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Established in 1871

Formerly: Schweizerische Medizinische Wochenschrift

Swiss Medical Weekly

Supplementum 167

ad Swiss Med Wkly
2008;138(47-48)
November 29, 2008

The European Journal of Medical Sciences

40th Annual Meeting Swiss Society of Nephrology

OLMA St. Gallen

December 3-5, 2008

Suppl. 167
ad Swiss Med Wkly
2008;138(47-48)
November 29, 2008

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Regular subscription price for 2008:
CHF 150.– (shipping not included)

Published fortnightly

Hypoxia-regulated gene expression in glomeruli from biopsies of patients with arterionephrosclerosis (ANS)

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Purpose: So-called “hypertensive nephropathy” is the second most common cause for incident dialysis. In contrast to this relevant role little is known about the pathogenesis of its histological correlate, ANS. We used a genomic approach to test whether glomerular hypoxia contributes to ANS.

Methods and materials: Gene expression profiles (HG-U133A) of microdissected glomeruli and tubulointerstitium from patients with biopsy-proven and clinically established ANS (n = 19; s-creatinine: 2.2 ± 1.5 mg/dl) and controls (n = 5, tumor nephrectomies) were analyzed.

Results: A significantly stronger overall gene regulation in the glomeruli than the tubulointerstitium of patients with ANS was seen. Functional annotation analysis of the glomerular data revealed a prominent activation of hypoxia-associated processes relevant to the progression of renal disease (e.g. angiogenesis, inflammatory processes and fibrosis). Therefore literature-derived target genes of the hypoxia-induced factors (HIF) were studied in glomeruli with ANS: 290 of a total of 476 genes were significantly regulated. To test the biological relevance of hypoxia and HIF in ANS, expression data of all above HIF target genes underwent unsupervised cluster analysis. This resulted in the clear segregation of the ANS biopsies from control samples. Among the regulated HIF target genes induction of genes known to be involved in angiogenesis [e.g. vascular endothelial growth factor (VEGF-A)] and inflammatory processes [e.g. chemokine (C-X-C) receptor 4 (CXCR4)] was observed. Besides through promotion of angiogenesis and modulation of inflammation hypoxia can influence the progression of renal disease by activation of fibrosis. In glomeruli of patients with ANS 73 genes known to be involved in renal fibrosis were studied and 42 were found to be regulated. Many of these are reported to be hypoxia induced [e.g. TIMP metalloproteinase inhibitor 1 (TIMP1), serpin peptidase inhibitor/plasminogen activator inhibitor type 1 (SERPINE1), and Fibronectin 1 (FN1)]. The induction of CXCR4 and FN1 was confirmed by real-time RT-PCR on glomeruli from an independent cohort of patients with ANS (n = 14) and controls (n = 6, donor kidneys): CXCR4 and FN1 were induced 3.6 ± 3.7-fold and 10.8 ± 8.3-fold in ANS, respectively (p < 0.05 each).

Conclusion: Our results show a prominent glomerular regulation of HIF response genes in patients with ANS, suggesting that glomerular hypoxia is a major contributor to ANS.

1.1

treatment reduced pendrin mRNA levels. In parallel to mRNA data KCl treatment decreased pendrin protein expression. In addition, pendrin protein levels were downregulated during NH4Cl treatment while combination of DOCA with NaHCO₃ caused upregulation of its protein levels.

Conclusion: In summary, both an alkali load, independent of the concomitant cation, as well as an acid load appear to regulate pendrin protein expression. However, it seems that chloride and acid-base status may be the key regulatory factors. AE1 appears to be also strongly regulated by acid and alkali load. No direct correlation with electrolyte status could be detected for AE1. Thus, AE1 appears to play a major role only in acid-base handling, whereas pendrin appears to be involved in acid-base and electrolyte (namely chloride) homeostasis.

Regulation of the renal Cl-/HCO₃-exchangers AE1 and pendrin

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Purpose: In the collecting duct, intercalated cells represent the minority cell type within the distal convoluted tubule (DCT), the connecting tubule (CNT), and cortical and medullary collecting duct and are crucial for renal net acid excretion. At least 2 types of intercalated cells have been classified based on the presence or absence of the anion exchanger AE1 (Band3, SLC4A1) and the subcellular distribution of the H⁺-ATPase. Type B intercalated cells have an apical Cl⁻/HCO₃⁻ exchanger pendrin (SLC26A4) which functions in concert with a basolateral H⁺-ATPase to mediate secretion of bicarbonate. Type A intercalated cells mediate secretion of H⁺ through an apical H⁺-ATPase, which functions together with the basolateral Cl⁻/HCO₃⁻ exchanger, AE1. The aim of this study was to investigate the regulation of AE1 and pendrin in response to changes in acid-base and electrolyte status and the effect of the mineralocorticoid DOCA (Deoxycorticosterone acetate).

Methods and materials: C57BL/6J mice were divided into 8 groups: group 1) control; group 2) 0.28 M NH₄Cl; group 3) 0.28 M NaHCO₃ and s.c. injections of DOCA at day 1 and 4; group 4) 0.28 M NaCl; group 5) s.c. injections of DOCA at day 1 and 4, group 6) 0.28 M NaHCO₃, group 7) 0.28 M KCl and group 8) 0.28 M KHCO₃. All animals were given 1% sucrose in drinking water, treated for 7 days and placed in metabolic cages for the final 4 days.

Results: mRNA abundance and protein expression of AE1 in the cortex were not significantly changed between different treatment groups. In contrast, medullary AE1 mRNA abundance was significantly increased in the NaHCO₃ group and during combined NaHCO₃ and DOCA treatment. Additionally, treatment with NaCl and KHCO₃ resulted in a trend towards enhanced mRNA abundance. In parallel, NaHCO₃ as well as combination of NaHCO₃ and DOCA, and NH₄Cl alone resulted in increased medullary AE1 protein expression. Pendrin mRNA abundance was significantly increased during NaHCO₃ and DOCA, NaCl, and KHCO₃ treatment. In contrast, KCl

1.2

Alport's syndrome: another inflammatory kidney disease?

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Purpose: Alport's syndrome is a hereditary glomerular disease linked to structural abnormalities of collagen type IV. In a mouse model interstitial T cells were involved in disease progression and fibrosis. Chemokines promote leukocyte recruitment to the kidney and the chemokine receptor CXCR3 is important for T cell infiltration in mouse models.

Methods and materials: We characterized a series of biopsies for the expression of the alpha 5 chain of collagen IV (to confirm the diagnosis), for the expression of CXCR3 and CD3 positive T cells. We compared 19 human renal biopsies, in which the diagnosis of Alport nephropathy was based on morphological criteria, to the renal tissue from pretransplant biopsies from donor kidneys (n = 9).

Results: In 18 of 19 biopsies a complete loss of alpha5-chain of type IV collagen from the glomerular tuft confirmed the diagnosis. A prominent number of CXCR3 positive cells was found in the tubulointerstitium, but only rarely within the glomerular tuft. Besides diffuse infiltrates the CXCR3 positive cells were found to form nodular infiltrates within the tubulointerstitium. The distribution of CXCR3 positive cells mirrored the distribution of CD3 positive T cells. The number of CXCR3 positive cells was significantly higher than in normal controls and correlated with serum-creatinin at the time of biopsy (p < 0,05).

Conclusion: We demonstrate that a non-inflammatory glomerular lesion with a structural defect of collagen IV leads to tubulointerstitial T cell accumulation. This is associated with the chemokine receptor CXCR3 and correlates with renal function. Targeting T lymphocytes, e.g. by CXCR3 blocking agents, might be a suitable approach to hold disease progression in patients with Alport's syndrome.

1.3

Proteomics for identifying mechanisms and biomarkers in acute kidney injury after extracorporeal circulation

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Purpose: Acute kidney injury (AKI) is a well-known complication following cardiac surgery using cardiopulmonary bypass (CPB) with high morbidity and mortality. CPB-associated AKI is still poorly understood. With the ultimate goal to identify early biomarkers for AKI, we analyzed the urinary proteome before and after CPB and compared the urinary proteome obtained on the first postoperative day between patients with and without later development of AKI with difference gel electrophoresis (DIGE). DIGE enables the separation of more than one sample in a single 2D gel. The use of an internal standard for normalization minimizes experimental variations thus increasing confidence in matching and quantifying different gels.

Methods and materials: Thirty-six patients undergoing elective CPB surgery were enrolled. Spot urine samples before and after CPB were collected. AKI was defined according to the RIFLE classification. To compare preoperative with postoperative urinary proteome, twelve DIGE gels were run simultaneously from six CPB patients with and six CPB patients without AKI (controls). Another six gels were run with postoperative urine of six AKI patients and six controls. Labeled proteins were visualized using a TyphoonTM 9400 imager and Spot matching, quantification, and statistical analyses were performed using Proteomweaver® software. Individual spots were cut from the gel and analyzed by Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-MS) and MALDI-MS/MS. We validated with Western blot in all 36 patients as well as in 2 extra AKI patients fulfilling all inclusion and exclusion criteria.

Results: Six out of 36 patients developed AKI. Maximal concentrations of plasma creatinine after CPB were 153 ± 38 mmol/l

1.4

in patients with AKI as compared with 84 ± 12 mmol/l in controls ($p < 0.01$). The mean time to reach maximal serum creatinine concentrations after CPB was 4.33 ± 1.4 days. Upregulated proteins after CPB were zinc-alpha-2-glycoprotein (ZAG), adrenomedullin-binding protein (AMBP), Ig kappa (IGKV 1-5 protein), leucine-rich alpha-2-glycoprotein (LRG), gelsolin, carbonic anhydrase 1 (CA-1), plasma retinol-binding protein (RBP), mannan-binding lectin serine protease 2 (MASP-2) and basement membrane-specific heparan sulfate proteoglycan (HSPG). The two downregulated spots were identified as uromodulin. In patients with AKI, albumin was upregulated and ZAG and AMBP downregulated. Downregulation of ZAG could be validated in all 38 patients. Albumin was not significantly upregulated when all subjects were considered.

Conclusion: First, RBP and AMBP are well-known markers of proximal tubular dysfunction of various etiology, including tubulopathy after cardiac surgery. A relevant mechanism of proximal tubular uptake of filtered proteins including RBP, AMBP, Ig light chains and albumin is receptor-mediated endocytosis by megalin and cubilin. The upregulation of RBP, AMBP and IGKV 1-5 in urine after CPB observed is in line with an impaired megalin mediated endocytosis. Second, ZAG expression is stimulated by glucocorticoids in adipocytes. After cardiac surgery total and unbound concentrations of cortisol are significantly increased. Thus, a glucocorticoid-mediated increased production is a reasonable candidate mechanism of the increased urinary ZAG excretion after CPB. Third, cardiac surgery with the aid of CPB induces a systemic inflammatory response syndrome (SIRS). The changes of the following proteins observed in the present study might be explained at least in part by CPB associated SIRS: LRG, MASP-2, HSPG. The identification of urinary markers predicting renal injury early after an insult to the kidney has occurred is a tremendous undertaking. ZAG and the albumin/ZAG ratio are potential markers for early prediction of AKI after CPB.

Induction of ER stress in human diabetic nephropathy

1.5

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Purpose: Chronic proteinuria and tubulointerstitial fibrosis, characteristics of established diabetic nephropathy (DN), correlate best with the degree of renal dysfunction. Recent studies have shown ER stress in cultured renal cells after protein overload. In this study, we therefore investigated ER stress and ER stress-induced apoptosis in kidneys of patients with proteinuria secondary to DN or minimal change disease (MCD) and in cultured human proximal tubular cells (PTC).

Methods and materials: Microarray analysis of DN patients ($n = 6$) and controls ($n = 3$, CON) were studied and confirmed by real-time RT-PCR (DN $n = 15$, MCD $n = 4$, CON $n = 10$). Protein levels were analyzed by immunofluorescence ($n = 5$ each). mRNA expression of ER stress related genes was also investigated in vitro in PTC treated with glucose, albumin or with the ER stress inducers tunicamycin (TM) and thapsigargin (TG). Apoptosis was analyzed using annexin V/PI staining and FACS-analysis.

Results: Microarray and RT-PCR data from biopsies with established DN revealed up-regulation of genes involved in the adaptive unfolded protein response (UPR). Immunofluorescence of renal biopsies from patients with DN confirmed the up-regulation for HSPA5 and HYOU1 on protein level in tubular epithelia, while this was less pronounced in MCD. Treatment of PTC with high glucose for 6 days induced ER stress gene expression, a response further enhanced by concomitant albumin exposure. Exposure of PTC to TM and TG at low doses resulted in a similar adaptive rather than a proapoptotic ER stress response.

Conclusion: The observed UPR in DN and MCD indicates that in proteinuric diseases tubular epithelial cells undergo ER stress responding with an adaptive, protective UPR. Glucosuria may have an additive effect to proteinuria, as indicated by the in vitro studies and the prominent staining of ER stress molecules in DN as compared to MCD. While this may protect the cells from ER stress, persistent hyperglycemia and proteinuria in DN could eventually overwhelm the adaptive UPR leading to apoptosis and tubular damage.

Proteomic analysis of a podocyte vesicles-enriched fraction from human normal and pathological urine samples

1.6

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Purpose: Podocytes or glomerular visceral epithelial cells are known to release vesicles into urine in physiological conditions. This vesiculation process seems to be increased in pathological conditions such as glomerulopathies. Podocyte vesicles-enriched fractions of urine were therefore the starting material for proteomic analysis and identification of potential biomarkers of glomerular diseases.

Methods and materials: We first prepared a podocyte vesicles-enriched fraction from normal (19 healthy donors) and pathological (10 patients with biopsy-proven renal diseases) urine samples using an immunoabsorption method. Enrichment of podocyte vesicles was assessed. We then identified proteins using SDS-PAGE and LC-MS/MS techniques.

Results: 76 unique proteins were identified using these techniques. Several of these proteins were previously described as potential markers of glomerular diseases. Interestingly, one protein, the serum paraoxonase/arylesterase 1 (PON-1), was newly identified in human urine. We confirmed this result and demonstrated by Western blot analysis the presence of PON-1 protein in normal urines. We further demonstrated by RT-PCR that PON-1 mRNA is expressed in the normal human kidney and by immunohistochemistry that PON-1 protein is localized in podocytes.

Conclusion: These results demonstrated the potential for using the urine samples enriched in podocyte vesicles as a starting material in studies aimed at disease biomarkers discovery.

Oral Presentations – General Nephrology

Histopathological patterns of nephrocalcinosis: the hyperphosphatemic type in acute phosphate nephropathy following colonoscopy can be distinguished from other types

2.1

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Purpose: Various conditions leading to nephrocalcinosis are known. Whether the histomorphological pattern of renal calcifications correlates with the cause or mechanism of nephrocalcinosis still remains to be elucidated. Thus, the aim of this study was to clarify, if the histopathological appearance of calcinosis provides information about the possible etiology.

Methods and materials: Native kidney biopsies of the last 50 years (1959 to 2008) with a diagnosis of nephrocalcinosis were identified and histological slides of all 48 cases were reevaluated by light microscopy. The cases were grouped into ten categories according to the likely etiology of nephrocalcinosis, such as hypercalcemia ($n = 6$), hyperphosphatemia after colonoscopy ($n = 5$), hyperparathyroidism ($n = 4$), sarcoidosis ($n = 3$). The total number, density, location, size, and structure of all calcification foci were documented. Five structure patterns (homogeneous, finely granular, globular, shell-like, onion

skin-like) were distinguished. In addition, von Kossa staining and polarized light were used to identify calcium phosphate or calcium oxalate deposits, respectively. Finally, the different morphological features were correlated with clinical and laboratory data.

