxic, cerebrovascular) including 64 (24.15%) patients with acute alcohol intoxication. Furthermore, underlying infections (44; 16.6%) or cardiovascular disease (26; 9.81%) were seen. Presumed pathogenetic mechanisms were inability to drink or loss of free water.
Conclusion: In two out of hundred patients presenting to an emergency department with an ESI of 4 or higher, hypernatremia was found. Patients frequently suffered from disturbance of vigilance, but non-specific complaints were described in more than half of the cases. Disorders of the central nervous system are the most frequent cause, but a broad spectrum of underlying diseases is observed. Hypernatremia at presentation is associated with a 7.5% mortality rate during hospitalization.

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Renal failure due to chronic pancreatitis

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Purpose: A 61-year-old male patient with a history of an ethanol induced toxic pancreatitis 16 years earlier was admitted to our hospital with a diagnosis of recent onset renal failure. His symptoms included fatigue, nausea, weight loss and the presence of fatty stools for several years. There was no history of kidney stone disease. The glomerular filtration rate (eGFR) was assessed to be 6 ml/min (MDRD). Other laboratory tests revealed a normochromic, normocytic anemia and a secondary hyperparathyroidism – indicating chronic renal failure. The computed tomography showed calcification of the pancreas, the kidneys were 9 cm in length and showed neither calcifications nor signs of hydronephrosis. Dialysis was begun.
Methods and materials: The workup revealed steatorrhoe and a pancreatic elastase of <15 mg/g (normal value >200 mg/g), pronounced hyperoxaluria (Oxalate/Creatinine 77.5 mmol/mol, normal value <39 mmol/mol) and an obvious oxalate nephropathy in the renal biopsy.
Results: Any alteration of intestinal fat absorption (such as in the context of chronic pancreatitis) will play an important role in the development of both oxalate nephropathy and calcium oxalate stone formation. Fat malabsorption leads to loss of calcium in the intestine and increased absorption of oxalate, inducing hyperoxaluria.
Conclusion: In cases with a history of chronic pancreatitis and/or other alterations of intestinal activity the bowel function must be investigated. If steatorrhoe or other disorders of malabsorption are identified then oxalate excretion needs to be measured. To normalize oxalate absorption, drug and dietary therapies should be undertaken so as to minimize the risk of calcium oxalate stone formation and ultimately, renal failure.

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An unusual cause of central diabetes insipidus

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Purpose: A previously healthy, 43-year-old male patient was admitted to our outpatient clinic unit with a history of polyuria, polydipsia and the report of an unusual bout of headache that he had experienced two month before. Laboratory testing showed an elevated serum-sodium (143 mmol/l), a normal glucose, a raised creatinine (93 mmol/l) and a urine osmolality value of 169 mosmol/kg which contrasted with a plasma osmolality of 300 mosmol/kg. The urine volume was 4200 ml/d.
Methods and materials: A partial diabetes insipidus centralis was confirmed by both a water restriction test and the intravenous administration of 2 mg of exogenous Antidiuretic Hormone (ADH). Because of the history of the headache episode we performed a MRT of the skull and pituitary gland, which showed an apoplexy of the neuropituitary.
Results: With the introduction of a nasal ADH-replacement therapy the polyuria and polydipsia resolved. There were no cardiovascular risk factors apart from an arterial hypertension and the cause of the apoplexy remained unclear.
Conclusion: Although several lesions involving the pituitary can commonly cause diabetes insipidus, an isolated apoplexy of the neuropituitary gland remains a rare cause of the same problem.

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Superior palatability of crushed lercanidipine compared to amlodipine among children

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Purpose: Among children, medication palatability is crucial for adherence to therapeutic regimen. Since there is a lack of appropriate formulations for children prescribed antihypertensive drugs originally designed for adults, parents crush available tablets and administer the medication mixed with solid food or a palatable drink. Aim of the study was to test the taste of equivalent doses of pulverized amlodipine and lercanidipine, two calcium channel blockers approved for administration once a day, among children with kidney disease.
Methods and materials: Twenty children (7 girls and 13 boys) were presented a test dose of 1 mg of amlodipine besylate and 2 mg of lercanidipine in a single-blinded fashion. Children indicated their preference by pointing to the appropriate face on a visual analogue scale that depicts five degrees of pleasure.
Results: A 4-year old boy was not able to express his taste preferences. The palatability score assigned to lercanidipine was significantly higher than that assigned to amlodipine both in 9 children 4–7 years of age and in 10 children 8-11 years of age. The preference for lercanidipine was statistically significant both in girls and boys and both in children initially presented amlodipine and in children initially presented lercanidipine.
Conclusion: From the perspective of Swiss children with kidney disease 4–7 years and 8–11 years, the taste of pulverized amlodipine, the most popular calcium channel blocker, is inferior to that of pulverized lercanidipine.

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Hypernatraemia in a patient with severe infection: a case report

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Purpose: Hypernatraemia is commonly observed in critically ill patients. Polderman et al. presented a case series of 22 intensive care unit-patients (ICU-patients) who developed hypernatraemia, demonstrating delayed or inadequate treatment. Thus, they considered its occurrence as an indicator of poor quality of care. More recently,

O'Donogue et al. studied 266 episodes of hypernatraemia and found that acquired hypernatraemia was an independent predictor of mortality (mortality rate of 33.5% in the hypernatraemia group versus 7.7% in the normonatraemia group, p <0.001, OR 1.97). Hypernatraemia usually results from loss of body-water, and indicates a deficit in total body water. We report a case of acquired nephrogenic diabetes insipidus (NDI) secondary to severe infection which highlights a relatively uncommon but important differential diagnosis of unexplained hypernatraemia.
Methods and materials: A 62-year-old man was admitted to the intensive care unit (ICU) of our hospital in poor general condition with a 3-day history of redness and swelling of the scrotum. The diagnosis of Fournier's gangrene was made. Intravenous broad-spectrum antibiotics were immediately started and repeated surgical debridements were performed. One week after the last intervention, the patient developed polyuria and hypernatremia. At this time, the laboratory data showed a rise in serum sodium concentration from 133 mmol/l to 155 mmol/l and serum creatinine concentration from 83 µmol/l to 240 µmol/l. The plasma osmolality was 341 mosmol/kg H2O with a normal range of 270–300 mosmol/kg H2O. Surprisingly, the urine osmolality remained always below the plasma osmolality (maximum of 290 mosmol/kg H2O). The calculated electrolyte-free water clearance (EWC) was +2.6 L/day indicating renal loss of electrolyte-free water. Based on the laboratory findings partial nephrogenic diabetes insipidus (NDI) was presumed. This could be confirmed by a water deprivation test. Acquired NDI is often secondary to metabolic disorders and drugs that interfere with the action of endogenous arginine vasopressin (AVP) in the renal tubule. Less frequently, acute illness induces NDI. We concluded that the patient developed NDI in presence of severe infection and acute renal failure probably due to renal tubular injury.
Results: –
Conclusion: Acquired NDI must be considered in the differential diagnosis of patients with unexplained hypernatraemia. The goal of clinical management should focus on early diagnosis and prompt treatment of hypernatraemia. To minimize difficulties in diagnosis, clinical tools such as urine osmolality, calculation of the EWC and water deprivation test are helpful.

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Case Report: Recurrent non-ST elevation myocardial Infarction due to postpartum hypertension and essential thrombocythemia

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Purpose: Normal pregnancy represents a procoagulant state. Myocardial infarction in pregnancy is considered to be rare, yet taking into account the low non-pregnant risk score of these young women it is still surprisingly frequent.
Methods and materials: We report the case of postpartum recurrent non-ST elevation myocardial infarction in a 40-year-old Caucasian woman, who was diagnosed with essential thrombocytemia in the presence of a positive JAK-2 mutation and an elevated anti-cardiolipin IgM antibody level.
Results: This is the first report of such a highly unlikely event as essential thrombocytemia preferably affects older people. In general, essential thrombocytemia can be linked to early spontaneous abortions in pregnancy that might be reduced by aspirin treatment. In the majority of cases of myocardial infarction in pregnancy or in the peripartal period, atherosclerosis, a thrombus or coronary artery dissection is observed.

Laboratory parameters at acute coronary syndromes (ACS)

	1. Episode ACS	2. Episode ACS	Normal Range
Hb	137	139 g/l	121–154
Hct	40	42%	36–44
Lc	8.6	8.0 G/l	3.5–10.5
Tc	**708**	**559** G/l	140–380
CK max	**280**	**196** U/l	<170
Troponin T max	**0.620**	**0.354** µg/l	<0.010
Antibodie			
ANA		**1:160**	<1:80
Anti-dsDNA-		32	<200
anti-histone		0.3	<1
IgM anticardiolipin		**13.1** MPL-U/ml	<5
IgG anticardiolipin		3 GPL-U/ml	<10

In the woman reported here, the combination of advanced age, pregnancy, postpartum hypertension, essential thrombocytemia, a coronary plaque and elevated anti-cardiolipin IgM antibody seem to be causative.
Conclusion: In summary, rare or unlikely conditions leading to severe events such as myocardial infarction must be considered in aging pregnant women. Overt thrombocytosis needs work-up before pregnancy and emphasizes the importance and merit of a pre-pregnancy check-up.