Results: Nephrocalcinosis was one of the major diagnosis in 48 of 12000 native kidney biopsies (0.4%). The clinicopathological correlation analysis revealed a specific pattern of nephrocalcinosis in the group of hyperphosphatemia after colonoscopy: all five cases showed predominance of cortical, intratubular, spheroidal deposits with outer shell-like calcifications (hyperphosphatemic type). In contrast, other groups, especially the group of hypercalcemia, had a different pattern with predominantly lumpy, homogeneous or finely granular calcifications (hypercalcemic type). The specificity of the hyperphosphatemic type could be reconfirmed in a blinded test by two nephropathologists using these given criteria. However, nephrocalcinosis in patients with nephrotic syndrome, in which hyperphosphatemia is also common, had a similar pattern.

Compared to the post-colonoscopy group these biopsies contained calcifications more often in the interstitium than in tubular lumina. **Conclusion:** Hyperphosphatemia-associated nephrocalcinosis can be distinguished histopathologically from nephrocalcinosis of other

causes by the presence of cortical, intratubular, spheroidal deposits with shell-like calcifications. Thus, the pattern of nephrocalcinosis in renal biopsies provides information about the etiology, especially in patients with acute phosphate nephropathy following oral sodium phosphate bowel purgative.

Renal amyloidosis revisited: relevance of histomorphological patterns, amyloid dynamics and chemical type

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Purpose: Renal amyloidosis is a well recognized disease resulting from protein misfolding of diverse precursor proteins and leads to progressive renal insufficiency. Recently management of amyloidosis has shifted from purely supportive care to an aggressive treatment depending on the amyloid precursor type present. Only few data are available concerning the relevance of the histomorphological patterns and the dynamics of the disease process within the kidneys.

Methods and materials: We retrospectively reviewed all cases of renal amyloidosis diagnosed in native kidney biopsies between 1968 and 2007 (n = 203). All cases were systematically evaluated for the presence of amyloid in the various renal compartments and its pattern of distribution. Each the extent (focal and segmental vs. global and diffuse) and severity of glomerular amyloid deposition was scored semiquantitatively (1 = minimal, 4 = severe). A glomerular amyloidosis score was calculated by simple multiplication. Total glomerular involvement was defined as minimal (score 1–4), mild (score 5–8), moderate (9–12), or severe (13–16). The degree of interstitial fibrosis and tubular atrophy of the cortex was estimated as area %. Since 1990 all cases have been characterized by immunohistochemistry to determine the amyloid type (n = 153). Morphological findings were correlated with clinical data available at the time of biopsy.

Results: The mean patient age was 57.6 ± 16.1 years, the male:female ratio was 1.23:1. According to the predominant site of amyloid deposition 84.6% showed a glomerular, 9.4% a vascular, and 6% a tubulointerstitial pattern. Regardless of the pattern most cases had additional less suspicious amyloid deposits in one or both of the other compartments. By immunohistochemistry 84/158 cases were identified as AL lambda, 68/158 cases as AA, 9/158 as AL kappa and 1/158 as ATTR. There was no correlation between the amyloid type and the histological pattern. For the glomerular pattern the dynamics of amyloid deposition was investigated. In the early stage mesangial amyloid fibrils are put down in a focal and segmental fashion. With increased deposition there is a diffuse segmental and later global affection of the glomeruli often accompanied by a vascular and/or tubulointerstitial involvement. Interstitial fibrosis with tubular atrophy is rare in minimal or mild glomerular amyloidosis but becomes much more frequent in moderate to severe disease. Serum creatinine correlated well with interstitial fibrosis and tubular atrophy (p < 0.001), proteinuria only with the glomerular amyloidosis score (p < 0.0001).

Conclusion: Our results show that renal amyloidosis consists of three easily distinguishable morphological patterns. These patterns do not correlate with the chemical type of amyloid deposited. The relevance of the renal amyloid patterns is unclear at the moment, but they may be due to the chemical properties of the amyloid fibrils in a given patient. This may become important in future anti-fibrillar therapies. The glomerular amyloidosis score as well as the amount of interstitial fibrosis with tubular atrophy will help predict the response rate in terms of kidney function to treatment.

2.2

Left renal vein entrapment: a frequent feature in children with postural proteinuria

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Purpose: The mechanisms underlying postural proteinuria are not well understood. In most Asian subjects with postural proteinuria ultrasonic imaging and Doppler flow scanning disclose entrapment of the left renal vein in the fork between the aorta and the superior mesenteric artery. Little information is available on the possible occurrence of left renal vein entrapment in European subjects with postural proteinuria.

Methods and materials: Renal ultrasound with Doppler flow imaging was performed in 24 Italian or Swiss patients with postural proteinuria (14 girls and 10 boys, aged between 5.2 and 16 years, median 14 years). The diagnosis of left renal vein nutcracker phenomenon was made when the antero-posterior diameter at the hilar divided by that at the aorto-mesenteric portion (= diameter ratio) or when the peak flow velocity at the aorto-mesenteric divided by that at the hilar portion (= flow velocity ratio) were >4.0.

2.3

Results: Ultrasonic imaging and Doppler flow scanning disclosed signs of aorto-mesenteric left renal vein entrapment in 18 of the 24 patients (75 percent). The diameter ratio and the flow velocity ratio were both >4.0 in 13, the flow velocity ratio was >4.0 (but the diameter normal) in 3 and the diameter ratio was >4.0 (but the flow velocity normal) in 2 patients. The diameter ratio and the velocity ratio were both normal, i.e. <4.0, in the remaining six patients.

Conclusion: Left renal vein nutcracker phenomenon is frequent both in Asian as well as in European subjects with postural proteinuria. We suggest ultrasonic imaging and Doppler flow scanning be useful in subjects with postural proteinuria to evaluate whether left renal vein nutcracker phenomenon is implicated or not.

Role of the antenatal and postnatal ultrasound in the diagnosis of vesicoureteral reflux

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Purpose: Antenatal hydronephrosis (ANH) is a frequent anomaly found on foetal ultrasound (US). There is no consensus recommendations for the postnatal follow-up and the necessity to practice a voiding cystourethrography (VCUG) for the diagnosis of the vesicoureteral reflux (VUR), thus leading to unnecessary and irradiating examinations. The goal of this study was to evaluate the role of the antenatal and postnatal US in the diagnosis of VUR in neonates with ANH.

Methods and materials: We prospectively followed 121 patients (pts) with ANH (anterior posterior diameter (APD) ≥5 mm after 20th week of gestation). All infants had two successive US examinations of the urinary tract at 5 days and 1 month after birth. Only children with persistence of dilatation with an APD ≥5 mm or a ureteral dilatation on one or two of the postnatal US had a VCUG at 6 weeks after birth.

Results: VCUG was done in 89 pts and a VUR was detected in 10, among those, 5 had high grade reflux (> grade II). A positive correlation was found between the severity of VUR and the degree of APD on the antenatal and postnatal US (p < 0.05). The ROC curve with a cut off level of 7–9 mm showed a sensibility of 90% and specificity of 12.6% for the antenatal ultrasound and a sensibility of 90% and specificity of 44.3% for the postnatal US. Children with a severe VUR had an APD ≥10 mm on the antenatal and prenatal US.

Conclusion: These data indicate that the US had a poor specificity for the diagnosis of the VUR. However it is useful in selecting patients at risk for a severe VUR. We recommend that all the newborns with ANH ≥7 mm have an US at 5 days and 1 month after birth; the VCUG should be done at 6 weeks if one of the US showed the persistence of an APD ≥10 mm or the presence of a ureteral dilatation.

2.4

Safety, tolerability and adherence of sirolimus in autosomal dominant polycystic kidney disease

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Purpose: Renal volume enlargement predicts the progression to end stage renal disease in autosomal dominant polycystic kidney disease (ADPKD).

Methods and materials: We performed a randomized controlled trial to assess the effect of sirolimus on renal volume change in 100 ADPKD patients. Patients with documented renal volume progression received either sirolimus 2 mg/day (A) or no treatment (B).

Results: Baseline characteristics of the patients in the two groups were similar, including age (29.2 ± 6.2 yr), kidney volume, eGFR (109 ± 24 ml/min), albuminuria (3.8 ± 4.5 mg/mmol) and blood pressure. The most frequent adverse events were transient and mild mucositis (A: 72%, B: 12%), upper airway infection (A 52%, B: 72%), acne (A: 72%, B: 12%) and flank pain (A: 36%, B: 44%). No serious drug-related adverse events occurred and none of the patients discontinued the drug prematurely. Electronic monitoring of medication adherence showed treatment adherence of >90%. After 6 months of treatment the eGFR and albuminuria were unchanged in both groups. Triglyceride (A: 1.4 ± 0.9, B: 1.2 ± 0.6 mmol/l), cholesterol (A: 4.9 ± 1.2, B: 4.5 ± 0.8 mmol/l) and LDL levels (A: 1.4 ± 0.4, B: 1.3 ± 0.4 mmol/l) remained in the normal range. Hematological parameters did not change: hemoglobin, leukocyte and platelet counts remained in the normal range.

Conclusion: We conclude that 2 mg/day sirolimus is safe and well tolerated and that treatment adherence is excellent in ADPKD patients (ClinicalTrials.gov, NCT00346918).

2.5

Why do so many patients start haemodialysis without definitive vascular access?

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Purpose: Although it is widely accepted that an av fistula is the best vascular access for haemodialysis (HD), a substantial number of patients start HD without definitive access. The aim of this retrospective study was to evaluate the proportion of patients starting HD without definitive access, to understand the reasons and discuss the potential for improvement.

Methods and materials: A database review was performed on all patients who started HD at our centre between January 2005 and June 2008, collecting patients' characteristics (age, nephropathy, evolution of kidney failure, time of referral to renal service) and the presence of definitive access when starting HD.

Results: Within the observation period 154 new HD patients were identified. We excluded 49 patients who required HD transiently and recovered renal function. Of the 105 patients analyzed only 32% (n = 34) had definitive access. 13% (14/105) were switched to HD from transplantation (n = 6) or peritoneal dialysis (n = 8). 92% (13/14) of the transplanted patients had a timely vascular access. Of PD-patients 62% (5/8) switched to HD without access due to acute complications. Of the patients naive to renal replacement therapy (RRT) 40% (36/91) were unknown to renal services until less than 4 months and started without definitive access. Of these 36 patients 30% (n = 11) had an acute renal failure, 56% (n = 20) had CKD but were unknown until the HD starting day and 14% (n = 5) were known since 2.6 months on average. 60% (55/91) of the patients naive to RRT were known to nephrologists for more than 4 months. 47%

2.6

(26/55) had an access, 53% (29/55) did not. The two main reasons for starting HD without definitive access among the known patients were delayed planning of access (13/29, 45%) and explicit refusal of timely access surgery by the patient (12/29, 41%). 2 further patients chose not to undergo RRT initially but changed their mind later on and another 2 patients had an unpredictable co morbidity with acute on chronic renal failure. Among patients with chronic renal failure, unknown patients were older than known patients (65.3 ± 13 vs. 59.4 ± 15 yrs, $p < 0.05$) but there was no difference between patients with definitive access or not. Patients with polycystic disease or glomerulonephritis started HD more frequently with definitive access than those with diabetic or hypertensive nephropathy (PKD 78%, GN 67% vs. Hypertensive 22%, Diabetes 11%, $p < 0.001$). Although a majority (17/28) of patients with diabetic nephropathy was known to renal services, only a marginal proportion started RRT with definitive access (3/17, 17%)

Conclusion: A majority of patients with chronic renal failure in our centre starts HD without definitive vascular access. Approximately half of these patients could have started HD in a planned manner but were either not identified or were not referred to renal services. The other half was known to renal services but failed to have a definitive access. A substantial proportion explicitly refused timely surgery. Beside organisational issues, a mental barrier against accepting the need for RRT might result in the denial of practical steps towards initiation of dialysis. In conclusion there is still a need to improve detection of CKD and timely referral to a nephrologist. There is a further need to increase understanding and acceptance of timely preparation for haemodialysis for patients and maybe also for nephrologists.

Oral Presentations – Transplantation

Everolimus (RAD)/Enteric-coated Mycophenolate Sodium (EC-MPS) therapy after Calcineurin inhibitor (CNI) withdrawal in de novo renal transplant patients: Final outcomes of the ZEUS study.

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Purpose: This 1-year, prospective, open-label, randomized, multicenter study compared the efficacy, safety and tolerability of Everolimus/EC-MPS to that of Cyclosporine (CsA)/EC-MPS in 300 *de novo* renal allograft recipients.

Methods and materials: After induction therapy with Basiliximab patients were treated with CsA, EC-MPS and corticosteroids for the first 4.5 months post transplantation. Patients were then randomized 1:1 to either continue CsA/EC-MPS or convert to Everolimus (trough 6–10 ng/ml)/EC-MPS. Corticosteroids were prescribed according to center practice. Renal function was determined by calculated GFR (Nankivell). Efficacy and safety endpoints implied rejection episodes (treated and biopsy proven), graft loss, death.

Results: Renal function outcomes of the first 147 subjects receiving Everolimus/EC-MPS and 139 receiving CsA/EC-MPS completing 12 months will be reported here. Final outcomes of all 300 subjects will be presented at the congress. Groups were similar at baseline (timepoint of randomization) for all reported renal function endpoints. Calculated GFRs (Nankivell formula) were 64.4 ± 17.7 and 64.2 ± 15.5 at baseline, respectively 72.3 ± 19.1 and 62.2 ± 17.5 mL/min/1.73 m² at month 12 for the Everolimus/EC-MPS and CsA/EC-MPS treatment group. Regarding efficacy and safety outcomes: For the 12-month study period BPAR was reported in 22/147 (15.1%) Everolimus/EC-MPS-treated patients and 20/139 (14.4%) receiving CsA/EC-MPS. No graft loss occurred. One death appeared in the CsA/EC-MPS treatment arm. The patients with drug discontinuation at 12 months were 23% in the Everolimus/EC-MPS group and 18% in CsA/EC-MPS group.

Conclusion: Early introduction of Everolimus/EC-MPS in *de novo* renal transplant patients after CNI withdrawal resulted in the expected improvement of renal function while being a safe and well-tolerated regimen.

3.1

Clinical relevance of pre-transplant donor-specific HLA-antibodies detected by flow beads

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Purpose: Conflicting results regarding the clinical relevance of preformed donor-specific HLA-antibodies (HLA-DSA) detected by single HLA-antigen flow beads (SAFB) have been published. However, all these studies had some limitations (e.g. small sample size, confounded by induction therapies such as ATG). The aim of this study was to determine the clinical impact of HLA-DSA detected by SAFB in a retrospective cohort of patients not having received an induction therapy modulating the development of antibody-mediated rejection (AMR).

Methods and materials: All 372 consecutive renal transplantations performed between 1999 and 2004 were investigated. Thirty-eight patients were excluded (no available pre-transplant serum (n = 13); ATG induction therapy (n = 25)) leaving 334 patients with negative CDC-crossmatches for the analysis. All day-of-transplant sera were analyzed by SAFB, and HLA-DSA determined by virtual crossmatching. Evaluated endpoints were occurrence of AMR and death-censored graft survival.

Results: Sixty-seven of 334 patients (20%) had HLA-DSA. The cumulative incidence of clinical/subclinical AMR at day 200 post-transplant was significantly higher in patients with HLA-DSA (37/67; 55%) than in patients without HLA-DSA (17/267; 6%) ($p < 0.0001$). Notably, 30/67 patients with HLA-DSA (45%) did not experience clinical/subclinical AMR. Death-censored allograft survival at five years was equal in patient without HLA-DSA (89%) and patients with HLA-DSA, but without AMR (87%) ($p = 0.95$). However, patients with HLA-DSA and AMR had significantly lower death-censored allograft survival (68%; $p = 0.002$). The number, class, and cumulative strength of HLA-DSA, as well as sensitizing events were not different between patients with HLA-DSA and/without AMR ($p \geq 0.19$).

Conclusion: More than half of HLA-DSA detected by SAFB are clinically relevant. Discriminating clinically relevant from irrelevant HLA-DSA will be important for further improvement of pre-transplant risk stratification based on SAFB results.

3.2

3.3

Regulation of allo-reactive human CD8 T cell response by CD40 and PD-L1 expression on renal tubular epithelial cells

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Purpose: Allo-reactive cytotoxic T lymphocytes (CTLs) induce tubulointerstitial injury during kidney transplant rejection. Previously we demonstrated that murine renal tubular epithelial cells (TECs) with high PD-L1 expression are partially protected from the attack of antigen-specific autologous CTLs. In the present study we investigated human allo-reactive CTL responses to renal TEC that express positive (CD40) or negative (PD-L1) costimulatory molecules.

Methods and materials: Human renal TEC line HK-2 cells or primary renal TEC cultures were pre-stimulated with IFN- and IFN- to induce high surface expression of PD-L1 and MHC molecules. These cells were then used as targets of allo-reactive CD8+ CTLs isolated from PBMCs of healthy donors. Cytotoxicity of allo-reactive CTLs were measured by non-radioactive CTL assays, in the presence or absence of specific blocking mAbs for PD-L1 or activating mAbs for CD40, respectively. T cell cytokines in the co-culture supernatants were also determined by ELISA kits.

Results: Allo-reactive CTLs demonstrated a strong cytolytic activity to the positive control targets Jurkat cells but not to renal TECs, though allogene-specific IFN- production was detected in both cases. Blocking surface PD-L1 on HK-2 cells with a specific mAb significantly increased IFN- production of allo-CTLs, but was still not able to induce the lysis of renal TECs. Importantly, when the CD40 co-stimulatory signal was triggered by an activating anti-CD40 mAb, the cytotoxicity of TECs was induced. These results indicate that positive and negative co-stimulatory molecules CD40 and PD-L1 were directly involved in the interaction of allo-reactive CTLs and TECs.

Conclusion: Since the co-stimulatory molecules B7.1 and B7.2 are not expressed by renal TECs, CD40 becomes the unique co-stimulatory surface molecule which is capable of stimulating allogeneic CTL responses to renal TECs. Strategies to downregulate CD40 and enhance PD-L1 expression on TECs might be therapeutically useful to prevent kidney transplant rejection.

Urinary CXCR3-binding chemokine levels correlate with the extent of subclinical tubulitis

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Purpose: Subclinical tubulitis, while occurring in less than 10% of all kidney transplants under current immunosuppression, can induce tubular atrophy and interstitial fibrosis. Defining populations at risk for subclinical tubulitis -preferably via non-invasive screening - would therefore be important. CXC-receptor 3 (CXCR3) binding chemokines (i.e. MIG, IP10, ITAC) are secreted by various leukocytes as well as tubular epithelial cells, and are involved in the recruitment of activated T cells into the site of inflammation. The aim of this study was to investigate how levels of urinary CXCR3-binding chemokines relate to the extent of subclinical tubulitis in kidney allograft recipients.

Methods and materials: Using ELISA, urinary CXCR3-binding chemokines and urinary tubular injury biomarkers (NGAL and 1-microglobulin) were measured in 65 renal allograft recipient and related to their histological grading of tubulointerstitial inflammation (normal tubular histology [n = 24], subclinical borderline tubulitis [n = 18], and subclinical tubulitis la/lb [n = 23]). Glomerular filtration rates were estimated using the MDRD equation.

Results: Total proteinuria, urinary levels of NGAL and 1-microglobulin and estimated glomerular filtration rates were similar across these histologically defined patient groups. By contrast, each of the three measured urinary CXCR3-binding chemokines were significantly higher in patients with subclinical tubulitis la/lb as compared to patients with subclinical borderline tubulitis (p ≤ 0.01) and patients with normal tubular histology (p < 0.0001).

Conclusion: These results demonstrate a correlation of urinary CXCR3-binding chemokine levels with the extent of subclinical tubulitis. If confirmed in a larger independent validation set, urinary CXCR3-binding chemokines might become a useful non-invasive biomarker to screen for subclinical tubulitis.

3.4

In vivo mechanisms leading to transplantation tolerance induced by regulatory T cells

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Purpose: The mechanisms by which CD4+CD25+Foxp3+ T cells (Tregs) regulate effector T cells in a transplantation setting and their in vivo homeostasis still remain to be clarified. Using a mouse adoptive transfer and skin transplantation model, we analyzed the in vivo expansion, effector function and trafficking of effector T cells and donor-specific Tregs, in response to an allograft.

Methods and materials: Antigen-specific Tregs were generated and expanded in vitro by culturing freshly isolated Tregs from BALB/c mice (H2d) with syngeneic dendritic cells pulsed with an allopeptide (here the Kb peptide derived from the MHC class I molecule of allogeneic H2b mice). Fluorescent-labelled CD4+CD25- naive T cells and donor-antigen-specific Tregs were transferred alone or co-injected into syngeneic BALB/c-Nude recipients transplanted with allogeneic C57BL/6xBALB/c donor skin.

Results: As opposed to their in vitro hyporesponsiveness, Tregs divided in vivo, migrated and accumulated in the allograft draining lymph nodes (drLN) and within the graft. The co-transfer of Tregs did not modify the early proliferation and homing of CD4+CD25- T cells to secondary lymphoid organs. But, in the presence of Tregs, effector T cells produced significantly less IFN- and IL-2 effector cytokines, while higher amounts of IL-10 were detected in the spleen and drLN of these mice. Furthermore, time-course studies showed that Tregs were recruited into the allograft at a very early stage post-transplantation and prevented infiltration by effector T cells.

Conclusion: Overall, our results suggest that suppression of graft rejection involves the early recruitment of donor-specific Tregs at the sites of antigenic challenge and that Tregs mainly regulate the effector arm of T cell alloresponses.

3.5

The differential expression of metzincins and related genes in renal allograft biopsies discriminates normal histology, acute rejection and chronic dysfunction

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Purpose: Acute rejection (AR) and chronic graft dysfunction based on interstitial fibrosis/tubular atrophy (IF/TA) remain crucial complications after renal transplantation. Metzincins (MET), including matrix metalloproteases (MMP), are tissue-remodelling proteases and contribute to inflammatory and fibrotic processes in the kidney. We hypothesized the involvement of MET and related genes in AR and IF/TA and investigated their expression in renal allograft biopsies and patient sera.

Methods and materials: Microarray analysis of RNA from kidney biopsies with normal histology (N; n = 7), AR (n = 15), and IF/TA without specific aetiology (n = 22) focused on two transcript-sets "MET" and "MERC" (metzincins and related genes); the latter extending MET by metzincin substrates, -regulators and -inhibitors. Potential marker genes were analyzed in an additional biopsy-set by qRT-PCR of microdissected glomeruli and tubuli, and by immunohistochemistry (IHC). Patient sera were examined by ELISA.

Results: Our first results (JASN, 18:3A, 2007) illustrated deregulation of MET in IF/TA including overexpression of MMP-7 and thrombospondin 2 (THBS2). Based on MERC expression-profiles IF/TA and N biopsies of our and two other microarray studies were correctly classified. Furthermore, we demonstrated the involvement of epithelial to mesenchymal-transition and the wingless-type pathway in ongoing IF/TA. Differential expression of MET and MERC were also observed in AR compared to IF/TA and N. A set of 30 MET correctly classified AR, N and IF/TA biopsies of our dataset. Unlike during IF/TA, mRNA levels of MMP7 and THBS2 did not considerably alter during AR (p > 0.05). However MMP9 showed particular AR over-expression in microdissected glomeruli and proximal tubuli, confirmed by IHC.

Conclusion: The identification of differential MET- and MERC-expression in IF/TA and AR may provide a step towards the establishment of a diagnostic marker-set and the identification of potential therapeutic targets.

3.6

Glycyrrhetic acid food supplementation lowers plasma potassium concentrations in chronic hemodialysis patients

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Purpose: Hyperkalemia (HK) is a life threatening problem in dialysis patients. Glycyrrhetic acid (GA), the active ingredient of licorice, inhibits the enzyme 11- β -hydroxy-steroiddehydrogenase type 2 (11- β -HSD2) and thereby increases access of cortisol to the colonic mineralocorticoid receptor. This has the potential to lower plasma potassium concentrations (K⁺). We hypothesized that the prolonged ingestion of GA lowers plasma K⁺ without inducing the renal side effects of sodium retention and hypertension.

Methods and materials: Ten patients were studied in a 6 month prospective, double blind, placebo controlled cross over study. Either cookies or bread rolls were supplemented with GA (500 mg or placebo) and given twice per day. Blood was drawn and 24-hour BP measured at baseline, week 6, 12, 18 and 24. Plasma K⁺ concentration was determined before each treatment session.

Results: The ratio of plasma cortisol/cortisone increased in all patients on GA (14.3 \pm 3.3) when compared to the baseline (8.1 \pm 2.1, p < 0.001) or placebo period (9.7 \pm 3.3, p < 0.01), indicating inhibition of 11- β -HSD2. Nine of ten patients exhibited a rapid and persistent decrease of predialysis plasma K⁺. On GA, mean plasma K⁺ concentrations were lower (4.5 \pm 0.58 mmol/l) than at baseline (5.5 \pm 0.61 mmol/l, p < 0.01) or during the placebo period (5.3 \pm 0.53 mmol/l, p < 0.05). On placebo plasma K⁺ levels were elevated above the upper limit of normal range in 76% of measurements (274 of 358), compared to 30% (107 of 357) on GA (p < 0.01). The frequency of relevant HK's (\geq 6 mmol/l) decreased from 9 to 0.6% (p < 0.01). No differences were found concerning parameters reflecting sodium retention, i.e. weight and BP measurements. The aldosterone/renin ratio was diminished during the GA administration (19 \pm 13) when compared to baseline (89 \pm 67, p < 0.01) or to placebo (39 \pm 36, p ns), an effect best explained by the diminished plasma K⁺.

Conclusion: Prolonged GA supplemented food persistently lowers plasma K⁺ without inducing weight gain or hypertension in dialysis patients. Thus, GA might be useful to prevent serious HK and to diminish aldosterone, a culprit of myocardial fibrosis.

4.1

correlated better with the risk of falls. The high negative predictive value of the test predicts fairly the patients who will remain free of falls. On the contrary, in case of a lower score, attention is warranted and efforts should be made to reduce individual risk factors such as low muscle mass, orthostasis and certain medications. However, further studies are needed to assess the impact of co morbidities on the predictive value of the Tinetti test in this population.

Predicting the risk of severe falls in maintenance haemodialysis patients with Tinetti test

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Purpose: Patients on maintenance haemodialysis (MHD) are at high risk of falls. In the general population, the risk of fall can be assessed by the Tinetti test. This is an easily reproducible clinical tool for balance and walking assessment with a maximal score of 26. The cut off value <20/26 predicts a high risk of falls. As this test has never been performed in patients on MHD, the purpose of this study was to assess the prevalence of severe falls and the ability of the Tinetti test to predict falls in this population.

Methods and materials: All patients on MHD in our centre between June 1, 2005 and July 31, 2008 were asked to participate. Tinetti test was performed by the same person (DH) before a dialysis session in all patients and in a subgroup of 12 patients also after dialysis. Thereafter, all severe falls defined by the need of hospitalisation and/or presentation in an emergency department, were documented prospectively.

Results: Eighty four patients (mean age 69.1 \pm 14.3 years) were included, of which 33% females and 46.4% diabetics. Predialytic Tinetti score was 19.0 \pm 6.6 (Mean \pm SD). In the subgroup of 12 patients tested before and after dialysis, mean scores were 20.6 \pm 4.4 and 16.3 \pm 7.2, respectively. After a mean follow up time of 16.6 months, severe falls were recorded in 24 patients (28.4% of all patients), resulting in 13 fractures (54.2% of patients with falls). Tinetti score in patients without falls was 20.2 \pm 5.6 and 16.0 \pm 7.9 in patients with falls 16.0 \pm 7.9 (p = 0.001). Of the 35 patients with a "classical" Tinetti cut off value of <20, 34.0% fell, versus 24.5% in patients with a score \geq 20 (sensitivity: 50%, specificity: 61.6%; p = 0.23). Of all tested cut off values (between 20 and 24), the highest sensitivity (70.8%) and specificity (53%) was found when using a cut off value of 21. Of the 45 patients with a score <21, 38.5% fell, versus 17.9% of patients with a score \geq 21 (p = 0.038). At this cut off value of 21, the negative predictive value was 82% and the positive predictive value was 37%.

Conclusion: Severe falls are a frequent complication in MHD patients, occurring in 21% of patients per year. Tinetti scores are remarkably low in our study, and drop further after a dialysis session, which raises questions of when to perform the test. Moreover, it suggests that the predialytic Tinetti score may underestimate the global risk, which might explain why the higher cut off value of 21

4.2

Is PAPP-A a useful parameter to predict morbidity and mortality of patients on maintenance hemodialysis?

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Purpose: Hemodialysis (HD) treatment is associated with a high morbidity and mortality, mainly due to cardiovascular (CV) complications. Thus, it would be desirable to have simple screening tools available to assess an individual patient's risk with regard to the occurrence of medical complications including death. PAPP-A (insulin-like growth factor binding protein-4 protease; IGFBP-4-protease), is responsible for the degradation of IGFBP-4, a potent inhibitor of IGF. Both IGF and PAPP-A are elevated in patients with acute coronary syndrome, and PAPP-A has recently been identified as a marker for plaque instability and as an independent predictor for CV mortality in patients with coronary artery disease. The aim of this study was to assess a) the prognostic value of PAPP-A as a marker of morbidity and mortality, including the frequency and duration of hospitalizations, and b) to compare PAPP-A with other cardiovascular risk markers.

Methods and materials: The study population consists of a total of 164 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 measurement of PAPP-A in serum 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 April 2008 for the occurrence and date of both hospitalizations and death and length of hospital stay. All events were analyzed regarding their relation to cardiovascular causes and to time of follow-up within the study cohort.