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Ovarian stimulation and renal risk

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Purpose: Endometriosis is defined as the growth of endometrial tissue outside the endometrial cavity and uterine musculature. Genitourinary involvement is less common.
Methods and materials: A 40 years Caucasian woman was admitted to emergency for asthenia and progressive abdominal pain for 1 month. She was treated for infertility by ovarian stimulation 4 months ago. Medical past: single localisation of ovarian endometriosis. The physical examination showed bilateral flank pain, blood pressure was 150/85 mm Hg, pulse rate was 95/mn and regular. Laboratory: creatinemia 750 mmol/l, urea 35 mmol/l, phosphatemia 2 mmol/l, calcemia 2.10 mmol/l, HCO3- 17 mmol/l, hemoglobin 81 g/l; urine dipstick: protein +, blood neg ++, leucocyte neg and glucose neg. The abdominal ultrasound showed bilateral pyelo-ureteral dilatation. Laparoscopic exploration was consistent with endometriosis witch involved the bladder, the ureters. Despite double J derivation, GnRH agonists to stop the progression of endometriosis and reimplantation of distal ureter, the renal function was not restored and the patient undergone haemodialysis. The optimal management of endometriosis is unclear, non prospective studies are available.
Results:

Case	Age	Presentation	Associated bladder endometriosis	Side involved	Site: upper, lower, middle 1/3	Type of treatment
1	50	Reccurent pylelonephritis, non functionning kidney	No	Left	Distal 1/3	Hormonal treatment before laparoscopic nephroureterectomy
2	39	Flank pain and hydronephrosis	No	Left	Distal 1/3	Ureteral stent followed by ureteroureterostomy
3	78	Hydronephrosis and pyelonephritis	No	Right 1/3	Distal	Ureteral stent followed by excision of distal ureter with reimplantation
4	78	Hydronephrosis	No	Right	Distal 1/3	Excision of distal ureter with reimplantation
5	48	Pelvic mass and hydroureter	No	Left	Distal 1/3	Resection of pelvic mass
6	54	Hydronephrosis	No	Left	Distal 1/3	Excision of distal ureter with reimplantation
7	41	Hydronephrosis with ureteric tumor	No	Left	Middle 1/3	Nephroureterectomy
8	40	Flank pain and bilateral hydronephrosis	Yes	Both 1/3	Distal	Hormonal treatment before excision of distal ureter with reimplantation

Summary of the clinicopathological features of our case in comparison with litterature (Al-Khawaja M, et al. Hum Pathol. 2008 Jun; 39(6):954–9)
Further questions concerning her future remain elusive:
– Endometriosis progression and renal transplantation: at the time of the recovery of renal function after renal transplantation, new endometriosis lesions could appear on graft or on bowel
– Cancer and endometriosis: epidemiological evidence from most large cohort studies suggests that endometriosis is an independent risk factor for epithelial ovarian cancer. There appears to be a causal association between endometriosis and specific types of ovarian carcinomas. No studies have evaluated the additive risk of a chronic immunosuppresion in renal transplantation for ovarian cancer.
Conclusion: In conclusion, infertility is a complex disorder with significant medical, psychosocial aspects. Great strides have been achieved in infertility therapy and with new and effective treatments available in the field of assisted reproductive technology. Our case demonstrates that great care is required when attempting with ovarian stimulation with gonadotropins in case of endometriosis.

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NCC is regulated by the Nedd4-2-Sgk1 pathway

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Purpose: Appropriate regulation of renal Na transport is essential for control of blood pressure and Na balance. Aldosterone stimulates Na reabsorption in the aldosterone-sensitive distal nephron, via the epithelial sodium channel (ENaC) in the connecting tubule and collecting duct and via the thiazide-sensitive NaCl cotransporter (NCC) in the distal convoluted tubule (DCT). Under aldosterone induction, Sgk1 phosphorylates the ubiquitin-protein ligase Nedd4-2, expressed along the distal nephron, including the DCT, thus preventing the interaction between ENaC and Nedd4-2 and avoiding ENaC ubiquitylation and degradation. Aldosterone increases NCC protein expression, without increasing NCC mRNA levels. The mechanism, however, is unknown.
Methods and materials:
– Coexpression in Hek293 cells
– Western blots on Hek293 cell and mouse kidney lysates
– Coexpression in Xenopus oocytes and measure of thiazide-sensitive 22Na uptake
Results: In the present work, we have identified Nedd4-2 as a regulator of NCC. We found that Nedd4-2 interacts with NCC in transfected Hek293 cells. Similarly, the two endogenous proteins interact in mouse kidney lysates. NCC activity in the absence or presence of Nedd4-2 and/or Sgk1 was assessed in *Xenopus* oocytes. Co-injection of NCC cRNA with wild-type Nedd4-2 cRNA, but not the catalytically inactive Nedd4-2 cRNA, dramatically decreases NCC-induced thiazide-sensitive 22Na uptake. This inhibition is prevented by addition of Sgk1 cRNA. Moreover, we show that, under high-salt diet, NCC expression is upregulated in inducible renal tubule-specific Nedd4-2 knockout mice (Nedd4-2/Pax8/LC1) versus control mice, whereas NCC expression and Nedd4-2 phosphorylation are reduced in Sgk1 knockout mice under low-salt diet.
Conclusion: These results strongly suggest that NCC activity is controlled by a regulatory pathway involving Nedd4-2 and Sgk1 and could provide an explanation for the well known aldosterone-induced increase in NCC protein expression.

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Hypoxia and CXCR4 in human nephrosclerosis (NSC)

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Purpose: Hypoxia contributes to interstitial fibrosis, but little is known about its implication for glomerular damage. As glomerular hypoxia was hypothesized to be involved in NSC we assessed the expression of hypoxia-associated genes in this common glomerulopathy.
Methods and materials: Genome-wide expression data from microdissected glomeruli of 14 patients with NSC and 4 controls were obtained. Confirmatory qRT-PCR was performed on 45 patients with other glomerulopathies and 6 controls.
Results: Expression levels of a majority (61%) of genes known to be regulated by the hypoxia-inducible factors (HIF) were significantly altered in NSC glomeruli while only 23% were altered in focal-segmental glomerulosclerosis (FSGS). Among these genes Lysyloxidase-like 2 (LOXL2) (foldchange: 2.6 ± 1.7, $p < 0.01$ vs. controls) and chemokine receptor CXCR4 (2.0 ± 1.1, $p < 0.05$) were confirmed by qRT-PCR to be increased in NSC glomeruli but not in other glomerulopathies including FSGS. Immunohistology revealed enhanced positivity for CXCR4 in podocytes of NSC. This CXCR4 positivity was associated with nuclear localization of HIF1-alpha in podocytes indicating transcriptional activity of HIF. The CXCR4 ligand CXCL12/SDF-1 was found to be constitutively expressed in podocytes. In cultured podocytes hypoxia led to induction of HIF1- and 2-alpha protein and CXCR4 mRNA. In an *in vitro* wound-healing assay with these cells a blocking antibody for CXCR4 caused inhibition of wound closure by 43% ($p < 0.01$), indicating CXCR4 dependent podocyte migration.
Conclusion: Our data suggest that hypoxia is not only involved in the progression of interstitial fibrosis, but also modulates glomerular damage in NSC. The CXCR4/CXCL12 system may contribute to the pathogenesis of human NSC.

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Dynamic changes in vesicle trafficking on the onset of hypertonic challenge

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Purpose: Changes in environmental osmolality affect a number of physiological processes. Cells of the renal medulla are especially subject to constant fluctuations of osmolality. On the onset of hypertonic challenge, cell shrinkage exerts harmful effects that, if unchecked, lead to apoptotic cell death. Cell volume is restored within minutes via a complex regulatory volume increase (RVI) mechanism, during which the cell undergoes major changes affecting cytoskeletal remodeling, channel/transporter activity and signal transduction. Such changes undoubtedly affect vesicle sorting between the cell surface and intracellular compartments. This led us to investigate the effects of hypertonicity on vesicle trafficking during the first 20 minutes of stimulation.
Methods and materials: Spinning-disk confocal microscopy was performed on live LLC-PK1 cells. These cells expressed various fluorescent-tagged proteins (Rab5, 7, 10, 11, ssGFP, AQP2 and V2R) or were loaded with FITC-dextran enabling us to separately monitor distinct vesicle sub-populations, including exocytotic vesicles and early, late and recycling endosomes. Movies were analyzed by Volocity and Image software.
Results: Cells exposed to isotonic (290 mOsmol/kg) and then hypertonic (500 mOsmol/kg) medium revealed a dramatic reduction of vesicle movement for all vesicle populations upon hypertonic exposure. Decreased vesicle movement was accompanied by reduced endocytotic and exocytotic activity. Vesicle movement resumed thereafter with different recovery times between vesicle subpopulations. AQP2-containing vesicles were among the first to recover (~5 min) and dextran-loaded early endosomes were among the last (~15 min). Recovery of vesicle movement was accompanied by a perinuclear accumulation of most vesicle subpopulations. However, the precise region in which vesicles accumulated depended on their cargo. For instance, AQP2 accumulated at the trans-golgi network whereas most perinuclear V2R co-localized with lysosomes. Hypertonicity also initiated autophagy as suggested by the formation of PI3K-dependent, ATG12-rich clusters which were especially apparent in cells overexpressing V2R.
Conclusion: These observations reveal that hypertonicity 'reprograms' vesicle trafficking/sorting events that participate in governing cell survival/function.