Results: Results are given as mean \pm SDV for all patients and for subgroups according to tertiles of PAPP-A (low: 7–17, medium: 18–23, and high: 24–46):

N	164	60	50	54	
PAPP-A, mIE/L	22 \pm 11	13 \pm 3	21 \pm 2	30 \pm 6	0.000
Age, yr	66 \pm 14	66 \pm 15	65 \pm 13	68 \pm 12	0.230
Hospital days	20.2 \pm 23	17.3 \pm 13	15.9 \pm 13	27.7 \pm 35	0.185
# CV endpoints	5	0	3	2	-
# Death, N	22	5	5	12	-
Comorbidities, N	1.8 \pm 0.9	1.8 \pm 0.9	2.0 \pm 1	1.7 \pm 0.8	0.500
Follow-Up, days	475 \pm 129	435 \pm 174	479 \pm 112	513 \pm 64	0.012
Days on HD	2104 \pm 2504	1409 \pm 1783	1424 \pm 1122	3328 \pm 3378	0.019
Kt/V	1.60 \pm 0.3	1.62 \pm 0.4	1.58 \pm 0.3	1.60 \pm 0.3	0.92
IL-6, ng/L	9 \pm 10	7.8 \pm 9	9.0 \pm 9	10.6 \pm 13	0.460
NT-pro-BNP, ng/L	12762 \pm 17481	9600 \pm 14969	11215 \pm 15533	17273 \pm 20282	0.094
MDA, μ mol/L	0.27 \pm 0.1	0.23 \pm 0.1	0.26 \pm 0.1	0.33 \pm 0.2	0.000
LDL, mmol/L	2.2 \pm 0.8	2.4 \pm 0.8	2.3 \pm 0.9	2.2 \pm 0.8	0.640
PTH, ng/L	281 \pm 260	198 \pm 125	297 \pm 261	346 \pm 332	0.015
CaxP	3.8 \pm 1.2	3.6 \pm 1.1	4.2 \pm 1.2	3.8 \pm 1.1	0.018
Osteoprotegerin, pmol/L	15 \pm 7	13.7 \pm 6	13.8 \pm 6	18 \pm 7	0.002

Conclusion: In this Swiss cohort of maintenance HD patients PAPP-A is associated with higher morbidity and mortality. This is reflected by more hospital days, CV occurrence and greater number of deaths in patients with higher PAPP-A serum concentrations. It remains to be determined whether PAPP-A is merely a marker for morbidity and mortality, or whether a causal link exists to cardiovascular disease pathogenicity. An indirect causality may exist through alterations in mineral metabolism, as suggested by the correlations found for PAPP-A with PTH and osteoprotegerin.

4.3

4.4

Simple and effective treatment of 25-OH-Vitamin D3 deficiency in hemodialysis patients

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Purpose: In 2007, we discovered a high incidence of 25-OH-D3 deficiency, defined as 25-OH-D3 level <50 nmol/l, in our dialysis patients (57% in June 2007, 39% in October 2007) and started a prospective 1-year-study to evaluate the safety and efficacy of augmenting the Dialvit® capsule, which every patient in our unit takes after dialysis (containing the hydrophilic vitamins B1, B2, B6 and C as well as folic acid), with 2000 IU of cholecalciferol. The present analysis presents 8-month-data of this study.

Methods and materials: Participating dialysis patients were divided in three strata, based on their 25-OH levels, which were classified in October 2007 as «normal» (25-OH >50 nmol/l), «low» (25–49.9 nmol/l) or «very low» (<25.0 nmol/l). 6 patients of each stratum (→18 patients)

were randomly selected for vitamin D supplementation, 8 patients from each stratum served as controls (→24 patients). For the 18 supplementation patients, the usual post-dialysis vitamin supplement (Dialvit®) was replaced in October 2007 by a special one which additionally contained 2000 IU of cholecalciferol. Serum calcium, phosphate, iPTH and 25-OH levels were followed bi-monthly.

Results: 8 month-followup data are given below as means ± SEM. Neither at month 0 nor at month 8 was there any difference in the use of phosphate binders, calcitriol or cinacalcet between the two groups. No side effects attributable to vitamin D supplementation were observed

Conclusion: Augmentation of the usual postdialytic hydrophilic vitamin replacement with 2000 IU of cholecalciferol completely eliminates vitamin D deficiency without any apparent disadvantage. Based on the present 8 month-followup data, this simple procedure appears to be effective and safe.

Month	Corrected Calcium	mmol/l	Phosphate	mmol/l	iPTH	ng/l	25-OH Vit-D3	nmol/l	25-OH-deficiency	%
	ViD+	Controls	ViD+	Controls	ViD+	Ctrl.	ViD+	Ctrl.	ViD+	Ctrl.
0	2.33±0.05	2.33±0.03	1.53±0.08	1.54±0.07	384±109	364±62	60±9	76±9	41%	38%
2	2.36±0.04	2.32±0.03	1.32±0.09	1.44±0.07	264±48	323±54	78±5**	48±7	11%*	54%
4	2.35±0.05	2.28±0.04	1.38±0.08	1.43±0.06	348±43	326±39				
6	2.31±0.04	2.23±0.03	1.68±0.09	1.39±0.06	365±51	261±30				
8	2.32±0.03*	2.20±0.04	1.43±0.11	1.55±0.07	344±56	307±51	135±9**	72±7	0%*	35%

*p <0.05 **p <0.001 versus controls

4.5

Accuracy of an interferon-gamma release assay for the diagnosis of latent tuberculosis infection in haemodialysis patients

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Purpose: The accurate diagnosis of latent tuberculosis infection (LTBI) in haemodialysis (HD)-patients awaiting kidney transplantation is of outstanding importance. The current “gold standard” tuberculin skin test (TST) lacks specificity due to cross-reactivity with Bacille-Calmette-Guerin (BCG)-vaccination and lacks sensitivity in immunocompromised patients. Interferon-γ release assays (IGRA) relying on *Mycobacterium tuberculosis* are more specific and predict LTBI accurately in immunocompetent patients. However interferon-γ (INF-γ) secretion is impaired in HD-patients due to immunosuppression caused by uraemia and this may lead to more inconclusive results.

Methods and materials: We took advantage of the mitogen positive-control reaction integrated in the QuantiFERON Gold InTube (QTF-GIT; ELISA-based IGRA) to assess the IGRA-accuracy in HD-patients. First the influence of lymphocyte count, HD-treatment measured by single pool (sp)Kt/v and nutritional status measured by serum albumin and normalized protein catabolic rate (nPCR) was assessed on the QTF-GIT performance. Second, we performed a head to head comparison between the QTF-GIT and the TST in HD-patients. HD-patients were enrolled at the HD-centre and healthy controls at the health services of the Kantonspital St. Gallen. QTF-GIT was performed in patients and controls, TST additionally in HD-patients. HD-patients with active malignancy or under immunosuppression were excluded. Medical histories were reviewed for LTBI risk factors. The study was approved by the local ethical committee.

Results: 39 HD-patients and 52 healthy controls were enrolled. HD-patients showed a significantly reduced immune reaction measured by INF-γ secretion in the positive reaction compared to the healthy controls (p <0.05). Nevertheless, only 1/39 QTF-GIT test result was inconclusive with a negative positive-control reaction; this result was obtained in a patient with diabetic nephropathy. Time on HD-treatment (median 31 months), spKt/v (median 1.59), serum albumin (median 36.1 g/dl), nPCR (median 0.86 g/kg/d), PTH (median 252 pg/ml) and ferritin (median 607 ng/ml) levels did not influence the QTF-GIT performance as measured by INF-γ secretion capacity after mitogenic stimulation. There was a trend for a lower lymphocyte count (median 6.9x10⁹/l) to be associated with a weaker INF-secretion (p = 0.07). In the head to head comparison of the QTF-GIT with the TST 31% (10/39) of the HD-patients had a positive QTF-GIT result in contrast to 9% (3/33) with a positive TST-result (cut-off 10 mm). We diagnosed 8 patients with probable LTBI only by QTF-GIT but not with TST (inter-test agreement of 72%). QTF-GIT results were more closely associated with probable LTBI: All positive QTF-GIT (10/10) but not all positive TST (2/3) showed an association with risk factors associated with LTBI.

Conclusion: TST is not reliable in the diagnosis of LTBI in immunocompromised HD-patients due to a high rate of negative /

anergic TST results. The QTF-GIT showed various advantages: a low rate of inconclusive results compared with the TST, reliable test in HD-patients, closer association with risk factors for LTBI, more easily performed than the TST avoiding the technical difficulty of intradermal injection and the subjectivity of read-out. Further studies are needed to evaluate the IGRA's performance in subgroups of HD-patients with diabetes or lower spKt/v or nPCR.

4.6

A new measurement of energy expenditure and physical activity in patients treated by maintenance hemodialysis

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Purpose: The accurate estimation of total energy expenditure (TEE) is essential to allow the provision of nutritional requirements in patients treated by maintenance hemodialysis (MHD). The measurement of TEE and resting energy expenditure (REE) by direct or indirect calorimetry and doubly labeled water are complicated, time-consuming and cumbersome in this population. Recently, a new system called SenseWear® armband (SWA) was developed to assess TEE, physical activity and REE. This device works by measurements of body acceleration in two axes, heat production and steps counts. REE measured by indirect calorimetry and SWA are well correlated. The aim of this study was to determine TEE, physical activity and REE on patients on MHD using this new device.

Methods and materials: Daily TEE, REE, step count, activity time, intensity of activity and lying time were determined for 7 consecutive days in unselected stable patients on MHD and sex, age and weight-matched healthy controls (HC). Patients with malnutrition, cancer, use of immunosuppressive drugs, hypoalbumemia <35 g/L and those hospitalized in the last 3 months, were excluded. For MHD patients, separate analyses were conducted in dialysis and non-dialysis days. Relevant parameters known to affect REE, such as BMI, albumin, pre-albumin, hemoglobin, Kt/V, CRP, bicarbonate, PTH, TSH, were recorded.

Results: Thirty patients on MHD and 30 HC were included. In MHD patients, there were 20 men and 10 women. Age was 60,13 years ± 14.97 (mean ± SD), BMI was 25.77 kg/m² ± 4.73 and body weight was 74.65 kg ± 16.16. There were no significant differences between the two groups. TEE was lower in MHD patients compared to HC (28.79 ± 5.51 SD versus 32.91 ± 5.75 SD kcal/kg/day; p <0.01). Activity time was significantly lower in patients on MHD (101.3 ± 12.6SD versus 50.7 ± 9.4 SD min; p = 0.0021). Energy expenditure during the time of activity was significantly lower in MHD patients. MHD patients walked 4543 ± 643 SD vs 8537 ± 744 SD steps per day (p <0.0001). Age was negatively correlated with TEE (r = -0.70) and intensity of activity (r = -0.61) in HC, but not in patients on MHD. TEE showed no difference between dialysis and non-dialysis days (29.92 ± 2.03 SD versus 28.44 ± 1.90 SD kcal/kg/day; p = NS), reflecting a

lack of difference in activity (number of steps, time of physical activity) and REE. This finding was observed in MHD patients both older and younger than 60 years. However, age stratification appeared to have an influence on TEE, regardless of dialysis day, (29.92 ± 2.07 SD kcal/kg/day for <60 years-old versus 27.41 ± 1.04 SD kcal/kg/day for ≥ 60 years old), although failing to reach statistical significance.

Conclusion: Using SWA, we have shown that stable patients on MHD have a lower TEE than matched HC. On average, a TEE of 28.79 kcal/kg/day, partially affected by age, was measured. This finding gives support to the clinical impression that it is difficult and probably unnecessary to provide an energy amount of 30–35 kcal/kg/day, as proposed by international guidelines for this population. In addition, we documented for the first time that MHD

patients exert a reduced physical activity as compared to HC. There were surprisingly no differences in TEE, REE and physical activity parameters between dialysis and non-dialysis days. This observation might be due to the fact that patients on MHD produce a physical effort to reach the dialysis centre. Age *per se* did not influence physical activity in MHD patients, contrary to HC, reflecting the impact of co-morbidities on physical activity in this group of patients.

Posters

Everolimus pulse treatment halts polycystic kidney disease progression long-lasting in the Cy/+ rat

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Purpose: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by enhanced proliferation of tubular epithelial cell (TEC) and activation of the protein kinase mTOR. Continuous treatment with specific mTOR inhibitors like everolimus retards rodent PKD. We aimed to examine the effect of everolimus on disease progression in Han:SPRD rat model of ADPKD by pulse therapy.

Methods and materials: Male heterozygous cystic (Cy/+) and wild-type normal (+/+) rats were administered everolimus for 12 weeks (continuous treatment) or for 5 weeks followed by 7 weeks without treatment (pulse treatment). BUN, creatinine, kidney weights, cyst volume density (CVD), glomerular volume (GV), proteinuria, glomerular-tubule (GT) disconnection were assessed.

Results: Kidney function (BUN, creatinine) was preserved by pulse and continuous everolimus treatment. Cyst volume density was reduced by pulse and also continuous treatment significantly. Interestingly, kidney weight and GV increased in pulse vs. continuous everolimus-treated Cy/+ rats. GT disconnection and proteinuria in Cy/+ rats was reduced by everolimus pulse and continuous treatment significantly.

Conclusion: Pulse therapy had a long-lasting inhibitory effect on cystogenesis which was accompanied by secondary glomerular hypertrophy in Cy/+ rats. Glomerular hypertrophy maybe induced by preventing GT disconnection in Cy/+ rats. Continuous everolimus treatment may protect the glomeruli by preventing secondary glomerular hypertrophy.

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In total, twenty processes and 264 documents had been created or updated and adapted to the requirements of the norm. They had been classified and positioned within the Informer®. Several quality projects have been realized. As a consequence, with time, more patients reached the aims of treatment: Kt/V 88% vs 77%, CaxPh 94% vs 87%, Hb 94% vs 67%. There were important effects on our unit and on other hospital services. No additional posts were created. The costs of the process, the certificate included, mounted to sFr. 31'331.–. Continuing maintenance and improvement of the system is now mandated.

Conclusion: Since implementation, more patients reach treatment aims, probably as a consequence of the regular reviews of outcomes on a station wide basis. Patients have the security, that quality standards are met also behind the scene. Team work between nurses and doctors in the dialysis unit has improved because of regularly held structured meetings covering review- and management processes. Many hospital services have reached new quality standards for interaction with the dialysis unit. Implementation of ISO 9001:2000 should be endorsed equally by doctors, nurses and the hospital administration.

Implementation of a quality management system according to ISO 9001:2000 in a public hemodialysis unit

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Purpose: In October 2005 nurses together with the nephrologists of the KSB dialysis unit decided to implement a quality management system according to the ISO 9001:2000 with the intention to increase the quality of care for our hemodialysis patients. Here we describe our experience with the implementation of this system.

Methods and materials: A budget was made, financial resources were secured. The KSB hospital management approved the project. A quality- and process-management consultant from Fresenius Medical Care D GmbH was engaged. A small team (nurse manager, responsible nephrologist, a newly designated quality nurse) was built up and began to work under the supervision of our quality consultant in October 2005. In April 2007 the Informer® (TQsoft), a software specially developed for the online management of documents was introduced hospital wide. Swiss TS was chosen as auditing company. Aims for the dialysis treatment were formulated: KT/V >1.2 (>1.4 for diabetics), Hb = 11–13 g/dl, CaxPh <4.8 mmol/L2 and controlled monthly from Jan 08 on.

Results: Many interfaces with other hospital units and services had to be defined and regulated. Innumerable meetings with responsible persons from other hospital units were held, a time consuming process only terminated in April 2007. After that, our key-processes were formulated or updated, a task that was comparably relatively easy. In October 2007, a first management review was held by our team and after that a rigorous internal audit was undertaken by our quality- and process-management consultant. In November 07, the certificate ISO 9001:2000 for hemodialysis treatment was achieved.

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Volume progression in ADPKD is detectable within 6 months by serial magnetic resonance imaging without contrast media

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Purpose: Kidney volume growth is considered the best surrogate marker to predict renal function decline in autosomal dominant polycystic kidney disease (ADPKD). To assess the efficacy of novel drugs, kidney volume changes need to be measured in a short time interval. We hypothesized that renal volume changes can be detected within 6 months by a manual segmentation method applied to enhanced magnetic resonance imaging (MRI).

Methods and materials: 100 ADPKD patients (37 females) with mean (\pm SD) age 31.2 ± 6.4 y and creatinine clearance 109.8 ± 25.5 ml/min were studied twice within 192 ± 15 days. Kidney volumes were measured on unenhanced T1-weighted MRI sequences by manually tracing the kidney contours followed by summing the area of each section multiplied by the section thickness. Cyst volumes were determined using a region-based thresholding technique applied to axial T2-weighted FSE sequences. 48 kidneys were measured twice by the same and again by an additional observer to assess the intra- and interobserver agreement. Volumetry data were correlated with clinical characteristics using uni- and multivariate analysis.