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CD4 lymphocytes drive tubulointerstitial damage in experimental autoimmune glomerulonephritis

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Purpose: Autoimmunity against the Goodpasture antigen α3IV-NC1 results in antiglomerular basement membrane (GBM) glomerulonephritis (GN). Little is known about the role of autoreactive T lymphocytes in the kidneys during the effector phase of disease.
Methods and materials: We used the mouse model of experimental autoimmune GN to investigate if T lymphocytes isolated from diseased kidneys recognized the autoantigen α3IV-NC1, and to determine to which extend CD4 T cells participate in kidney damage.
Results: Repeated immunization of DBA/1 mice with α3IV-NC1 resulted in proteinuria, loss of kidney function, and crescentic GN at 9–11 weeks. Kidneys showed IgG depostion along the GBM and a 4fold increase in interstitial T cells. Following stimulation of renal T cells with α3IV-NC1, a 3–4fold increase in IFNγ spots was detected with the ELISPOT assay compared to unstimulated or mock-stimulated cells. Antibody depletion of CD4 cells at 8 and 9 weeks did not influence the number of glomerular crescents or levels of circulating or deposited antibodies. However, there was a significant attenuation of tubulointerstitial damage. Using flow cytometry, only very low frequencies of CD4+ cells were detected in kidneys of depleted mice and remaining CD4 cells largely failed to produce IFNγ upon polyclonal restimulation in vitro.
Conclusion: Our data provide direct evidence of an autoantigen-specific mechanism to amplify the cellular immune response within the kidneys and indicates that CD4+ cells have important functions during the progression of kidney destruction in crescentic GN.

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Urine calcium regulation by circadian rhythm

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Purpose: The kidneys play a key role in calcium homeostasis by regulating the amount of calcium reabsorbed or lost in the urine. In human, a circadian rhythm has been described for urinary calcium as well as for plasma calcium and parathormone concentrations, and has been involved in bone turnover control and kidney stone genesis. The molecular mechanisms accounting for the observed circadian rhythm in calcium metabolism are unknown. We assessed circadian variations of calcium in the blood and urine of mice and correlate them with expression levels of genes known to be involved in calcium transport.
Methods and materials: We determined plasma, urine calcium and PTH levels in C57BL/6 mice every 4 hours for 24 hours. In addition, mRNA and protein expression levels for several genes related to calcium reabsorption in the kidney (the apical calcium channel TRPV5, the basolateral sodium/calcium exchanger NCX1, the basolateral calcium pump PMCA and the intracellular chelator Calbindin-D28k) were assessed by quantitative PCR and Western blot.
Results: Plasma calcium corrected for albumin was following a cosine function with amplitude of 6% over 24 h hours, a peak at Zeitgeber Time (ZT) 4 h and a nadir at ZT 16 h. Urinary calcium was changing over a cosine by 42% over 24 hours, with a peak at ZT 8 h and a low at ZT 20 h. PTH was varying by ~3 times over 24 h with a peak at ZT 0 h and a nadir at ZT 12 h. When analyzed by quantitative RT-PCR, mRNA expression of TRPV5, NCX1, Calbindin D28k and PMCA were all cycling with the same rhythm, presenting a peak at ZT 16 h and a low at ZT 8 h. Protein levels did vary with lower amplitudes.
Conclusion: Our results show that plasma, urine calcium and PTH levels are cycling in the mouse over 24 hours, following a cosine function. We also show that the expression of several genes involved in renal calcium reabsorption is cycling. These results suggest that part of the circadian rhythm observed for calciuria might be due to either variation in the PTH levels or to rhythmic expression of genes involved in calcium reabsorption.

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Aldosterone regulates placental growth

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Purpose: In pregnancy adequate trophoblast growth is required to support placental function. The role of increasing aldosterone levels in pregnancy is considered as to promote placental perfusion by plasma volume expansion. In preeclampsia, placental size is small in the presence of low aldosterone levels. As aldosterone acts proliferative in many tissues, we asked the question whether aldosterone enhances placental growth and thus adapts the feto-maternal interface to environmental challenges.
Methods and materials: Primary extravillous cytotrophoblasts isolated from first trimester placentas and immortalized human trophoblast cell lines (JEG-3 and HTR-8/SVneo) were cultured. Proliferation was assessed by 3H-thymidine-incorporation assays. Confocal immunofluorescence microscopy verified expression and agonist-stimulated nuclear translocation of the mineralo- and the glucocorticoid receptor. Pregnant SD rats and SD1 mice were maintained on standard chow (0.42% NaCl) during either aldosterone blockade with spironolactone (0.625 ug/g body weight/hr) or control treatment, respectively. Umbilical blood flow, placental weight and fetal size were assessed. Serum aldosterone was assessed in 1st and 3rd trimester in the rats and in 1st trimester in pregnant women and placental mass was obtained.
Results: Incubation of trophoblasts with aldosterone (10-7M) increased 3H-thymidine incorporation in cultured trophoblasts (primary trophoblasts 357 ± 15% of control; $p < 0.001$). Glucocorticoids led to a small, but consistent growth inhibition ($p < 0.0001$ in primary trophoblasts). Exposure of animals to spironolactone tended to reduce placental and fetal weight, and severely impaired umbilical blood flow (69 ± 1 vs. 100 ± 4 cm/s; $p < 0.0001$) when compared to controls. The change in serum aldosterone from 1st to 3rd trimester predicted placental mass in rats and above average 1st trimester serum aldosterone levels predicted a placental mass above the 20th percentile corrected for gestational age ($p = 0.04$).
Conclusion: In conclusion, aldosterone supports trophoblast proliferation in culture, fetal well-being in animals and correlates with placental mass. Thus, in addition to plasma volume expansion high aldosterone levels appear to be required for normal placental development offset by inappropriate low aldosterone in concert with enhanced cortisol availability in preeclamptic pregnancies.

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Distinct and opposing effects of palmitic acid and palmitoleic acid on ER-stress, apoptosis and necrosis in podocytes

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Purpose: Apoptosis of podocytes occurs during the course of diabetic nephropathy. As free fatty acids (FFA) are elevated in states of insulin resistance we examined the effect of the saturated palmitic acid and the monounsaturated palmitoleic acid on apoptosis and necrosis in podocytes. Further, the apoptotic response resulting from endoplasmic reticulum (ER) stress was investigated.
Methods and materials: Podocytes were incubated with increasing concentrations of palmitic acid complexed to bovine serum albumin (BSA) for different time points. Apoptosis and necrosis were determined by flow cytometry. Annexin V-single positive cells were counted as apoptotic and annexin V/Propidium iodide (PI)-double positive cells as necrotic cells. ER-stress was assessed by Western blots of the ER chaperone BiP (heavy chain binding protein) and CHOP (C/EBP [CCAAT/enhancer binding protein] homologous protein).
Results: 125, 250, and 500 µM palmitic acid induced apoptosis and necrosis in podocytes in a dose- and time-dependent manner. After 38 h, 500 µM palmitic acid increased apoptosis and necrosis 2.5 to 3-fold. Similarly, palmitic acid increased the expression of the proapoptotic transcription factor CHOP. After 24 h CHOP was increased 9-fold after exposure to 500 µM palmitic acid. The ER-chaperone BiP was 4 to 5-fold upregulated after exposure to 500 µM palmitic acid for 16 and 24 h. The monounsaturated palmitoleic acid, that strongly attenuated the induction of CHOP, could prevent the apoptotic and necrotic effect of palmitic acid in podocytes.
Conclusion: Palmitic acid and palmitoleic acid have distinct and opposing effects on apoptosis, necrosis and ER-stress in podocytes; thereby, palmitic acid induces apoptosis and ER-stress. These studies identify FFAs as potential factors for viability of podocytes in the pathogenesis of diabetic nephropathy and support the involvement of ER-stress in this apoptotic pathway.

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Expression of the chemokine receptor CCR6 in human renal inflammation

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Purpose: Nodular inflammatory cell infiltrates with defined microarchitecture, i.e. tertiary lymphoid organs (TLO), develop in the renal tubulointerstitium during chronic inflammation. CCR6 and the corresponding ligand CCL20 are involved in the formation of gut associated lymphatic tissue. We hypothesized that this chemokine/chemokine receptor pair might be involved in TLO formation in the kidney.
Methods and materials: CCR6 and CD20 positive B cells were localized in renal biopsies with crescentic glomerulonephephritis (cGN, n = 11), IgA nephropathy (n = 13), membranous nephropathy (n = 12), and chronic interstitial nephritis (n = 13). Allograft biopsies taken before implantation served as controls (n = 8). Additionally, CCR6 and CCL20 mRNA were quantified by real-time RT-PCR in 51 renal biopsies of the same disease entities.
Results: CCR6 mRNA was significantly upregulated in the tubulointerstitium of IgA nephropathy and cGN biopsies, with prominent mRNA expression of the corresponding ligand CCL20. Expression of CCR6 was present on infiltrating as well as on endogenous kidney cells. Areas of nodular inflammatory cell accumulations were uniformly CCR6 positive. A major part of the CCR6 positive cells were CD20 positive B cells, but CD3 positive T cells were also found to express CCR6. CCR6 was constitutively expressed on the endothelium of peritubular capillaries and on glomerular endothelial cells. Staining of glomerular capillaries was lost with progressive injury in cGN. Some tubular epithelial cells expressed CCR6 only in inflamed kidneys, most commonly on the basolateral side.
Conclusion: CCR6 was predominantly expressed on T and B cells organized in TLOs. The functional role of CCR6 particularly as a therapeutic target in chronic kidney diseases needs further evaluation.

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The Chinese herb Shakuyaku-kanzo-to for the treatment of cramps during hemodialysis: finally a magic bullet?