Results: The mean total kidney volume (TKV) was 1003 ± 568 ccm at baseline and increased by 31.8 ± 72.0 ccm ($2.71 \pm 4.82\%$) in 6 months ($P < 0.001$), which corresponds to an extrapolated annual growth rate of $5.36 \pm 9.47\%$. The total cyst volume was 476 ± 440 ccm at baseline and increased by 32.8 ± 92.5 ccm ($5.45 \pm 14.28\%$, $P < 0.001$). The change in TKV was directly correlated with the change in TKV ($r = 0.780$, $P < 0.001$). The baseline volumes of the right and left kidney of the same patient were highly correlated ($r = 0.905$, $P < 0.001$) and their growth rates also ($r = 0.702$, $P < 0.001$). The concordance correlation coefficient (95% CI) was 1.000 (0.999–1.000) for intraobserver and 0.996 (0.995–0.999) for interobserver agreement. The change in renal volume correlated with baseline TKV in all age subgroups. TKV correlated positively with male sex, hypertension, albuminuria and history of macrohematuria and negatively with creatinine clearance. Albuminuria was associated with accelerated volume progression. A significant volume decrease was found in 13 kidneys of 10 patients. In 7 cases, the volume decrease could be attributed to the rupture of large cysts.

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Conclusion: We conclude that kidney volume progression can be determined over a period as short as 6 months on unenhanced MRI sequences in ADPKD patients with preserved GFR. The volume determinations were reliable as demonstrated by an excellent reproducibility of measurements. The measured growth rate was identical to a previously published cohort with 3 years follow up. Furthermore, we demonstrated for the first time that cyst ruptures contribute to relevant volume changes over the short term.

16 Comparison of urinary oxalate assessment between six international reference laboratories

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Purpose: Hyperoxaluria is a major risk factor for kidney stone formation. Although urinary oxalate measurement is part of every basic stone risk assessment, there is no internationally recognized and standardized method for this measurement.

Methods and materials: In order to compare urinary oxalate assessment methods, 10 urine samples from 24 h urine collection covering a broad range of oxalate concentrations were aliquoted and sent in duplicates for oxalate measurement to six blinded international reference laboratories. Three laboratories used a commercially available oxalate oxidase kit (labs A, B, E), two laboratories used a HPLC-based method (labs D, F), and one lab used both (lab C). HPLC-based methods were developed in each center independently and used different protocols. All centers used internal controls to check for quality.

Results: We first evaluated intra-laboratories reliability by analysis of the duplicates. Intraclass correlation (ICC) showed variability between 0.808 (95% confidence interval: 0.427–0.948) and 0.998 (95% confidence interval: 0.994–1), with lower values for HPLC-based methods. We then compared laboratories between them using ICC (table 1) and limits of agreement. Among laboratories that run the oxalate oxidase method, the highest reliabilities were obtained between labs B, C, and E, while lab A exhibited very low correlation with the three other labs, suggesting problems with sample handling. Among HPLC-based methods, lab D showed better ICC than lab C or F. In general, HPLC-based methods showed more dispersibility between them and compared to oxalate oxidase kit.

Conclusion: In conclusion, urinary oxalate measurements by oxalate oxidase method showed better ICC and limits of agreement compared to HPLC-based methods, if samples were handled properly. HPLC-based methods showed more dispersibility. In order to compare urinary oxalate values between labs, our data urges the need for a standardization of the method of measurement.

17 Atheroembolic disease – a frequently missed diagnosis: results of a 12-year matched-pair autopsy study

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Purpose: Diagnosis of atheroembolic disease (AD) is challenging, since no specific test is available and AD often masquerades other clinical conditions. The aim of this study was to investigate the relative frequency of autopsy-proven AD over time, to describe the clinical presentation and to identify risk factors for AD.

Methods and materials: All autopsy reports of the Department of Internal Medicine at University Hospital in Zurich from 1995 to 2006 (n > 1900) were screened for AD. For each case a control patient without AD was matched for age, sex and autopsy year. Therapeutic interventions (operations, catheter interventions and drug treatment) in the last 6 months before death, and clinical and laboratory parameters during the last hospitalisation were retrieved from electronic charts.

Results: Fifty-one AD patients were identified, and among these only 6 (12%) had been diagnosed clinically. The organs most often affected were kidney (71%), spleen (37%) and lower GI tract (22%). Surprisingly, the relative AD frequency decreased over time from 3.5 to 0.5/100 autopsies, whereas the frequency of clinically suspected AD remained constant. Among clinical signs, skin lesions (livedo, blue toe) and proteinuria were increased in AD patients, whereas no other laboratory parameter including eosinophilia was different between groups. Vascular interventions within 6 months before death were highly associated with AD (55 vs 14%, p = 0.01), and in a multivariate analysis this remained the only significant risk factor for AD.

Conclusion: Diagnosis of AD is frequently missed. No particular clinical sign or laboratory parameter was significantly associated with AD. Vascular interventions represent a highly significant risk factor for AD. The relative frequency of autopsy-proven, but not of clinically suspected AD decreased over time. Whether this is due to a selection bias or due to a higher use of protective drugs (aspirin, statins, steroids) is currently under investigation.

18 Blood pressure modifies the association between serum adiponectin and uric acid, in a sex-dependent manner

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Purpose: Plasma adiponectin and serum uric acid (SUA) levels are negatively correlated. To better understand the possible mechanisms linking adiponectin and uric acid, we analyzed whether the association between adiponectin and SUA differed by hypertension status (or blood pressure level) and by sex.

Methods and materials: We analyzed data from the population-based CoLaus study (Switzerland). Fasting plasma adiponectin levels were assessed by ELISA and SUA by uricase-PAP. Blood pressure (BP) was measured using a validated automated device and hypertension was defined as having office BP 140/90 mm Hg or being on current antihypertensive treatment.

Results: In the 2897 men and 3181 women, aged 35–74, BMI (mean ± SD) was 26.6 ± 4.0 and 25.1 ± 4.8 Kg/m², systolic blood pressure (SBP) was 132.2 ± 16.6 and 124.8 ± 18.3 mm Hg, median (interquartile range) plasma adiponectin was 6.2 (4.1–9.2) and 10.6 (6.9–15.4) mg/dL, and hypertension prevalence was 42.0% and 30.2%, respectively. The age- and BMI- adjusted partial correlation coefficients between log-adiponectin and SUA were 0.09 and 0.06 in normotensive men and women (P < 0.01), and 0.004 (P = 0.88) and 0.15 (P < 0.001) in hypertensive men and women, respectively. In median regression adjusted for BMI, insulin, smoking, alcohol consumption, menopausal status and HDL-cholesterol, there was a significant three-way interaction between SUA, SBP and sex for their effect on adiponectin (dependent variable, P = 0.005), as well as interactions between SBP and sex (P = 0.014) and between SUA and sex (P = 0.033).

Conclusion: Plasma adiponectin and SUA are negatively associated, independently of BMI and insulin, in a population-based study in Caucasians. However, BP modifies this inverse relationship, as it was significant mainly in women with elevated BP. This observation suggests that the link between adiponectin and SUA may be mediated by sex hormones and the hypertension status.

19 Low adiponectin is associated with increased ambulatory pulse pressure and activation of the renin-angiotensin system in subjects of African descent

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Purpose: Adiponectin, arterial stiffness, as well components of the renin-angiotensin system are associated with cardiovascular risk. This study was aimed to investigate whether plasma adiponectin was directly linked with pulse pressure (PP), as a marker for arterial stiffness, and the renin-angiotensin system (RAS).

Methods and materials: A family-based study in subjects of African descent enriched with hypertensive patients was carried out in the Seychelles. Fasting plasma adiponectin was determined by ELISA, plasma renin activity according to the antibody-trapping principle and plasma aldosterone by radioimmunoassay. Daytime ambulatory blood pressure (BP) was measured using Diasys Integra devices. PP was calculated as the difference between systolic and diastolic BP. The association of adiponectin with PP, plasma renin activity and plasma aldosterone were analyzed using generalized estimating equations with a gaussian family link and an exchangeable correlation structure to account for familial aggregation.

Results: Data from 335 subjects from 73 families (152 men, 183 women) were available. Men and women had mean (SD) age of 45.4 ± 11.1 and 47.3 ± 12.4 years, BMI of 26.3 ± 4.4 and 27.8 ± 5.1 kg/m², daytime systolic/diastolic BP of 132.6 ± 15.4 / 86.1 ± 10.9 and 130 ± 17.6 / 83.4 ± 11.1 mmHg, and daytime PP of 46.5 ± 9.9 and 46.7 ± 10.7 mmHg, respectively. Plasma adiponectin was 4.4 ± 3.04 ng/ml in men and 7.39 ± 5.44 ng/ml in women (P < 0.001). After adjustment for age, sex and BMI, log-transformed adiponectin was negatively associated with daytime PP (–0.009 ± 0.003, P = 0.004), plasma renin activity (–0.248 ± 0.080, P = 0.002) and plasma aldosterone (–0.004 ± 0.002, P = 0.014).

Conclusion: Low adiponectin is associated with increased ambulatory PP and RAS activation in subjects of African descent. Our data are consistent with the observation that angiotensin II receptor blockers increase adiponectin in humans.

Evaluation of a renal risk score in the Swiss population: results from a pilot screening project

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Purpose: The prevalence of chronic kidney disease (CKD) in the Swiss population is not really known. The mostly asymptomatic progression and the low grade of awareness about kidney diseases in the general population motivated a pilot project for information and detection. In the context of the World Kidney Day 2008 a renal risk score was developed and used for visitors to pharmacies. The project was also designed to test feasibility of such screening in public pharmacies.

Methods and materials: 25 pharmacies in the canton St. Gallen and in Lausanne participated to the pilot project and 293 patients' scores were analysed. Participants were interviewed in the pharmacies, their blood pressure (BP) measured and a urine sample was run for a semiquantitative assessment of the albumine/creatinine ratio. The responsible pharmacists were specifically trained for screening activities and consulting. The renal risk score included 12 items: age, sex, family history (FH) and personal history (PH) for CKD, diabetes and cardiovascular disease, systolic and diastolic BP (2 best values of 3 sitting measurements), microalbuminuria ratio to creatinine in a urine sample (mg/mmol). Points were attributed to each item and the sum of all points corresponded to the risk score. <2 defined a low risk for kidney disease, between 2 and 4 a moderate risk and >4 a high risk. A visit to the general practitioner was recommended for moderate and high risks.

Results: 67% (195/293) of the participants were >50 y old and 73% (213/293) were women. Overall 38% (112/293) showed a high total risk score (>4), 37% (108/293) a moderate score (between 2 and 4) and 25% (73/293) a low score. CKD was known in 12% of FH and 18% of PH; diabetes was present in 25% of FH but treatment for diabetes only in 4% of PH, FH was positive for a myocardial infarction in 25% and for other vascular disease in 37% whereas treatment for cardiovascular disease was present in 21% of PH. Systolic BP was measured >140 mm Hg in 26% of the participants and <140 mm Hg in all others. A diastolic BP above 90 mmHg was found in 15% of the participants with no case >110 mm Hg. Microalbuminuria ratio was measured between 2 and 20 mg/mmol in 23% of the participants; 3 cases had clear-cut albuminuria >20, the others were negative <2. Only 16% of the participants with a high renal risk score had a normal BP and no microalbuminuria.

Conclusion: This pilot project shows that it was feasible to screen for the risk of CKD in public pharmacies. Participants were mostly women >50 years old. 75% showed a moderate or high renal risk score with hypertension and/or microalbuminuria. Concerns due to a high proportion of positive family or personal history for kidney disease, diabetes or cardiovascular disease might have motivated these participants to undergo the risk evaluation. To acquire useful epidemiological data the project needs to be continued and evaluated in other parts of Switzerland.

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Hb target achievement with Darbepoetin Alfa at extended dosing intervals – an interim analysis of FLEXTEND at 6 months

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Purpose: European Best Practice Guidelines (EBPG) for anemia management in hemodialysis (HD) patients recommend hemoglobin levels ≥ 110 g/l, but data describing the achievement of these targets are limited. The objective of this ongoing survey in Switzerland is to evaluate, in a clinical practice setting, the effectiveness of darbepoetin alfa (DA) administered in extended dosing intervals in pre-dialysis and dialysis patients.

Methods and materials: FLEXTEND (Evaluation of Hb target achievement with the flexibility to use Aranesp[®] at extended dosing intervals in dialysis and pre-dialysis patients) is a multicenter, retrospective/prospective, non-interventional, practice-based survey to collect anemia related key treatment parameters for up to 18 months. Erythropoiesis-stimulating agent (ESA) naïve or pre-treated patients ≥ 18 years are enrolled in this survey and data are documented monthly. This interim analysis was performed on the data of 330 patients from 22 sites (303 on hemodialysis, 27 in predialysis) with a mean follow-up time of 6 months.

Results: EBPG target Hb levels of ≥ 110 g/l were achieved in 77% of hemodialysis patients and in 67% of pre-dialysis patients. Demographics of the two groups were similar [60 and 63% male, mean age (\pm SD) 66 \pm 14 and 57 \pm 20 years, mean weight 73 \pm 17 kg and 73 \pm 18 kg, respectively]. DA dosing intervals of one week, two weeks and one month were used in 48%, 39% and 13% of dialysis patients and in 22%, 41% and 37% of pre-dialysis patients.

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Setting	Before – after	N	Mean Hb (\pm SD) @ baseline	Mean Hb @ followup
Dialysis	DA – DA	265	117 \pm 13	118 \pm 13
	rHuEpo – DA	27	120 \pm 15	122 \pm 9
	no ESA – DA	11	109 \pm 10	122 \pm 12
	Total	303	117 \pm 13	119 \pm 13
Predialysis	DA – DA	14	122 \pm 14	118 \pm 13
	no ESA – DA	13	100 \pm 11	108 \pm 16
	Total	27	111 \pm 17	114 \pm 15

During the 6 months' followup, mean hemoglobin increased from 117 g/l to 118 g/l in the dialysis patients and from 111 to 114 g/l in the pre-dialysis patients. In the 27 dialysis patients switched from rHuEpo to DA, Hb levels were maintained despite a dose decrease of -26% . Hb target achievement in dialysis patients with extended dosing intervals appeared unimpaired (Hb ≥ 110 g/l in 67% with weekly DA, 81% with bi-weekly DA, 90% with monthly DA).

Conclusion: A variety of individual practice patterns and a heterogeneous patient population contribute to the results of this observational study. Nevertheless, the 77% target achievement (Hb ≥ 110 g/l) in hemodialysis patients compares favourably to the findings of observational studies in Europe, such as DOPPS II. The dose savings observed in dialysis patients switched from short-acting ESAs to DA confirm previous results from larger trials. Extended (bi-weekly and monthly) DA dosing intervals in dialysis patients were associated with a higher degree of target achievement. In the pre-dialysis setting, extended dosing intervals are the preferred mode of administration.

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Kidney volume enlargement in unilateral autosomal dominant polycystic kidney disease (ADPKD)

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Purpose: Autosomal dominant polycystic kidney disease (ADPKD) with contralateral renal absence or dysplasia has rarely been described. Reduced renal mass is a condition that causes marked acceleration of progression in various models of renal disease. Renal volume enlargement is a surrogate marker of disease progression. Herewith we report on kidney volume development in patients with unilateral ADPKD.

Methods and materials: Among a cohort of 181 ADPKD patients screened for our SUISSE ADPKD study, we identified 3 patients with unilateral polycystic kidney disease and contralateral absence of the kidney or dysplasia. Renal volumes were measured within 6 months by analysing two unenhanced MRI scans. Renal function was assessed by creatinine clearance and albuminuria was determined in the spot urine.

Results: The MRI scans of the 2 females and 1 male, aged 24, 38 and 41 years, showed enlarged unilateral polycystic kidneys and absence of the contralateral kidneys (2 patients) or a dysplastic renal rudiment. The volumes of the cystic kidneys amounted to 485 cm³, 780 cm³ and 732 cm³ and increased by 30 cm³ (6.1%), 40 cm³ (5.1%) and 32 cm³ (4.4 %) within 6 months, respectively. GFR at baseline were 73, 98 and 60 ml/min and remained unchanged during follow-up. The urinary protein excretion was below 250 mg/day in all 3 patients.

Conclusion: Our results of renal volume changes in 3 unilateral ADPKD patients show a growth rate above the age and volume matched mean of bilateral ADPKD and may reflect accelerated disease progression.

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Acute renal failure due to hypovolemia after construction of ileostomy

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Purpose: An ileostomy in colon surgery results in the loss of sodium, potassium and bicarbonate. Most patients adapt to these daily losses through subtle changes in salt and water intake and changes in urine volume and electrolyte and acid excretion. However, patients with daily drainage of 1 L or more are prone to symptomatic volume depletion.

Methods and materials: Here we report on 7 patients with new onset of prerenal failure after construction of ileostomy. 5 out of 7 patients were male. Median age at onset was 68 years. The time from ileostomy to renal failure varied from 2 weeks to 2 years after ileostomy construction. The reason for hypovolemia was increased ileostoma output in 6 patients and nausea and vomiting in 1 patient.

Serum creatinine varied from 167 to 893 mmol/l. 5 patients had metabolic acidosis. All patients showed features of hypovolemia with diminished or even blunted urine sodium excretion. The ratio of sodium/potassium as a marker of secondary hyperaldosteronism was between 0.1 to 0.8.

Results: One patient had to start dialysis immediately. Management of volume depletion and improvement of renal function differed according to the underlying disease of the patients. 4 patients had closure of ileostomy, 2 patients had medical treatment of ileostoma output with opioids and rehydration and 1 patient received intravenous fluid and antibiotics. Follow-up creatinine normalized only in 2 patients, but all remained independent of dialysis.

Conclusion: These cases illustrate the importance of recognizing the risk in patients with an ileostomy for the rapid development of life-threatening acid-base and electrolyte disorders, as well as volume depletion. Acute treatment consists of vigorous volume repletion with isotonic saline. Maneuvers to decrease ileostomy output or closure of the ileostomy are important to prevent recurrence. Removal of the colon is an experiment in nature that emphasizes the importance of the normal function of the gastrointestinal tract in maintaining acid-base homeostasis, as well as sodium and potassium balance.

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Nephrology in Armenia 20 years later – the Zurich contribution. Unexpected results of an SSN initiative

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Purpose: The relief operation prompted by the SSN following the earthquake in Armenia exactly 20 years ago (7.12.1998) did not end after some weeks, but became the starting point of a long-term commitment. The start of the programme was somewhat chaotic in midst of the breakdown of the Soviet Union; hence some leading Swiss nephrologists were initially opposed to engage in such a venture. 20 years later it has evolved – despite many obstacles – into a strong partnership programme with Zurich in nephrology and paediatrics. We aim to demonstrate the various stages of the programme and the steps taken to develop a strong basis in (paediatric) nephrology and other disciplines.

Methods and materials: The programme is based on close contacts and continuous careful evaluation of the needs. Highest priority has education both in Yerevan (regular teaching courses and bed side training; 33 visits of EL) and in Zurich (3–6 months). Young colleagues for training were carefully selected, helped by language courses (mainly English) given by VAD. Funding: Own charity organisation (Verein Armenienhilfe Direkt = VAD), SNSF, canton of Zurich (basis of the official partnership with the Kinderspital Zurich since 2005), and much goodwill from individuals and companies.

Results: Three time periods can be distinguished, i.e. I (first 5 years – major political and economic problems): Introduction of contemporary diagnostic methods (e.g. biopsy, serum chemistry, stone analysis) to replace many Soviet concepts; integrated psycho-social and educational care. Additional basic material support. – II (1994–2001 – slow stabilisation): Modern nephrology installed, Arabkir becoming the only centre of paediatric nephrology and the leading one of adult nephrology in Armenia. Essential other disciplines (radiology, lab, paediatric disciplines) were developed to form a strong basis for comprehensive nephrology. Stimulation by successful studies (stones, FMF) and publications – III (2002–08): RRT finally integrated into Nephrology with Haemodialysis expanded (primarily adult patients; mainly supported by Porrentruy and Antwerp) and restart of renal (life donor) transplantation (Antwerp and ISN). Training programme activated and strongly extended to most paediatric disciplines. Additional joint nephrology training programme in the Ukraine and Moldova. Training activities and costs during the last 4 years: 71 teaching visits (average 10 days) from Zurich to Yerevan; 17 colleagues for training from Yerevan to Zurich (total 26 months); respective costs 96'000 and 64000 CHF. Education amounted to 30%, infrastructure and material to 67% and administration to <3% of total costs of 533000 CHF during this period.

Conclusion: 1) Long-term personal commitment from both sides over decades, not years, is needed and was essential (thus opposite to current trends), 2) Accepting new concepts in medicine and abandoning old ones takes more than one generation in most post-Soviet countries, 3) Creation of a strong basis in nephrology was crucial for developing RRT, 4) Such a partnership programme is cost-effective and stimulating for either side, 5) A catastrophe rarely initiates a successful long-term programme.

Where has all that phosphate gone..., the answer my friend, ...Phosphate nephropathy, a serious problem lurking out there?

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Purpose: Phosphate nephropathy (PNP) is a rare, and by its silent and clinically non-spectacular presentation often an unrecognized or misdiagnosed complication of the use of phosphate containing bowel cleansing solutions for the preparation for colonoscopy. Two cases of PNP are presented to awaken the awareness of the clinician to this potentially preventable syndrome.

Methods and materials: Two case reports of typical patients with PNP.

Results: case presentation: Two patients seeking nephrological attention for evaluation of raised serum creatinine levels are presented. Both patients were elderly white females, treated with ACEi or ARB, and diuretics for hypertension, suffered from mild diabetes and consumed occasionally NSAID. Both underwent colonoscopy either for investigation of abdominal pain (patient 1) or as a control for diverticulitis diagnosed 6 years prior to this evaluation (patient 2). Oral sodium phosphate purgatives (Colophos[®], 90 ml containing about 60 g of sodium-phosphate) were used in both cases. Serum creatinine in patient 1 was 69 micromol/l and 105 micromol/l (while consuming NSAID) one year respectively three months prior to colonoscopy. Three months after colonoscopy serum creatinine was 258 micromol/l, and no significant improvement has occurred since. Patient 2 displayed a normal (69 micromol/l) creatinine level 6 months prior to the colonoscopy. Forty eight hours after colonoscopy, prior to a CT scan with contrast, serum creatinine was measured at 168 micromol/l, with no improvement since. In both patients no electrolyte disorders or proteinuria could be found. Kidney size and structure were normal, and no calcifications were documented on ultrasound or CT. Seven months after colonoscopy patient 1 underwent renal biopsy, which revealed mainly a tubulo-interstitial nephropathy characterized by degenerative changes in proximal tubules, interstitial fibrosis, and tubulo-interstitial precipitations containing phosphate (von Kossa stain), suggestive of nephrocalcinosis.

Conclusion: Discussion: Colophos[®], a well tolerated and efficient bowel cleansing agent, is widely used since its introduction in the early 1980s and is generally considered as safe. Although intake of phosphate containing purgatives provide a considerable phosphate load, independent of renal function, and severe transient hyperphosphatemia with symptomatic hypocalcemia has been documented, only a small proportion of exposed individuals develop PNP. Screening for electrolyte and renal function disturbances might therefore be of questionable importance. Electrolyte disorders develop within days after consumption of sodium phosphate. Alternatively, renal failure can be an incidental finding weeks or months after sodium phosphate exposure, presenting with mild symptoms and with no abnormalities of serum phosphate or calcium. Slow progression to end stage renal failure is common, complete remission of renal failure is rare. PNP may be a rare but serious complication associated with the use of phosphate containing cleansing agents for colonoscopy, but the large number of colonoscopies performed each year, probably guarantees a respectable total number of cases, many of which may stay unrecognized or misdiagnosed due to the silent presentation of PNP, temporally distant from the exposure to phosphate. Several risk factors for PNP such as age, female gender, treatment with ACEi, resp. ARB, hypovolemic states, diuretics, pre existing CKD, diabetes or heart failure were identified, but their individual importance remains debated. Significant gaps in the understanding of nephrocalcinosis and PNP persist, prospective studies are not available, and the true incidence of PNP is still not known. The role of PTH, Vitamin D, phosphatonins as well as the role of inhibitors such as citrate, fetuin-A, matrix Gla protein need to be defined for the understanding of the pathophysiology of PNP. Understanding of the pathophysiology of PNP may reveal some of the mystery the mechanisms leading to nephrocalcinosis, nephrolithiasis, and eventually give some insight to mechanisms of ectopic calcifications in general.

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Immune-complex glomerulonephritis in patients with Waldenström's macroglobulinemia

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Purpose: Renal insufficiency has been considered a rare complication in patients with Waldenström's macroglobulinemia (WM). Classical pathological findings include infiltration of lymphocytes or plasmacytoid cells, amyloidosis that can be accompanied by nephrotic syndrome, and immune-mediated glomerulonephritis with deposition of IgM or cryoglobulins. In single cases, a variety of other glomerulopathies has been seen in association with WM.

Methods and materials: We report on two patients suffering WM associated glomerulopathy. We focused on the clinical outcome under immunosuppressive therapy, including histological findings in serial kidney biopsies.

Results: Most important clinical facts of the two patients and histological results of the kidney biopsies as well as data of immunosuppressive therapy are summarized in the following two tables:

Table 1

Patient 1, female, 68 years old.

time	07/07	10/07	01/08	04/08	07/08
clinical symptoms	hypertension, weight gain, nephrotic syndrome				
diagnosis of WM	08/07				
biopsies	<i>first:</i> diffuse intra- and extra-capillary GN (fibrils missed by EM), severe IF/TA		<i>second:</i> fibrillary GN with less in-flammation compared to bx 1, severe IF/TA		
Crea	319	301	285	293	246
UACR	1371	1137	756	696	398
treatment	methylprednisolon iv cyclophosphamide (6x pulse) iv	prednisone po tapered + cyclo-phosphamide iv (pulses)	prednisone po + MMF po	idem	idem

Table 2

Patient 2, male 40 years old.

time	03/98	09/01	06/03	09/05	07/07
clinical symptoms	fever, weight loss, arthralgia, eczema				
diagnosis of WM	09/01				
biopsies	<i>first:</i> extracapillary necrotizing pauci-immune GN, minimal IF/TA		<i>second:</i> segmentally sclerosing IC GN, moderate IF/TA		<i>third:</i> progressive sclerosing GN, severe IF/TA, severe arteriopathy
Crea	83	76	82	129	172
UACR	17	98	20	66	26
treatment	cyclophosphamide po + prednisone, followed by azathioprin po	cyclophosphamide po + prednisone	azathioprin po, then MMF po	rituximab iv	idem

WM: Waldenström's macroglobulinemia, GN: glomerulonephritis, Crea: creatinine [mmol/l], UACR: urine albumin creatinine ratio [mg/mmol], EM: electron microscopy, IF/TA: interstitial fibrosis and tubular atrophy, MMF: mycophenolate mofetil, IC: immune-complex. In spite of immunosuppressive therapy renal outcome was poor. Serial kidney biopsies revealed ongoing glomerulonephritis with increasing areas of interstitial fibrosis, tubular atrophy and glomerulosclerosis.

Safety and tolerability of ferric carboxymaltose (FCM) for treatment of iron deficiency in patients with chronic kidney disease and in kidney transplant recipients

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Purpose: Iron deficiency is common in patients with chronic kidney disease (CKD) and in kidney transplant recipients (KTR). We analyzed the safety and tolerability of the new intravenous iron preparation ferric carboxymaltose (FCM) in these two patient groups.

Methods and materials: Adverse events (AE) after the administration of the drug were assessed by using a questionnaire. Vital signs and laboratory data were collected before and after the application of FCM.

Results: A total of 46 FCM doses were applied to 44 patients (17 with CKD and 27 KTR) either as single bolus injection of 100 or 200 mg (n = 42) or as short infusion with up to 500 mg (n = 4). Mild and transient AE (metallic taste, headache, dizziness) occurred in 6 patients. The estimated glomerular filtration rate (eGFR) remained unchanged by the FCM administration.

Conclusion: We conclude that the safety and tolerability of FCM were excellent. Compared with other intravenous iron preparations the considerably shorter administration time of FCM allows to save time and to reduce costs.

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Improved management of secondary hyperparathyroidism based on repeated NKF/KDOQI targets measurements: data of 3 Swiss dialysis units

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Purpose: Secondary hyperparathyroidism (sHPT) is common in chronic renal insufficiency and progresses over time. Most patients treated with conventional therapies often fail to simultaneously achieve the NKF/KDOQI recommended targets for PTH, Ca, P and CaxP. The objective of this ongoing project is to record and analyze changes in the use of sHPT therapeutic regimens, and to explore the effect on target level achievement over time.

Methods and materials: Information on baseline characteristics, laboratory values and concurrent medications were collected at 3 sites at 2 time points (t1 and t2) in unselected dialysis patients. NKF/KDOQI target level achievements were presented to the centers after data collection at t1. The second data collection at t2 took place at 6, 8 and 10 months respectively at site 1, 2 and 3; during this period the treating physician continued management of the disease according to local standard of care (no pre-set drug protocol).

Results: At time point t2, 55.6% of the 160 patients were male, mean age (SD) was 65.4 (14.6) years and mean weight (SD) was 75.1 (17.0) kg. 60.6% were treated with vitamin D sterols and 80.3% received ≥1 phosphate binder. Calcimimetics were used in 27.5% of patients. **Conclusion:** NKF/KDOQI target achievement improved in all centres (t1 vs t2) for all 4 parameters simultaneously. Interestingly, this difference was observed in both analysis populations ('all patients' and 'patients with data at t1 and t2'). Changes in the use of different drug regimens were noted at all sites; in particular, calcimimetics were used more often.

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Table 1

[%] of patients within NKF/KDOQI targets and drug use per centre.
SHPT Center analysis: T1 (2007) vs T2 (2008): Table 1

	Site 1		Site 2				Site 3					
	all patients*		pts with data t1 & t2**		all patients*		pts with data t1 & t2**		all patients*		pts with data t1 & t2**	
	t1 (n = 66)	t2 (n = 58)	t1 (n = 54)	t2 (n = 54)	t1 (n = 65)	t2 (n = 63)	t1 (n = 47)	t2 (n = 47)	t1 (n = 35)	t2 (n = 39)	t1 (n = 26)	t2 (n = 26)
corr Ca, P, CaxP, PTH within targets (%)	14.1	21.1	17.3	22.6	8.8	13.0	9.5	15.9	6.1	13.2	8.3	11.5
Vitamin D in %	71.2	72.4	72.2	75.9	41.5	34.9	46.8	36.2	54.3	74.4	61.5	80.8
Phosphate Binder in %	63.6	79.3	66.7	79.6	78.5	79.4	83.0	83.0	80.0	82.1	76.9	84.6
Calcimimetics in %	28.8	46.6	33.3	46.3	10.8	20.6	14.9	25.5	11.4	15.4	15.4	23.1

* (including death, transplantation, loss of follow-up & new patients on dialysis) ** patients with data at both t1 and t2

Site key Site 1: SZ Biel (06.2007 / 01.2008) Site 2: HUG (10.2007 / 06.2008) Site 3: KS Frauenfeld (09.2007 / 07.2008)

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Effects of Aliskiren in a patient with severe hyperreninemic hyperaldosteronism: a case report

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Purpose: The inhibition of the renin-angiotensin-aldosterone system (RAAS) with ACE inhibitors (ACEI) or angiotensin receptor blockers are effective in controlling hypertension. However, these agents are not more effective than other antihypertensive agents in reducing major cardiovascular events. Aliskiren, the first in a new class of effective direct renin inhibitors, blocks angiotensin (Ang) I production directly at its rate-limiting step.