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Purpose: Muscle cramps are a common complication of hemodialysis treatment, occurring in 33–86% of patients. The pathogenesis is poorly understood, and its treatment unsatisfactory.
Methods and materials: We report the case of a 84 year old woman on maintenance hemodialysis (MHD) for diabetic and hypertensive nephropathy; she also suffers from congestive heart failure and paroxysmal atrial fibrillation. Almost every dialysis session is complicated by extremely painful cramps, which only partially respond to IV saline treatment. MHD-prescription was as followed: 3x/week, 3 h per session with a Fresenius HF 80S filter; blood flow was 350 ml/min, dialysate flow 500 ml/min, dialysate temperature 35.5 °C, Sodium 138 mmol/l, Potassium 2 mmol/l and Ca 1.25 mEq/l. Monthly controls of dialysis quality showed mean spKt/V of 1.58, eKt/V of 1.38, nPCR 0.98 and a URR of 75%. Her dry weight was 50 kg and the pre-dialysis arterial pressure around 160/60 mm Hg. The interdialytic weight gain was 1.5–2 kg. The patients medication included aspirine, metoprolol, diltiazem, furosemid, calcium-acetat, distraneurin, levemir, pravastatin and esomeprazol.Over a period of 10 months, different therapeutic approaches were tried: first of all, intensified restriction of dietary sodium, followed by progressive augmentation of dialysate sodium concentration up to 145 mmol/l, then augmentation of the dry weight progressively to 56.5 kg, of session length up to 3.30 h, in combination with intradialytic physical training by bed-bike. Besides, IV albumine (20% 100 ml) was administered, without effect on the apparition of cramps.
Results: Once the patient had come to the point that she wanted to stop all MHD, one of the authors proposed the intradialytic peroral administration of Shakuyaku-kanzo-to (2.5 g at the beginning of each MHD session), a Chinese herb also known as White Peony Root (Radix Paeoniae Alba). The frequency of cramps fell from 91% to 13% of the sessions. The patient also reduced her serum levels of potassium from a medium of 5.2 mmol/l to 4.5 mmol/l; sodium polystyrene sulfonate could be stopped, and dialysate potassium content could be raised from 2 mmol/l to 3 mmol/l.
Conclusion: In the traditional Chinese and Japanese medicine the herb is widely prescribed to treat muscle cramps and spasmodic abdominal pain. The herb is a mixture of more than 20 substances, including glycyrrhetinic acid. Intestinal absorption is within minutes, and mechanisms of action involve inhibition of muscle contraction and twitch response of nerves. The main 'side effect' is hypokalemia. The prescribed dose was based on a case series of 23 Japanese MHD patients, where 88.5% of cramps vanished completely within 10 minutes after drug administration. Considering the spectacular results obtained in our patient, it seems reasonable to undertake a randomized controlled trial to further evaluate the benefit-risk profile of this seemingly magic bullet against cramps in patients on hemodialysis.

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Role of heme oxygenase-1 in protecting regulatory T cells from apoptosis in chronic hemodialysis patients

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Purpose: End-stage kidney disease (ESKD) and especially chronic hemodialysis (HD) have been reported to induce regulatory T cells (Tregs) apoptosis. Given that there is a relationship between Tregs dysfunction and oxidative stress that may determine the inflammatory state of HD patients. A decrease in the micro-inflammation related to Tregs function recovery in these patients may be associated with decreased oxidative stress.
Methods and materials: We studied the regulation of oxidative stress in the induction of Tregs apoptosis (annexin V and DNA fragmentation). Total antioxidant capacity (TAC), antioxidants (superoxide dismutase (SOD) glutathione peroxidise (GPX), reduced glutathione (GSH) and catalase), and biomarkers of oxidative stress were evaluated in plasma and Tregs from 15 HD patients with ESKD chronically hemodialyzed. Furthermore, heme oxygenase-1 (HO-1), an integral part of the anti-oxidant response element of cells was analyzed in order to prevent HD Tregs apoptosis. Indeed, induction of HO-1 in T cells may allow survival of the cell from oxidative injury and may also modify the inflammatory cascade to one of resolving inflammation.
Results: There was significantly decreased plasma TAC, decreased activities of antioxidant enzymes and decreased GSH levels along with increased thiobarbituric-acid-reactive substances and 8-hydroxy-2-deoxyguanosine (8-OHdG) levels in Tregs. The blood GPX activity was significantly reduced compared with patients with ESKD not yet on HD. Interestingly, pre-induction of HO-1 by hemin prevented HD-induced Tregs apoptosis, whereas inhibition of HO-1 activity (treatment with tin protoporphyrin, SN-P) enhanced HD-induced Tregs apoptosis *in vitro*. To further analyse HO-1 anti-apoptotic effect on Tregs, we used vitamin E-coated dialysis membranes. Indeed, these membranes have been demonstrated to reduce levels of oxidative stress in PBMCs of patients undergoing chronic HD. In this study, it was observed that Tregs harvested from patients hemodialyzed with vitamin E-coated membranes had greater expression of HO-1 and lower Tregs apoptosis.
Conclusion: We suggest that oxidative injury associated with chronic HD plays a role in Tregs apoptosis, and that pre-induction of HO-1 may attenuate HD-induced Tregs apoptosis. Use of antioxidants (vitamin E) may be used in an attempt to improve biocompatibility of HD, to reduce Tregs apoptosis and thus to improve micro-inflammation encountered in chronic HD patients.

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Dose conversion to C.E.R.A in hemodialysis patients with previous low dose ESA treatment. Results from a multicenter trial

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Purpose: C.E.R.A. is a third generation erythropoesis stimulating Agent (ESA) that was introduced in Switzerland in 2007. Different than in other agents there is no conversion factor from other ESA. Instead conversion is done in three strata. Patients with epoetin alpha/beta treatment below 8000 IU/week or darbepoetin alpha below 40 µg are converted to 120 µg C.E.R.A. Patients on epoetin 8000–16000 IU or 40–80 µg of darbepoetin alpha are converted to 200 µg C.E.R.A. Patients with higher doses receive 360 µg of C.E.R.A. Aim of this analysis was to determine if this conversion scheme is appropriate for patients with very low doses below 4000 IU of epoetin or 20 µg of darbepoetin that were included in the MIRACLE study.
Methods and materials: The MIRACLE study is a single arm, open label, multi center study to asses the long term maintenance of hemoglobin levels with once-monthly intravenous administration of C.E.R.A in hemodialysis patients with chronic renal anemia. Patients on hemodialysis with prior ESA treatment and hemoglobin levels between 11 and 13 g/dl during the past two month were eligible for inclusion in the study. Patients with doses of epoetin >16.000 IU and darbepoetin >80 µg were excluded for logistic reasons. After inclusion into the study ESA treatment was switched to C.E.R.A. once monthly according to the strata in the label. Target level for hemoglobin was 11–13 g/dl. Hemoglobin values were recorded in weeks 1, 2, 4 and fortnightly thereafter. Patients were stratified according to the mean dose in the last 4 weeks before conversion into the "low dose" (LD) group (epoetin <4000 IU/week, darbepoetin alpha <20 µg/week) or "high dose" group. Hemoglobin values were defined as being above target range when exceeding 13.5 g/dl in the first 16 weeks.
Results: 26 patients (34%) fell into the LD group, 50 (66%) into the HD group. In the LD group within the first 16 weeks in 13 patients (50%) hemoglobin values above 13.5 g/dl occurred. In the HD group the number of patients with hemoglobin values above 13.5 g/dl was significantly lower (12 pat., 24%; p = 0.02). The majority of these hemoglobin values above target occurred in the first 8 weeks after conversion (91% in LD; 74% in HD). In patients with hemoglobin values above target range the highest values were on average 13.85 g/dl in the LD and 14.1 g/dl in the HD group. During episodes of hemoglobin levels above target range, no related adverse events occurred. After correction of dose (n = 24) or temporary cessation (n = 1) the hemoglobin values returned to <13.5 within an average of 2.8 weeks.
Conclusion: The conversion strategy of using three strata generally works when converting patients to C.E.R.A. from other ESA. It might be appropriate to use lower doses than the recommended 120 µg in patients on very low doses of less than 4000 IU epoetin/week or 20 µg of darbepoetin alpha/week even though there were no adverse clinical events during episodes with hemoglobin above target. This measure might further increase hemoglobin stability. After correction or withholding of the dose hemoglobin returned to target levels within a short period of time.

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Flexible usage of darbepoetin alfa in daily clinical practice in Switzerland (FLEXTEND): Hb target achievement, dosage intervals and iron status

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Purpose: FLEXTEND is an ongoing (2007–2009) multi-center, observational survey in Switzerland designed to evaluate the use of Darbepoetin alfa (Aranesp®; DA) administered at different dosing intervals, such as once weekly (QW), every two weeks (Q2W) and once monthly (QM) for the treatment of anemia in patients with chronic kidney disease (CKD), stages 4 and 5. ESA treated patients ≥18 years with CKD including dialysis and pre-dialysis patients are included in this survey and will be documented on a monthly base for up to 18 months.

Methods and materials: This interim analysis of 12 months' data in 415 dialysis patients (HD/PD only) focuses on EBPG target Hb achievement (≥110 g/L) and the impact of iron status on Hb variability. Hb variability was defined as the SD of Hb during the observation period. 60% of the patients were male. Mean age (±SD) was 65 (±14) years and mean weight 73 (±17) kg.
Results: Mean Hb rose from 116 g/L to 118 g/L during the one year observation period. The mean weekly dose of DA at one year was 42.5 µg (0.58 µg/kg). The percentage of patients on on extended dosing (Q2W or QM) increased from 39% at baseline to 47% at 12 months. The Hb target of ≥110 g/L was reached in 71% at baseline and in 77% at 12 months. Target achievement was not different between weekly dosing (74% with Hb ≥ 110) and extended dosing (80%). Hb variability in patients with absolute iron deficiency at baseline (defined as ferritin <100 µg/l, n = 20) was significantly greater than in patients with adequate iron status (ferritin ≥100 <800 µg/l and TSAT ≥20%, n = 165): the mean SD of Hb during the observation year was 11.7 g/l (SD 5.1) in iron deficient patients and 9.1 g/l (SD 4.3) in iron-replete patients (p <0.05).
Conclusion: Hb target level achievement in this study compares favorably with other European observational studies such as DOPPS II. Extended DA dosing intervals such as Q2W and QM did not impair Hb target achievement or influence Hb variability in dialysis patients. Iron deficiency at baseline was associated with an increased Hb variability over 12 months.

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Single center post-marketing evaluation of efficacy and safety of methoxy polyethylenglycol-epoetin beta (Mircera®) in peritoneal dialysis patients

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Purpose: Methoxy polyethylenglycol-epoetin beta (Mircera®) is a continuous erythropoetin receptor activator (CERA) with a very long half-life (~130 h) which allows extended dosing intervals in patients with renal anemia. Therefore it might be particularly useful in peritoneal dialysis (PD) patients. However it has not been extensively studied in this patient population. The purpose is to evaluate the efficacy and safety of CERA given once every 4–6 weeks *sc* in maintaining stable hemoglobin (Hb) levels in PD patients converted directly from *sc* darbepoetin alfa or *sc* epoetin beta.
Methods and materials: We studied 14 stable PD patients with a mean time on PD of 41.6 ± 21.2 months and a baseline Hb level of 10.7 ± 1.6 g/dL. The baseline blood pressure was 137/83 mm Hg (± 9/22 mm Hg). At the time of conversion to CERA, 2 patients were erythropoiesis-stimulating agent naïve, 10 patients were on darbepoetin alfa (mean dose 56.5 ± 44.8 mg/wk) and 2 patients were on epoetin beta (mean dose 8000 ± 2828 IU/wk) for the previous 3 months. All PD patients were switched from weekly or bi-weekly sc darbepoetin alfa or weekly sc epoetin beta to CERA monthly. 3 months after conversion we switched to *sc* CERA with prolonged injection interval of 5 weeks in all patients.
Results: After conversion to CERA the Hb level increased from 10.7 ± 1.6 g/dL to 11.1 ± 0.8 g/dL after 11 months of treatment. The mean dose of CERA at conversion was 170 ± 98 µg per month and 157 ± 105 µg every 5 weeks 11 months after conversion. Slight dose adaptations were necessary in 7 patients after 1 month and in 7 patients between month 1 and 3. The prolongation of the dosing interval to 5 weeks at month 3 caused a dose adaptation in 8 patients. An overcorrection of the Hb level (more than 12.5 g/dL) was seen in 1 patient after 1 month, in 3 patients after 3 months, in 1 patient after 6 months and in 4 patients after 9 months, mostly due to a concomitant correction of iron-deficiency. A drop of the Hb level (less than 10.0 g/dL) was seen in two patients (5 months and 10 months after conversion), which was due to the unadjusted dose of CERA for the prolonged dosing interval in one case and the missed administration in the other case. Overall there were no specific adverse events during the 11 month treatment phase. Even the blood pressure remained stable.
Conclusion: Conversion from epoetin beta or darbepoetin alfa to CERA administered every 5 weeks sc was effective in patients on PD. Regular monitoring of Hb levels was necessary and required dose adaptations early in the treatment course. The extended dose intervals allowed the administration on regular outpatient visits, which ensures optimal patient compliance. The drug tolerance was excellent.

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Effects of vitamin D supplementation in maintenance hemodialysis patients

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Purpose: End-stage renal disease (ESRD) is associated with disturbances in mineral metabolism, its main determinants being serum calcium, phosphorous, parathyroid hormone (PTH) and vitamin D. Derangements in mineral metabolism are believed to be relevant for both bone and cardiovascular pathology. Supplementation with oral and/or intravenous vitamin D and vitamin D analogues has become standard therapy to ameliorate disturbances in mineral metabolism. However, apart from controlled trials with restricted patient selection, only limited data from regular practice experience using vitamin D are available. It was the purpose of the present study to assess clinical and biochemical parameters in association with vitamin D supplementation in a Swiss maintenance hemodialysis (HD) cohort.
Methods and materials: The study population consists of a total of 172 patients participating in the *monitor!* trial, a prospective dynamic hemodialysis cohort study assessing a wide range of clinical, laboratory and anthropometrical parameters. A baseline assessment was performed at time of inclusion into the *monitor!* cohort, which continuously occurred between summer of 2006 and winter of 2008. Medical charts of all study participants were reviewed in July 2009 for living status and hospital days since inclusion into the cohort. Patients were stratified according to type of vitamin D supplementation (none, 25-OH vitamin D, or paricalcitol), which had to be administered for at least 3 months during an 18 months follow-up period after inclusion into the trial.
Results: The mean baseline serum concentrations in the study cohort for 25-OH vitamin D, calcium, phosphate and PTH were: 20.0 ± 16 µg/L, 2.29 ± 0.18 mM/L, 1.70 ± 0.46 mM/L, and 281 ± 260 ng/L, respectively. Results are given as mean ± SDV for subgroups stratified by type of vitamin D supplementation.

Type of vitamin D supplementation

	None	25-OH	Calcitriol	Paricalcitol	P
N	68	37	58	9	–
Age, yr	64.0±15	68.6±11	67.4±13	61.2±13	0.218
Alive, %	65.7	86.8	80.4	77.8	0.074
Hospital days, n	17.2±26	8.2±12	6.8±11	10.0±11	**0.014**
Calcium, mM/L	2.27±0.16	2.22±0.14	2.23±0.18	2.28±0.18	0.802
Phosphate, mM/L	1.63±0.50	1.57±0.30	1.64±0.44	1.95±0.61	0.409
Ca×P product, mM2/L2	3.71±1.2	3.51±0.7	3.66±1.0	4.38±1.3	0.402
PTH, ng/L	330±366	196±103	360±186	411±95	0.084
CRP, mg/L	11.3±16	11.0±13	9.4±11	16.1±22	0.780
IL-6, ng/L (<3.3)	9.9±7	11.2±14	14.9±20	16.2±15	0.567
Cupper, µmol/L (12-24)	15.7±4	15.6±4	16.4±3	15.7±4	0.855
Selenium, µmol/L (0.89-1.9)	0.68±0.2	0.85±0.2	0.59±0.2	0.63±0.2	**0.015**
NT-pro-BNP, ng/L (<400)	12706±16372	10271±9980	10789±14944	8062±6141	0.879

Additional analyses with pooled data for patients with "any" vitamin D versus patients without vitamin D ("none") were performed for survival status and length of hospital stay: Among patients with and without vitamin D supplements survival was 82.5% and 65.7%, respectively (P = 0.017). Similarly, length of hospitalization was 7.6 and 17.2 days with and without vitamin D supplements, respectively (P = 0.001). These differences remained significant by logistic and multiple regression analyses (adjusting for age) for survival status (P = 0.007) and length of hospitalization (P = 0.001), respectively.
Conclusion: In this Swiss maintenance HD cohort 60% of patients were on vitamin D supplements for at least 3 months during the follow-up period, with calcitriol being the primary vitamin D analogue prescribed. In view of current recommendations with regard to 25-OH vitamin D target levels >40 µg/L, baseline concentrations in our cohort were rather subtherapeutic. No significant differences regarding serum calcium, phosphate and PTH levels were found in association with vitamin D supplementation. In contrast, patients on vitamin D supplements seem to have significantly lower mortality and morbidity based on better survival and fewer hospital days compared to patients without vitamin D therapy.

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Stable hemoglobin values and lower dose requirements after complete conversion from epoetin beta to C.E.R.A. A single center experience

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Purpose: CERA (Mircera®) is a third generation Erythropoiesis-Stimulating Agent (ESA) that allows treatment of renal anemia with a once monthly dosing interval. Important considerations after a switch include hemoglobin stability as well as cost parity. Phase III trials have shown that both hemoglobin stability as well as cost effectiveness are given after a switch. To confirm these data in a "real life" situation in Switzerland we analyzed hemoglobin values and iron parameters as well as development of dose and cost after change of treatment from epoetin beta to CERA in a Swiss center.
Methods and materials: In February of 2008 all Patients were converted from Epoetin beta (Recormon), two to three times per week, to once monthly CERA according to the label. We retrospectively analyzed hemoglobin values of these patients from three months before conversion to fifteen month after the conversion and the corresponding ESA doses. In addition iron parameters before and after conversion were analyzed. An analysis of cost for ESA was performed based on list prices for the respective ESA in Switzerland.
Results: 14 patients were eligible for analysis. The mean Hemoglobin values of the patients were not significantly different in the last three months before and fifteen months after conversion (11.81 g/dl vs. 11.28 g/dl; p = ns). The mean epoetin beta dose in the three month prior to conversion was 16641 IU/week. The mean dose of CERA in the fifteen months after conversion was 214 µg/month and the dose at month fifteen was 198 mg/month. Cost calculations using the list prices for Switzerland resulted in mean costs of CHF 1340 per patient and month on epoetin beta. During the fifteen months after conversion to CERA the average monthly cost per patient was CHF 848. At month fifteen the average cost was CHF 802. Values for transferrin saturation measured at month fourteen were comparable to baseline values (20.3 vs. 13.6%, p = 0.1). Ferritin was significantly higher at month fifteen compared to baseline (466 vs. 152 ng/ml; p = 0.005). This difference depended on four patients with low transferrin saturation and high ferritin as well as signs of inflammation.
Conclusion: This single center survey was intended to evaluate long term development of hemoglobin values and CERA doses after conversion from epoetin beta to CERA. Hemoglobin values remained stable throughout the observation period of fifteen months. The switch to CERA resulted in considerable costs savings from CHF 1340/month at baseline to CHF 802 at month fifteen. Dose and cost remained stable even though a high proportion of patients showed signs of inflammation at month fifteen.