Methods and materials: n/a.

Results: Case report: We present a 47-year-old woman with hypertension and end-stage renal failure due to polycystic kidney disease, who received a kidney from her sister-in-law in 2000. The allograft function (sirolimus 2 mg/d and prednisone 5 mg/d) is stable (serum creatinine concentration: 130–150 µmol/l). The hypertension due to a severe hyperreninemic hyperaldosteronism persisted after transplantation. For several years, her antihypertensive therapy consisted of ACEI and spironolactone. Under this medication, her blood pressure values ranged from 100/65 mm Hg to 140/90 mm Hg

(range over the last five years). This therapy was stopped and aliskiren was initiated for better blood pressure control at a serum creatinine concentration of 145 µmol/l. Two months after starting aliskiren, her blood pressure was 110/75 mm Hg (range from 104/76 to 125/85 mm Hg during treatment) and serum creatinine was 132 µmol/l. Renin concentration rose from 710 mU/l to 1732 mU/l, while plasma aldosterone decreased from 1.98 nmol/l to 0.45 nmol/l. Renal protein excretion decreased from 47 to 21 mg/mmol creatinine. FE-K (ACEI + spironolactone vs. aliskiren) remained unchanged (18 vs. 19%).

Conclusion: This case demonstrates the antihypertensive efficacy of once-daily aliskiren 150 to 300 mg in a patient with a kidney transplant and moderate hypertension probably due to polycystic kidney disease and activated RAAS. Aliskiren suppresses plasma renin activity although renin concentration increases during treatment due to loss of feedback inhibition by Ang II on renin release. Aliskiren inhibits the RAAS at its rate-limiting step and probably favors more complete blockade. However, the ultimate role of aliskiren in target organ protection and improvement in cardiovascular outcomes has still to be determined in prospective studies with clinical endpoints.

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Cinacalcet in chronic kidney disease stage 4 – case report

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Purpose: Secondary hyperparathyroidism (sHPT) begins early in the course of chronic kidney disease (CKD) and is associated with elevated serum parathyroid hormone (PTH) levels. Traditional sHPT therapies such as vitamin D sterols and calcium-based phosphate binders are not always adequate to achieve K/DOQI goals for sHPT. In this case report vitamin D was replaced due to Calcitriol intolerance (side effects such as nausea, vomiting and loss of appetite) by Cinacalcet to control sHPT.

Methods and materials:

	start	month 1	month 2	month 3	month 4	month 5	month 6	month 7	month 8	month 9
Ca (mmol/l)	2.39	2.49	2.10	2.30	2.30	2.29	2.39	2.27	2.09	2.10
P (mmol/l)	1.33	1.36	1.35	1.32	1.48	1.34	1.35	1.28	1.93	1.23
PTH (pmol/l)	34.4			48.4	44.6	38.1		53.6	14.9	8.2
Calcitriol (g/week)	0.75	0.75	0.75	1.50	3.00	stop				
Cinacalcet (mg/day)							15	30	30	30

Table 1

Levels of parathyroid hormone, calcium, phosphorus during treatment with Calcitriol and Cinacalcet.

Persistent norovirus infection in renal allograft recipients – a new concern for hospital hygiene

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Purpose: Noroviruses are responsible for 80–90% of acute gastroenteritis outbreaks in adults and older children worldwide. In immunocompetent recipients norovirus infection is self-limited. We are aware of only a few rare patients with either stem cell or intestinal allografts and of only one single patient with another solid allograft (heart), in whom persistence of norovirus infection has been described. Here we report on persistent norovirus infection in four adult renal allograft recipients.

Methods and materials: Diarrhea is a frequent clinical complaint in the renal transplant outpatient clinic; infection and drug side effects are the most common causes. A systematic screening for viruses, bacteria and parasites is usually performed in our patients with new onset diarrhea. In patients with proven norovirus infection, norovirus shedding by PCR was monitored over time. Furthermore, clinical symptoms were recorded, and CRP was measured at each consultation. Viral RNA samples were stored for genetic analysis of the two most variable open reading frames.

Results: We report 4 renal allograft recipients (29 to 57 years old) with prolonged infection and persistent norovirus shedding over several months. Norovirus infection occurred between 39 days up to >10 years posttransplant. Duration of norovirus shedding ranged from 196 to 630 days. All patients received standard triple immunosuppression regimes at the time of diagnosis. Reduction of immunosuppression (mainly prednisone and mycophenolate, which was replaced by azathioprine in one patient) led to norovirus clearance in 2 patients. In the other 2 patients norovirus shedding persisted despite reduction of immunosuppression, but clinical symptoms resolved. No rejection episode occurred upon reduction of immunosuppression. Genetic testing of viral RNA for analysis of clustering (as evidence for a potential outpatient transmission) and of accumulation of mutations over time (as evidence for an antigenic drift, which could explain the failure of virus clearance due to an immune escape mechanism) are under current investigation.

Conclusion: We report for the first time persistent norovirus infection in adult renal allograft recipients under stable immunosuppression. Reduction of immunosuppression led to resolution of symptoms in all our patients, but achieved viral clearance in only 2 out of them. This finding has important implications for hospital hygiene procedures due to the high infectivity of this virus and its resistance to common hand disinfection solutions. We recommend norovirus testing in patients with prolonged diarrhea.

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failure (n = 1). 36 patients were randomised (study arm n = 17, control arm n = 19). The primary endpoint, i. e. renal function, was not different in both arms after 6 months. Secondary endpoint, i.e. biopsy proven rejection was detected in 7 patients (1 BPCAR (6%) and 6 SCAR (35%)) and 3 patients (1 BPCAR (5%), 2 SCAR (10%)) in the study and control arm, respectively. In 39 non-randomised patients, 5 biopsies showed histological signs of SCAR (13%): 3 after 3 months, another 2 after 6 months. No new insulin-dependent diabetes mellitus was diagnosed whereas CNI-free IS led to significantly lower triglyceride levels after 6 months (p = 0.02). **Conclusion:** An immunosuppression with TAC/MPS/SIR in the absence of corticosteroids is a safe and efficient option in the prevention of acute rejection following kidney transplantation (13% rejection rate including SCAR). Renal function after 6 months was not superior under SIR/MPS compared to TAC/SIR/MPS. Dual therapy led to a higher number of SCAR but not BPCAR compared to triple therapy. More studies are needed comparing directly CNI and mTOR inhibitors in their ability to prevent posttransplant rejections.

Rituximab and intravenous immunoglobulin treatment for chronic antibody-mediated renal allograft rejection

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Purpose: B cells play a dual role in allograft rejection: (1) they are precursors of alloantibody-secreting plasma cells, and (2) they efficiently process alloantigen to stimulate T cell responses. Current anti-rejection therapies potentially block cellular, but less efficiently antibody-mediated effector mechanisms. Whereas for acute antibody-mediated rejection (AMR), therapy mainly relies on plasmapheresis or immunoadsorption, no studies for treatment of chronic AMR are available. This pilot study tested the efficacy and safety of rituximab combined with intravenous immunoglobulin (IVIg) for late humoral allograft rejection.

Methods and materials: Renal allograft recipients were included in this pilot study based on the following criteria: (1) deteriorating allograft function, (2) no efficacy of standard treatments (steroids, increase of calcineurin inhibitors, T cell-depleting antibodies), (3) evidence for AMR in biopsy (C4d+) or serology (donor-specific antibodies [DSA]). Study patients received rituximab 375 mg/m² on day 1, and all except one patient also received IVIg 0.4 g/kg on days 2–5. eGFR, proteinuria and DSA were monitored.

Results: Four male patients (39–64 y) were included 1 to 27 years post kidney allotransplantation. They experienced a loss of eGFR between 19 and 57% in the 6 months before treatment with rituximab. Three patients were sensitized according to the panel-reactive antibody test (max. PRA 47%), and all tested positive for DSA (2 anti-class II, 1 anti-class I and 1 both anti-class I&II). Three biopsies stained diffusely positive for C4d in peritubular capillaries, 2 showed transplant glomerulitis or glomerulopathy, 2 had cellular vascular rejection and 1 displayed intense infiltration with CD20+ cells. If classified according to the Colvin scheme for chronic AMR, one patient was in stage I, 2 in stage II and 1 in stage IV. Upon treatment with rituximab all patients had improvement of GFR, which remained significant until 6 months post treatment. One patient developed acute cellular rejection one year after rituximab (without evidence for a raise of DSA), and one patient experienced severe, possibly rituximab-associated lung toxicity. DSA levels 3–8 months after rituximab dropped in two and remained unchanged in the other two patients.

Conclusion: Rituximab/IVIg represented an effective short-term treatment for chronic AMR of a renal allograft. However, severe toxicity occurred in one patient. Larger studies are needed to identify the appropriate target patient population for such treatment and to determine the optimal treatment protocol.

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An open, single centre, prospective study to investigate a steroid free immunosuppressive regimen for de novo renal transplant recipients followed by a two arm randomisation to a CNI-sparing and a CNI-free maintenance immunosuppression after 3 months

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Purpose: Corticosteroids as well as calcineurin inhibitors (CNI) have well known side-effects when given over long periods after kidney transplantation. We investigated the efficacy and safety of a steroid free immunosuppressive regimen in the early posttransplant period followed by CNI withdrawal after three months.

Methods and materials: 75 patients receiving a kidney transplant were enrolled from 1.1.2005 to 31.12.2007. Induction therapy consisted of methyl-prednisolon i.v. for 3 days and basiliximab on days 0 and 4. Maintenance immunosuppression (IS) consisted of tacrolimus (TAC) and sodium-mycophenolate (MPS). Sirolimus (SIR) was added on day 4. When protocol biopsy after 3 months showed no signs of rejection, patients were equally randomized in two groups: study arm without CNI (MPS/SIR) and control arm with low-level TAC, MPS and SIR. Primary endpoint was renal function and study follow-up ended with a second protocol biopsy after 6 months.

Results: 75 patients were enrolled in the study. In the early posttransplant period (first 3 months) a total of 6 biopsy proven clinical acute rejections (BPCAR) occurred, 4 of them were antibody mediated vascular rejections. The first protocol biopsy after 3 months of steroid free IS revealed another 4 subclinical acute rejections (SCAR), 3 of them with an interstitial (cellular) origin resulting in an overall rejection rate of 13% (clinical rejection rate 8%) after 3 months in this steroid free protocol. Randomization for the second part of the study was not possible, apart from the mentioned acute rejections, due to sirolimus side effects (n = 14), steroid therapy for dermatological or rheumatological reasons (n = 4), delayed graft function (n = 3), refused biopsy (n = 3), BKV infection (n = 2), surgical complications (n = 1), thrombotic microangiopathy (n = 1) or prerenal

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Does the addition of a mTOR inhibitor reduce the incidence of post-transplant skin cancers?

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Purpose: Skin cancers develop in 20 to 40% of renal transplant recipients beyond 10 years after transplantation and represent a relevant source of morbidity and mortality. The immunosuppressive mTOR inhibitors, Sirolimus (Siro) and Everolimus (Evero), have been reported to be both antiproliferative in vitro and beneficial in a variety of clinical malignancies, including skin cancer, lymphomas and renal cell carcinomas. It is, however, unknown whether the addition of a mTOR inhibitor reduces the occurrence of de novo skin cancers in longterm transplant recipients. The present retrospective analysis was designed to evaluate the effect of adding an mTOR inhibitor to the

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immunosuppressive regimen on the incidence of cutaneous squamous cell carcinomas (cSCC) in renal transplant recipients already suffering from these tumours.

Methods and materials: Retrospective analysis of renal transplant recipients followed in Aarau and Basel who a) had an mTOR inhibitor added to immunosuppression at least 3 years after transplantation and b) had at least one biopsy-proven spinalioma (excluding carcinoma-in-situ) in the 2 years before this change and c) remained on the mTOR inhibitor drug regimen at least 2 years after the change. All patients were examined for skin cancers at their annual check-up. The primary parameter was the number of cSCC in the two years before and after the mTOR switch. A control group was formed from patients transplanted in the same year, who were on non-mTOR immunosuppression during the same 4 years as their index patient and had at least one cSCC during this period. The present data represent an interim analysis of data from Aarau patients only.

Results: All 5 mTOR patients meeting the inclusion criteria were male. Mean age was 69 years (range 51–79), 3 had a first transplant and 2 were living donor kidney recipients. No control patient could be found for patient No 3. Data are presented below:

mTOR patients	Immunosuppression		N of cSCC /24 months	
	before mTOR	with mTOR inhibitor	before mTOR	with mTOR
1	CyA-mono	Evero/CyA-low	9	3
2	CyA/Pred	Siro/CyA-low/Pred	5	1
3	CyA/MMF	Evero/CyA-low/MMF	3	10
4	FK-mono	Evero-FK-low	4	0
5	FK/Aza	Siro/FK-low	1	1
Mean			4.4	3.0
Controls (throughout)			(same 24 months)	(same 24 months)
1a	CyA/MMF	2	6	
2a	CyA/Aza/Pred	1	0	
4a	FK-mono	0	1	
5a	FK-Aza	0	3	
Mean			0.75	2.5

CyA = Cyclosporin A; FK = Tacrolimus; CyA-low/FK-low = minimal dose CyA/FK; Pred = prednisone

Thus, the number of cSCCs decreased in 3 of 5 patients after adding mTOR inhibitors but increased in 3 of 4 controls during the same time. Due to the small number of patients, the effect of the mTOR switch was nonsignificant ($p = 0.12$).

Conclusion: These preliminary data indicate that some patients with post-transplant cSCCs appear to benefit from the addition of mTOR inhibitors to their immunosuppressive regimen. By the end of 2008, the study will be extended to the entire Basel/Aarau transplant population, and hopefully yield conclusive results. It may then form the basis of a national registry to clarify the potential benefit of mTOR inhibitors in transplant recipients with cSCCs.

Psychosocial evaluation of 189 consecutive potential living kidney donors in Basel

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Purpose: Psychosocial evaluation of potential organ donors is mandatory in Switzerland. However, little is known about the extent of the psychosocial evaluation and how frequent objections regarding the transplantation are.

Methods and materials: An explorative study in 189 consecutive potential living kidney donors was performed.

Results: From January 1, 2004 until of July 31, 2008, 189 potential donors were evaluated. Mean age was 53 (range: 28–82), 127 were female (68%), 46 were non-Swiss (26%). 80 were genetically related (43%), 65 were emotionally related (35%). 32 (17%) had a distant relation to the potential recipient and 9 (5%) were unrelated. 154 were evaluated once and in 35 (19%) an additional psychosocial evaluation was necessary. As a result of psychosocial evaluation, 16 (8%) potential donors were rejected. In 6 cases, another living donor was chosen. In the remaining 10 cases without another potential living donor, 6 agreed with rejection for psychosocial reasons and 4 disagreed with the final decision.