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KDOQI target achievement is improved with cinacalcet in clinical practice – the swiss OPTIMIZE survey

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Purpose: Secondary hyperparathyroidism (SHPT) is a common complication in patients with stage 5 chronic kidney disease (CKD), and is associated with adverse clinical outcomes. Cinacalcet has been shown to be an effective treatment for SHPT, significantly reducing serum parathyroid hormone (PTH) while simultaneously lowering Ca, P and CaxP levels, thus increasing the proportion of patients achieving KDOQI targets.
Methods and materials: OPTIMIZE (Optimized Usage of Mimpara® in SHPT Treatment) is a multi-center, observational survey designed to collect data from Swiss dialysis patients with SHPT. Patients started cinacalcet at baseline for up to 12 months following a free treatment regimen at physician's discretion.
Results: This analysis includes full data set from 130 patients from 20 different centers in Switzerland. At baseline mean ± SD age was 62.6 ± 14.7 years; iPTH was poorly controlled (mean 62 ± 40 pmol/L); 51% of patients were receiving vitamin D and 87 % were at least on one phosphate binder. Following cinacalcet initiation an increase in the percentage of patients within KDOQI targets for PTH, P and CaxP levels was observed. The mean ± SD cinacalcet dose was 56 ± 30 mg/day at month 12.

	Baseline (%)	12 Month (%)	Δ (%)
iPTH (16.5–33.0 pmol/L)	17	36	19
Corr Ca (2.1–2.4 mmol/L)	53	50	–3
P (1.13–1.78 mmol/L)	41	54	13
CaxP (<4.5 mmol2/L2)	65	86	21
PTH & CaxP within targets	12	30	18
All 4 parameters within targets	4	10	6

Conclusion: A higher percentage of patients with stage 5 CKD and SHPT achieved KDOQI targets with cinacalcet compared with baseline. The observed effectiveness of cinacalcet in clinical practice is consistent with findings from randomized, phase III clinical trials.

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NKF/KDOQI target achievement for PTH, Ca, P and CaxP in different Swiss dialysis centres – a snap-shot analysis

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Purpose: Disturbances in bone mineral metabolism cause secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD). Most dialysis patients receiving phosphate binder- and vitamin D-based therapy do not reach the NKF/KDOQI target values for PTH, Ca, P and CaxP. The purpose of this snap shot analysis was to document in dialysis patients the target achievement at two time points, analyzing patients with and without cinacalcet separately.
Methods and materials: Of the 305 patients only 13% achieved the combined NKF/KDOQI target values (PTH, Ca, P, and CaxP) at t1. However, at t2 the target achievement increased to 18% (+5%). When patients with and without cinacalcet were analyzed separately, the increase in target achievement was more pronounced in patients on cinacalcet (+11% vs. +3%). Interestingly, the mean daily dose of cinacalcet was similar at both time points (49.1 mg [t1]) and 50.4 mg [t2]), but the numer of patients on cinacalcet increased. Co-medication with phosphate binders and vitamin D was slightly higher in patients on cinacalcet at both time points.

Results:

cinacalcet	+	+	+	–	–	–
	t1	t2	Δ	t1	t2	Δ
n	61	84		244	208	
age (yrs)	64	65		65	67	
weight (kg)	78	76		72	72	
vitamin D	62%	64%	2%	50%	54%	4%
P binder	82%	86%	4%	68%	75%	7%
PTH, CaxP in target	20%	37%	17%	26%	33%	7%
PTH, Ca, P, CaxP in target	8%	19%	11%	14%	17%	3%

Conclusion: Overall the NFK/KDOQI target achievement improved at time point t2, suggesting that the physician's reflection of their own centre data led to optimized patient management. Patients treated with cinacalcet displayed a slightly better target achievement at t2. The higher use of phosphate binders and vitamin D in this group at both time points (t1 and t2) may contribute to this finding, however the more frequent use of cinacalcet may also have improved the target achievement results.

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Use of high Volume hemofiltration in patients with refractory septic shock and acute kidney injury

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Purpose: High Volume Hemofiltration (HVHF) has been used successfully in animal models with sepsis and preliminary data have shown that this technique may improve the haemodynamics in patients with refractory septic shock. HVHF was used compassionately in our patients having acute kidney injury (AKI) and refractory septic shock.
Methods and materials: HVHF was offered to patients with AKI (stage I-F according to the Rifle classification) and septic shock (Bone criteria) and requiring norepinephrin doses >0.2 µg/kg/min. Treatment was implemented within the first 24 hours of septic shock diagnosis. Patients were treated with CVVHDF (Prismaflex® Gambro) with an AN69 ST 1.5 m^2 membrane. The ultrafiltration rate was 70 ml/kg/hr until reversal of shock or death.
Results: From July 07 to December 08, 25 patients (mean age: 64 ± 12 years, mean SAPS II: 65 ± 14 and Apache II 29 ± 8, mean serum creatinine: 262 ± 153 µmol/l) were treated with HVHF. ICU and 28 day mortalities were respectively 48 and 52%. Compared to non-survivors, survivors were younger (61 ± 12 vs 67 ± 12 years old) and had lower severity scores (SAPSII: 60 ± 17 vs 70 ± 7 and APACHE II: 26 ± 8 vs 32 ± 5).
Conclusion: Although survivors and non-survivors on day 28 differ in terms of age and severity scores, we cannot exclude a beneficial impact of HVHF in our patients with refractory septic shock and AKI. As mortality is very high in this population, HVHF should be offered on a compassionate basis to the patients with refractory septic shock until results from RCTs on HVHF in this population are available.

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Late steroid withdrawal after ABO blood-group incompatible kidney transplantation: high rate of mild cellular rejection

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Purpose: Little is known about the safety of steroid withdrawal after ABO blood group-incompatible living donor kidney transplantation.
Methods and materials: Between September 2005 and November 2007, a total of 15 patients were successfully transplanted over the blood group barrier in our transplantation centres. Similarly to transplant recipients with normal immunological risk, we aimed to taper and eventually stop oral prednisone because of the well known negative impact of steroids on cardiovascular morbidity and mortality which in turn is limiting graft survival.
Results: Up to now, patient and graft survival was 100% after a median follow-up of 839 days (range 513–1281 days). On the basis of serial protocol biopsies, late steroid withdrawal could successfully be performed in 5 out of 11 patients. The remaining 6 patients showed histological signs of mild and subclinical acute rejection shortly after complete withdrawal or even during steroid tapering.
Conclusion: With this elevated risk of at least subclinical acute rejection after late steroid withdrawal we propose that steroid withdrawal in ABO blood group-incompatible kidney graft recipients should only be performed after a protocol biopsy showing normal tissue and together with a thorough clinical and in doubtful cases also histological follow-up.

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Renal transplantation does not normalize cardiovascular rhythmicity in children with chronic kidney disease

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Purpose: Children with chronic kindey disease display blunted circadian (24 h) and ultradian (12 h, 8 h, and 6 h) cardiovascular rhythms. Altered circadian rhythmicity is an independent cardiovascular risk factor, and abnormal ultradian rhythms have been linked to renal dysfunction. The integrity of cardiovascular rhythmicity in patients post kidney transplantation is unknown.
Methods and materials: We analyzed the prevalence and dimensions of circadian and ultradian rhythms by Fourier Analysis of 24h ABPM profiles in 123 kidney transplanted children from 3 university centers (age 3–20 yrs, GFR 79 ± 28 ml/min/1.73 m², time since transplantation 3.8 ± 3.2 yrs). Results were compared with data of 938 age-matched healthy subjects and 408 children with chronic kindey disease (stage 2-4; GFR 49 ± 22).
Results: The prevalence of hypertension was 87% and 62%, and of uncontrolled hypertension 31% and 37%, in the transplanted and chronic kidney disease cohorts, respectively. Non-dipping was found in 36% of the transplanted and 27% of patients with chronic kidney disease compared to 10% of controls ($p < 0.0001$). While the prevalence of 12 h rhythms was slightly increased in transplanted (55%) and chronic kidney disease (54%) children vs. controls (40%, $p < 0.0001$), the amplitudes of the 24 h, 12 h, 8 h, and 6h rhythms were reduced in transplanted compared to controls ($p < 0.0001$ for 24 h, 8 h, and 6 h), similar as in the children with chronic kidney disease cohort. Acrophases were delayed compared to controls ($p < 0.05$ for 24 h and 8 h). Similar results were found for heart rate rhythmicity.
Conclusion: Pediatric allograft recipients exhibit a high prevalence not only of hypertension but also of abnormal circadian and ultradian cardiovascular rhythmicity. The relevance of these alterations for long-term graft function and cardiovascular health awaits further examination.

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Clinico-pathological evolution of patients with polyoma BK-viremia treated with reduction of immunosuppression

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Purpose: Polyoma BK-virus associated nephropathy (PVAN) is a serious complication after renal transplantation and its treatment is mainly based on reduction of immunosuppression. The aim of this study was to investigate the efficacy (i.e. clearance of BK-viremia) and safety (i.e. occurrence of allograft rejection) of an immunosuppression reduction regimen in patients with BK-viremia.
Methods and materials: Two hundred and six consecutive renal allograft recipients transplanted between January 2005 and June 2008 with ≥1year follow-up were included. Screening for BK-replication was performed by urinary Decoy-cells, and if positive, BK-viremia was determined by real-time PCR. Presumptive PVAN was defined as BK-viremia >10000 copies without histological evidence of PVAN, definitive PVAN as BK-viremia and positive SV40-antigen immunohistochemistry in allograft biopsies. Adaptation of immunosuppression consisted of reduction from triple to dual therapy, lowering CNI target levels, and reduction of mycophenolate-mofetil.
Results: Overall, 38/206 patients experience BK-viremia (18%). Nine of 206 patients (4%) had BK-viremia <10000 copies, 17/206 patients (8%) had presumptive PVAN, and 12/206 patients (6%) developed definitive PVAN. Upon reduction of immunosuppression, clearance of BK-viremia was observed in 34/38 patients (89%) after 28-844 days (median 192). Following clearance of BK-viremia 4/34 patients (12%) experienced clinical and 5/34 patients (15%) subclinical rejection. No allograft loss due to PVAN or subsequent rejection was observed. From peak BK-viremia to last follow-up, serum creatinine decreased in 26/38 patients (68%) and increased in 12/38 patients (32%). Notably, five patients had an increase >20% and four of them had experienced allograft rejection after clearance of BK-viremia.
Conclusion: Reduction of immunosuppression effectively helps to clear BK-viremia, but is associated with a relevant risk for subsequent allograft rejection. Parameters that can predict clearance of BK-viremia might be beneficial to adjust the extent and speed of immunosuppression reduction in order to prevent subsequent rejection episodes.

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Impact of pure protocol biopsies on patient management

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Purpose: Since 2001 we routinely perform renal graft protocol biopsies in the absence of any clinical signs of graft dysfunction (pure protocol biopsies). Although there is good data correlating the results from protocol biopsies in the first 6 months with later graft outcome, the benefit of protocol biopsies and their risk-benefit ratio still remain controversial. The purpose of this study was to determine how often pure protocol biopsies lead to an intervention and to assess the impact of the intervention on graft function, graft survival and patient survival after 1 year.
Methods and materials: We performed a retrospective analysis of all transplantations performed between February 2001 and August 2007 at the Basel University Hospital. Only patients in whom pure protocol biopsies after 3 *and* 6 months were available were considered. eGFR (MDRD) and the urine albumin to creatinine ratio (alb/crea) were analyzed on the days of biopsy and 1 year after transplantation. Interventions were classified as acute rejection therapy, modulation of maintenance immunosuppression or "other". Changes in eGFR (Δ eGFR) and alb/crea (Δ alb/crea) were calculated.
Results: 304 pure protocol biopsies in 152 patients were analyzed. Demographic data are shown in table 1. In 90 out of 152 patients (59.2%) the 3 and/or 6 month biopsy led to an intervention. 33 of these patients (21.7%) had an intervention after 3 months, 33 patients (21.7%) had an intervention after 6 months and 24 patients (15.8%) had an intervention after 3 *and* 6 months. In the remaining 62 patients (40.8%) neither biopsy led to an intervention (details see table 2). One year patient and graft survival was 100% in patients with or without intervention. The type of intervention is shown in table 3. An improvement of graft function (positive Δ eGFR between two points in time) was observed in approx. 60% of patients with an intervention and equally often in patients without an intervention (see table 4). Similarly an increase in Δ alb/crea was observed equally often in the two groups (see table 5). The differences between groups were not statistically significant. No serious adverse events in the context of the protocol biopsies were observed.

Table 1
Patient characteristics

Number of patients(n)	152
Median age (years)	54 (16–71)
Male/female (%)	68.4/31.6
Living donor/Cadaveric donor (%)	59.9/40.1

Table 2
Number of biopsies followed by intervention

Total	**At 3 months**	**At 6 months**	
n	304	152	152
With Interv.	114 (37.5%)	57 (37.5%)	57 (37.5%)
No Interv.	190 (62.5%)	95 (62.5%)	95 (62.5%)

Interv. = Intervention

Tabel 3
Type of intervention

Total (n = 114)	**At 3 months**	**At 6 months**	
Acute rejection therapy	71 (62.3%)	31 (54.4%)	40 (70.2%)
Modulation of IS 42 (36.8%)	26 (45.6%)	16 (28.1%)	
Others	1 (0.9%)	0 (0%)	1 (1.7%)

IS = Maintenance Immunosuppression

Table 4
Improvement of graft function (= positive Δ eGFR) after protocol biopsy [% (number of biopsies)]

Course after biopsy	Total	At 3 months	At 6 months
With Interv.	58.8% (67)	59.6% (34)	57.9% (33)
No Interv.	59.5% (113)	57.9% (55)	61.1% (58)

Table 5
Improvement of graft function (= decrease of Δ alb/crea) after protocol biopsy [% (number of biopsies)]

Course after biopsy	Total	At 3 months	At 6 months
With Interv.	57.0% (65)	52.6% (30)	61.4% (35)
No Interv.	57.4% (109)	64.2% (61)	51.6% (49)

Conclusion: In nearly 60% of patients the pure protocol biopsy 3 or 6 months after transplantation led to an intervention. The majority of interventions were therapy of acute rejection despite lack of clinical signs of deteriorating graft function. Pure protocol biopsies thus had a major impact on patient management. Patient and graft survival 1 year after transplantation was excellent and not different in the intervention or no intervention group, suggesting that the interventions had a positive impact.

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Renal transplantation in children and young adults in Armenia

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Purpose: Renal transplantation (Tx) is the optimal treatment of ESRF in children and young adults. Due to poor earlier (1983–1996) results in Armenia with deceased donors only (patient survival 75% at 1 year; n = 45), a new Tx program was started in 1999 with living related donors, based on partnership programs with Zurich (mainly nephrology) and Antwerp (dialysis and Tx).
Methods and materials: Work-up of patients was according to European protocols. Tissue typing was done locally (initially checked in Antwerp). Immunosuppression based on cyclosporine (CsA) or tacrolimus (in 1), prednisone and azathioprine (MMF in selected cases) was provided by the government. Blood CsA levels are determined locally. Transplant biopsies are evaluated in Yerevan and Zurich.
Results: From 1999 until December 2008 61 living donor Tx were performed. Of these, 19 patients (13 males) were <25 years (range 13–25). Dialysis before Tx lasted 2 to 64 weeks. Primary disease was glomerulonephritis (5), amyloidosis of FMF (1), obstructive uropathy (5), hypoplasia/dysplasia (1), and other/unknown (7). One patient required temporary dialysis for delayed graft function. All patients survived. Actuarial graft survival was 100% at 1 year and 95% at 2 years. One graft was lost due to reduced immunosuppression for Kaposi sarcoma (1). Three patients were treated for CMV disease; one had measles. One patient required intervention for ureteral stenosis. All but one regained good to excellent quality of life. No problems with transition of patients from pediatric to adult unit arose because Arabkir – basically a pediatric hospital – has the only Tx unit in Armenia.
Conclusion: Kidney Tx is an important treatment modality even in countries with limited resources. Integrated care for pediatric and adult patients is an alternative for a small unit run by a pediatrician. Instrumental to success was solid training, sufficient – albeit modest – infrastructure, and continuous support from many sides.

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C4d-fixing capability of low-level donor-specific HLA-antibodies is not predictive for development of early antibody-mediated rejection

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Purpose: Low-level donor-specific HLA-antibodies (HLA-DSA) (i.e. positive by solid-phase assays, negative by CDC-crossmatch) are strongly associated with early antibody-mediated rejection (AMR) in renal allograft recipients. However, several studies indicate that not all such HLA-DSA have a detrimental clinical impact. The aim of this study was to investigate whether the C4d-fixing capability of HLA-DSA allows distinguishing harmful from presumably clinically irrelevant HLA-DSA.
Methods and materials: The 64 patients included in this study derive from a retrospective study and all have been transplanted in the presence of preformed low-level HLA-DSA detected by single-antigen flow-beads (SAFB). Thirty-four of these 64 patients (53%) experienced early AMR (DSA/AMR group), 30 patients (47%) did not (DSA/noAMR group). Notably, HLA-DSA characteristics (i.e. number, titer, class), frequency of re-transplants and prior pregnancies, as well as immunosuppressive regimens of these two groups were not different. Pre-transplant sera were re-analyzed using a modified SAFB-assay measuring C4d-fixation induced by HLA-antibodies.
Results: C4d-fixing HLA-DSA were detected in 6/34 patients (18%) of the DSA/AMR group and in 5/30 patients (17%) of the DSA/noAMR group (p = 1.0). Overall, C4d-fixation correlated weakly – but significantly – with the amount of HLA-antibodies bound to SAFB (r2 = 0.02, p = 0.009).
Conclusion: The C4d-fixing capability of low-level HLA-DSA was not predictive for the development of early AMR limiting the usefulness of this assay to define their clinical relevance.

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Clinical characteristics of posttransplant anemia and practice patterns regarding anemia management in a Swiss renal transplant cohort

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Purpose: A cross sectional analysis of 1040 patients after renal transplantation among five Swiss transplant centers performed in 2008 revealed a prevalence for anemia of 21 percent with only 48% of anemic subjects receiving treatment with an erythropoietin stimulating agent (ESA). It was the purpose of this study to further characterize factors associated with posttransplant anemia in this cohort, especially its temporal relation to time after transplantation, iron status and immunosuppressive regimen. In addition, practice patterns regarding anemia treatment with ESA and iron substitution were analyzed with particular emphasis on center effects.
Methods and materials: The present analyses are based on a national survey to which five Swiss transplant centers (Basle, Berne, Geneva, Lausanne, and Zurich) were contributing data to anemia status and therapy. Data were collected between June and August 2008 in a cross sectional manner, allowing all patients to be included from which information on hemoglobin concentration, graft function, anemia therapy, immunosuppression and comedication affecting erythropoiesis was available at some timepoint within 12 months prior to data assessment. Additional information (if available) was gathered on iron metabolism, inflammation and parathyroid function. Temporal effects on anemia status were analyzed after stratification of the entire cohort into five time intervals according to transplant vintage.

Results:

Patient characteristics regarding anemia and treatment status stratified according to period after TPL

Time since TPL, yr							
	All groups	**<1**	**1–4**	**4–7**	**7–11**	**>11 P**	
N of pts.	1037	182	287	171	152	245	–
Hb (g/L)	122.9±17	118.8±18	126.2±17	122.8±16	124.2±16	121.4±17	0.000
Anemia (Hb ≤110 g/L), %	20.8	29.7	16.7	18.1	17.8	22.9	0.008
On ESA (%)	19.7	17	11.8	22.8	20.4	26.5	0.000
ESA dose (IU/week)	7149±5979	11'355±7804	6453±4858	5291±5533	7195±4623	6599±5569	0.000
Ferritin (µg/L)	260±302	386±414	251±268	211±205	221±256	219±279	0.000
On iron (%)	12	10.7	7.9	17.3	13.3	10.9	0.000
GFR (ml/min)	50.9±21	50.6±20	54.7±20	49.8±20	50.1±23	48.0±23	0.007
CRP (mg/L)	7.3±18	11.6±33	6.6±13	5.7±13	6.1±9	6.2±13	0.180
Albumin (g/L)	39.1±5.4	38.2±5.6	40.1±4.5	40.0±4.0	38.7±7	38.2±5	0.000
PTH (ng/L)	110±124	126±170	106±116	106±96	88±77	118±133	0.207
Age (yr)	54.6±13	52.8±12	52.5±14	54.0±13	55.9±14	58.0±13	0.000

Treatment combinations containing mycophenolates (MPA) ± calcineurin inhibitors (CNI) ± azathioprine (AZA) ± steroids (STR) were analyzed with regard to differences in anemia status and management, and related factors. Among pts. on CNI+MPA vs. CNI+AZA or CNI+STR, only time since TPL was significantly shorter in the MPA containing group. Among pts. on MPA+CNI+STR vs. AZA+CNI+STR ESA dosage, but not percentage of patients on ESA therapy, was higher in the MPA containing regimen. Logistic regression analysis with anemia (Hb ≤110 g/L) as the dependent variable, and treatment group and time since transplant (plus ESA dose for the comparison of MPA+CNI+STR vs. AZA+CNI+STR) as covariates did not reveal an effect on any treatment combination (except for MPA+CNI vs. STR+CNI with "treatment group" being an independent predictor of anemia; P = 0.039). Practice patterns and possible center

effects among the 5 participating hospitals were analyzed: Mean Hb concentrations ranged from 116.6 to 129.7 g/L (P = 0.000) among centers and the percentage of patients on ESA substitution from 10.0 to 34.5 (P = 0.000), with ESA dosages being administered ranging from 4800 to 9200 IU/week (P = 0.002). Hb concentration and the likelihood of being anemic (Hb ≤110 g/L) are significantly related to center affiliation, both in bivariate correlation as well as in multivariate regression analysis (with GFR, time since transplant, and ESA substitution as covariates). Similarly, the likelihood to receive ESA treatment was significantly associated with center affiliation.
Conclusion: Anemia is highly prevalent among patients with a renal graft treated in Swiss transplant centers. Prevalence is highest within the first year after transplantation, and lowest between 2 to 4 years posttransplant. Time after transplantation is a significant predictor of anemia status, even after taking into account graft function, age, and ESA substitution. Most likely, this reflects type and degree of immunosuppressive therapy, which are maximal during the first 12 months after transplantation. Surprisingly, treatment with mycophenolates (MPA) is not associated with lower Hb concentrations in most circumstances, even after correction for potential confounders. Finally, anemia status seems to be affected by local factors. Similarly, anemia management is heterogeneous among centers, i.e. with regard to ESA substitution practices.

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H1N1 influenza A presenting with agranulocytosis in a renal transplant patient

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Purpose: Pandemic H1N1 2009 influenza A virus has been identified as the cause of a worldwide outbreak of febrile respiratory infection. Although most infections have been self-limited, the risk of influenza complications may be higher in some subpopulations, including patients on immunosuppressive therapy. We report a renal transplant patient who presented with fever and extreme agranulocytosis which turned out to be due to H1N1 influenza.
Methods and materials: This 56 year old white male had received an ABO incompatible kidney transplant in 2007 from his sister for end stage renal disease due to adult polycystic kidney disease. He had been stable with serum creatinin 133 umol/l on an immunsuppressive regime including tacrolimus (2.5 mg/d) and mycophenolate mofetil (2x 500 mg/d). He presented to the emergency room with a 3-day history of fever (38 °C), sore throat, arthralgia, myalgia, shivering and new onset occipital headache. On admission the temperature was 38.3 °C, BP 115/85 mm Hg, heart rate 107/min, sore enoral mucosa and no lymphadenopathy; there was no meningeal irritation. Laboratory findings showed leucopenia of 2,300 G/l with complete agranulocytosis (10 G/l) but normal lymphocyte count (890G/l) with some atypical lymphocytes (40 G/l). His renal function was unchanged relative to his usual baseline (serum creatinine 131 µmol/l). Hemoglobin, platelets, liver function tests chest X-ray and urinalysis were normal. After taking blood and urine cultures and a pharyngeal swab for H1N1, the patient was put into isolation and empiric treatment with cefepime and oseltamivir (150 mg/d) was begun. Mycophenolate mofetil was replaced by prednisone 20 mg/d. Cultures and CMV screening (pp65 antigen) as well as serological tests for HHV-6, Hepatitis A, B and C, were negative. When after 24 hours a positive result of the H1N1 PCR was received (6101 Geq/ml), cefepime was stopped and oseltamivir continued for total 5 days. After 72 hours, the patient became afebrile and the granulocyte count increased to 520 G/L. Further recovery was uneventful until the patient's discharge on day 6 with a granulocyte count of 7290 G/l.
Results: n.a.
Conclusion: H1N1 may present as agranulocytosis in renal transplant patients.

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Validity of two sleep quality items for the swiss transplant cohort study in renal transplant recipients

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Purpose: Poor Sleep quality (SQ) and poor daytime functioning (DF) affect many renal transplant patients (RTx). The aim of this study was to evaluate (following the American Psychological Association criteria) the validity of 2 items for the Swiss Transplant Cohort Study (STCS) assessing SQ (STCS-SQ) and DF (STCS-DF), using the Pittsburgh Sleep Quality Index (PSQI) as the gold standard for validation.
Methods and materials: We used a cross-sectional correlational design, in 135 RTx aged 21–76 years (mean: 51.6 ± 11.9) and measured demographics, depressive symptomatology (HADS) and perceived health status (EQ-5D) coincident with the PSQI and the 2 SQ items. Content validity was evaluated using the Content Validity Index (CV-I). Evidence based on response process, internal structure and relations to other variables of the 2 SQ items relative to selected clinical outcomes were assessed using Spearman's correlation coefficients.
Results: The prevalence of poor SQ based on the PSQI was 47.4% (median score: 5, Inter Quartile Range (IQR): 3-8) and 30.7% using the STCS-SQ item (median score: 8 IQR: 6–9) and 34.1% of subjects reported poor DF (median score: 8 IQR: 5.6–9). Content validity was good for the STCS-SQ item but poor for the STCS-DF item. As hypothesized the STCS-SQ item was moderately correlated with the STCS-DF item (Spearman's rho: 0.520 p <.01) showing a structure of two different constructs that interact. The evidence in relations to other variables revealed that there were significant correlations between the combined two STCS items and the PSQI total score (Spearman's rho: –0.784, p <.001), depressive symptomatology (Spearman´s rho: –0.680, p <.001), perceived health status (Spearman's rho: 0.619, p <.001) and subjective health status on the visual analogue scale (Spearman´s rho: 0.671, p <.001) in the expected direction.
Conclusion: There was good support for the validity of the STCS-SQ items while findings are mixed for the STCS-DF item suggesting that this item may not be an adequate measure of daytime functioning.

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Differences in determination of blood everolimus concentration in kidney transplant recipients

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Purpose: Clinical management of transplant recipients depends on therapeutic drug monitoring (TDM) and regulation of immunosuppressive therapy. Individualization of Everolimus (ERL) dosage is mandatory to achieve an optimal therapy assessing the risk of acute rejection while limiting the incidence of drug-related adverse events. We compared an immunoassay for ERL levels with the high-performance liquid chromatography (HPLC) method.
Methods and materials: A total of 81 pre-dose samples of 7 kidney transplant patients who took ERL were analyzed with two methods: the semi-automated immunoassay (Innofluor® Certican® Assay System, Seradyn Inc) using fluorescent polarization immunoassay (FPIA) technology on Abbott® TDxFLx analyzers and HPLC.
Results: The correlation between everolimus concentrations measured by FPIA and HPLC showed a Pearson coefficient of 0.83. However the FPIA gave a mean overestimation of 36.6 % ± 3.3 (CI 95%) compared to HPLC. The comparison of patients results yielded the following Deming regression equation FPIA = 1.103 x HPLC + 2.63. There was no difference between patients receiving calcineurin inhibitor co-medication or not.
Conclusion: Compared to HPLC the immunoassay method shows a relevant positive bias in the determination of ERL blood concentrations. The overestimation of the immunoassay is probably due to cross-reactivity of the FPIA antibody with ERL metabolites. This result is comparable to other studies but in the clinical settings interpretation of the ERL levels requires attention to the method used for determination. When speaking about TDM and levels of immunosuppressant agents, be aware of the applied analytic test.

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