Conclusion: In a minority of potential donors, an extended psychosocial evaluation is necessary. In most potential donors who are rejected for psychosocial reasons they agree with the decision, and very few are rejected against their explicit wish to donate.

FoxP3 positive T-cells in graft biopsies from living donor kidney transplants after donor-specific transfusions

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Purpose: Donor-specific transfusions (DST) induce allograft tolerance in animals. Evidence is growing that FoxP3 positive regulatory T-cells are associated with tolerance in humans.

Methods and materials: 44 biopsies from 69 living donor kidney transplant recipients (LDT) after DST, 53 biopsies from 69 matched deceased donor transplant recipients (DDT), obtained for graft dysfunction, and 12 rejection biopsies from LDT without DST were retrospectively analyzed according to the Banff classification and for immunohistological markers including C4d and FoxP3.

Results: Biopsies showing acute rejection were equally distributed (27% in LDT/DST vs. 22% DDT, not significant). FoxP3 positivity was more frequent in LDT/DST than in DDT biopsies (67% vs. 44%, $p = 0.02$). Considering only biopsies with acute rejection, FoxP3 positivity was observed in 92% (11/12) after LDT/DST, but only in 50% (6/12) after DDT ($p = 0.03$). The number of FoxP3 positive T-cells per total infiltrating cells in rejection biopsies was higher ($p < 0.05$) from LDT/DST (4.1%) than from DDT or LDT (2.6%) without DST (2.5%). Positive C4d staining of peritubular capillaries was generally rare (5% vs. 2%, ns). Calcineurin inhibitor toxicity was more frequent in LDT/DST (31% vs. 13%, $p = 0.03$), but interstitial fibrosis and tubular atrophy were important in both groups (39% vs. 49%; ns). Six-year graft survival was better in patients with LDT/DST than with DDT (87.5% vs. 79.7%, $p = 0.04$).

Conclusion: The present investigation demonstrates an association between DST and FoxP3 positive T-cells. The effect of DST on regulatory T-cells deserves further analysis in transplantation.

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Prevalence, etiology and therapy of anemia after kidney transplantation in Switzerland: Results of a national survey

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Purpose: Posttransplant anemia has not been given much consideration so far. Previous analyses from a single Swiss transplant centre have revealed that about 25 percent of patients with a renal graft do not meet targets for minimum hemoglobin requirements as defined by NKF-K/DOQI guidelines for hemodialysis patients. However, this analysis did not take into account factors that might be causative for anemia, such as iron deficiency or concomitant medication. Moreover, no data are available on the use of erythropoietin stimulating agents (ESA) in the Swiss renal

posttransplant population. Thus, it was the aim of the present study to gather information on the prevalence, etiology and therapy of posttransplant anemia in Switzerland.

Methods and materials: We conducted a national survey to which all Swiss centres performing renal transplants were invited to participate. 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, renal function, therapy for anemia, 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, parathyroid function, and systemic acid/base status.

Results:

	Hb, g/L	Hb <110 g/L	Hb ≥130 g/L	Hb, g/L	Hb <110 g/L	Hb ≥130 g/L	Hb, g/L	Hb <110 g/L	Hb ≥130 g/L
N (%)	220 (100)	81 (36.8)	50 (22.7)	144 (65.5)	36 (25)	44 (30.5)	76 (34.5)	45 (59.2)	6 (8)
Hb, g/L	116.6±18	98.7±9	141±10.9	122±17	101.6±6.9	142±11.2	106.9±15	96.3±9.8	134.2±4.5
Ferritin, µg/L	336±357	464±436	125±100	244±260	350±328	122±114	438±420	536±482	134±50
Transferrin Sat., %	27.1±13	26.8±16	25±9	24.5±12	24.4±16	23.2±10	29.8±14	28.1±16	29.1±5
GFR, ml/min	44±21	37±21	54±19	50±20	45±20	57±17	33±18	32±19	33±18
CRP, mg/L	9.9±24	12.1±19	3.5±5	9.5±25	12.6±17	3.8±5	10.8±23	11.8±21	1.8±1
PTH, ng/L	148±105	220±141	104±61	131±90	138±22	98±53	178±124	235±148	152±107
On ESA, N (%)	76 (34.5)	45 (55.5)	6 (12)	0	0	0	76 (34.5)	45 (57.7)	6 (8)
ESA dosage, IU/wk	9205±7386	11336±7637	5422±5270	NA	NA	NA	9205±7386	11336±7637	5422±5270
Age, yr	56.1±14	57.2±14	55.6±13	56.0±14	57.3±15	56.4±13	56.3±14	59.2±14	49.8±14
Time since TPL, yr	7.7±7	7.4±8	8.3±7	7±6	6.1±7	8±7	8.9±7.5	8.5±8	10.7±5

Conclusion: Posttransplant anemia is very common in a Swiss cohort of patients with a renal graft, with 37% of patients having Hb concentrations below 110 g/L. Among them, only 55% receive ESA

therapy, leaving room for improving anemia status. The main determinant of Hb concentration is graft function. The inverse correlation of ferritin and Hb is intriguing, but needs further assessment.

Protein A immunoabsorption for treatment of acute antibody-mediated renal allograft rejection

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Purpose: No evidence-based data from randomized controlled studies are available for treatment of acute antibody-mediated rejection (AMR) in kidney allografts. However, it is generally accepted that a method for alloantibody removal should be used as part of the regimen, which often includes also steroid pulses, intravenous immunoglobulin and/or rituximab. Plasma exchange (PEX) and immunoabsorption (IADS) are the two main modalities available. The latter may have advantages due to the selective removal of immunoglobulins, since no disturbance of the coagulation system or other serum proteins is expected. Here we report our preliminary experience with this technology.

Methods and materials: In July 2007 the technique of IADS with Protein A-coated columns for treatment of acute AMR was introduced in our dialysis and apheresis unit. Acute AMR episodes were treated with 6–8 sessions of IADS together with intravenous immunoglobulin substitution at a dose of 0.1 g/kg per treatment. Due to logistic reasons, one episode was treated with PEX. In this patient, substitution was performed with fresh frozen plasma or albumin. The rejection treatment further consisted of steroid pulses and change to tacrolimus/mycophenolate mofetil. DSA (Luminex mix for class I or class II), total immunoglobulin and albumin levels were measured before and after each treatment. Allograft function, proteinuria and DSA were monitored over time.

Results: Between August 2007 and July 2008 five episodes of acute AMR (defined by allograft dysfunction, diffuse C4d staining of peritubular capillaries and positive DSA by Luminex single antigen beads) occurred in four different patients (24–61 years old). Two episodes occurred in the first month after transplantation, and one of these patients had a relapse about 6 months later. Two episodes were late acute AMRs, one due to non-compliance and one due to too much reduction in immunosuppression. Currently, patient and graft survival are 100% with a follow-up between 1 month and 1 year after treatment. However, a substantial loss of allograft function was observed in all 4 patients. Immunoglobulin removal by IADS was very efficient reaching levels below 1 g/l total IgG after 2 treatments with concomitant reduction of DSA. With the first two IADS treatments, which both occurred early after transplantation, bacterial infections at the operation site requiring prolonged hospitalisation were seen. Thereafter the protocol for immunoglobulin substitution was changed to one infusion after every 3 IADS sessions with no further infectious complications.

Conclusion: IADS with protein A column can be successfully performed on a regular hemodialysis unit familiar with apheresis technology and is efficient for treatment of acute AMR in renal allograft recipients.

Surveillance biopsies after steroid withdrawal in adult renal transplant recipients

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Purpose: Since 2005 the policy in our centre includes surveillance biopsy (SBx) after steroid withdrawal (SWD) in renal transplant recipients. To our knowledge there are only few reports in the literature regarding surveillance biopsies in relation with steroid withdrawal in adult kidney transplant recipients.

Methods and materials: 42 adult kidney recipients transplanted between 11/03 and 1/08 from deceased or living donors were included. All had a surveillance biopsy within 24 months after transplantation preceded or rarely followed by prednisone (PDN) withdrawal within 90 days from biopsy. The following data were analysed: patients and transplant characteristics, histology including immunofluorescence, changes of immunosuppressive therapy (IS), short term follow-up regarding graft function and acute rejection. Values are given as median and range. Age at transplantation 52 years (19–69), first / second graft in 40/2 patients, deceased / living donor transplant in 26/16 patients, no sensitized patients (CDC PRA last / peak 0/0 except 6 recipients with max. 11/35). Baseline IS consisted of basiliximab, cyclosporinA (CsA), mycophenolate and PDN in 35 patients, in the other 7 cases various regimens were used. Only two patients had biopsy-proven acute rejection before SWD. The SBx took place at 9 mo (6–24) post-transplant. In 40 patients complete SWD preceded the biopsy by 20 days (0–77), in 2 patients it followed the biopsy by 43 and 57 days respectively, both were on a PDN dose of 2.5 mg/d at SBx. Follow-up after SBx was 17 months (0–42). Changes of IS after SBx were tailored individually considering not only the actual SBx but also preceding biopsies, immunological risk profile and previous side-effects of immunosuppression.

Results: Only 17/42 (41%) SBx were normal or unchanged with regard to time zero biopsies. The remaining 25 biopsies showed CsA-toxicity in 12 cases, borderline cellular rejection in 8 cases, 1 acute tubulo-interstitial rejection (Banff 1a), acute vascular rejections in 3 cases (negative C4d), 50% C4d positivity of peritubular capillaries in 1 case and nephrocalcinosis in another. IS remained unchanged in 23/42 (55%) patients, whereas in 10/42 (24%) the calcineurin inhibitor dose was markedly reduced. In patients with tubular rejection PDN was restarted or mycophenolate increased. Acute vascular rejections were treated with ATG, PDN and switch to tacrolimus. The isolated C4d positivity was rebiopsied after x months and mycophenolate increased in view of an increase of the positivity. During follow-up after SBx transplant function remained stable, both in patients with normal histology as in those with pathological SBx. The slope of estimated creatinine clearance at last follow-up compared to the biopsy date was +0.2 (±0.9) ml/min/month in all 42 recipients and was not different between those with normal or pathological SBx.

Conclusion: Surveillance biopsies after late steroid withdrawal in mostly low-risk renal transplant patients can help to guide immunosuppression adjustment. This combination of steroid withdrawal with surveillance biopsy may contribute to the safety of steroid withdrawal.

Switch to Sirolimus-based immunosuppression in stable renal transplant recipients

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Purpose: Sirolimus (SRL) has been used to replace calcineurin inhibitors (CNI) for various indications including CNI-induced toxicity. The aim of this study was to evaluate the efficacy and safety of switching from CNI to SRL in stable renal transplant recipients (RTR) with low grade proteinuria (<1 g/24 h).

Methods and materials: Between 2001 and 2007, 41 patients (20 females, 21 males; mean age 47 ± 13) were switched after a median time post-transplantation of 73.5 months (range 0.2–273.2 months). Indications for switch were CNI nephrotoxicity (39%), thrombotic micro-angiopathy (14.6%), post-transplantation cancer (24.4%), CNI neurotoxicity (7.4%), or others (14.6%). Mean follow-up after SRL switch was 23.8±16.3 months. Mean SRL dosage and through levels were 2.4 ± 1.1 mg/day and 8 ± 2.2 ug/l respectively. Immunosuppressive regimens were SRL + mycophenolate mofetil (MMF) (31.7%), SRL + MMF + prednisone (36.58%), SRL + prednisone (19.51%), SRL + Azathioprine (9.75%), or SRL alone (2.43%).

Results: Mean creatinine decreased from 164 to 143 µmol/l (p <0.03), mean estimated glomerular filtration rate (eGFR) increased significantly from 50.13 to 55.01 ml/minute (p <0.00001), mean systolic and diastolic blood pressure decreased from 138 to 132 mm Hg (p <0.03) and from 83 to 78 mm Hg (p <0.01), but mean proteinuria increased from 0.21 to 0.63 g/24 h (p <0.001). While mean total cholesterol didn't increase significantly from 5.09 to 5.56 mmol/l (p = 0.06). The main complications after SRL switch were dermatitis (19.5%), urinary tract infections (24.4%), ankle edema (13.3%), and transient oral ulcers (20%). Acute rejection after the switch occurred in 7.3% of patients (n = 3), and 2 acute rejections were successfully treated with corticosteroids and 1 did not respond to treatment (not related to switch). SRL had to be discontinued in 17% of patients (2 nephrotic syndromes, 2 severe edema, 1 acute rejection, 1 thrombotic micro-angiopathy, and 1 fever).

Conclusion: In conclusion, we found that switching from CNI to SRL in stable RTR was safe and associated with a significant improvement of renal function and blood pressure. Known side-effects of SRL led to drug discontinuation in less than 20% of patients and the acute rejection rate was 7.3%. This experience underlines the importance of patient selection before switching to SRL, in particular regarding pre-switch proteinuria.

Case report: Toxoplasmosis in kidney transplant recipients – easily missed diagnose

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Purpose: Toxoplasmosis is a rare, infrequent, often difficult and potentially lethal disease in kidney transplant recipients.

Methods and materials: Following case will be discussed and the current literature will be reviewed.

Results: We report a case of a 47 year old man (Living donation 5 years ago, poor function for several reasons, Prednisone, MMF, sirolimus) who complained of increasing fatigue and remittent fever (up to 38 °C) since a fortnight. He presented with high fever (40.7 °C) and weak epigastric pain associated with nausea, Lc 6600x109/l (slight leftward shift 16%), CRP of 123 mg/l (<5), Procalcitonin of 6ng/ml (<0.25), Bilirubin of 24 µmol/l (<20), slightly elevated transaminases and acute on chronic, dialysis depending, kidney transplant failure. Additional abdominal sonography lead to the initial presumption of acute cholecystitis (without gallstone) but empirical Piperacillin/Tazobactam treatment (twice a day 4.5 g) reached no benefit. Blood and urine cultures remained negative, further investigations included negative hepatitis-, HIV-, CMV- and Cryptococcus serology, an EBV reactivation (PCR: 1667 log/ml), negative RF and ANA, elevated circulating C1q-Immunkomplex 32% (<10%), lowering CH50, C3 and C4 and beside raising transaminases a Ferritin of 18700 ng/ml (30–400). Transplant biopsy showed tubularnecrosis and interstitial fibrosis, whereas liver biopsy showed extensive starcell siderosis expressing possible haemophagocytosis. Therefore steroids were increased: prednisone from 15 to 100 mg/d. The physical condition of the patient impaired dramatically and 3 days later he died of acute congestive heart failure. The autopsy showed a generalized toxoplasmosis (toxoplasma gondii trophozoites) accompanied by a severe myocarditis leading to congestive heart failure.

Conclusion: Parasitic infections constitute an important subset of post-transplantation infection – even in Europe –, but the index of suspicion is low. Because they are usually curable if diagnose is made in time, clinician awareness of the clinical syndromes could save many lives.

SOP DIDACT – a Swiss survey on the practicability of DIDACT

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Purpose: Progresses in transplantation medicine have led to very good patient and graft survival rates. However a significant number of patients are still suffering from adverse side effects of their immunosuppressive therapy. When severe, these side effects could lower patient compliance and secondary increase the risk of acute rejection [i],[ii]. The DIDACT study [iii] investigated the influence of non-immunosuppressive factors on the incidence of severe diarrhoea in renal transplant recipients. The Swiss survey on the practicability of DIDACT (SOP DIDACT) assessed whether specialists in charge for transplant patients were familiar with the DIDACT study, how quality and practicability of DIDACT were rated and whether the algorithm as described in DIDACT was applicable.

Methods and materials: Area of expertise, number of transplant recipients seen per week, knowledge of the DIDACT study and whether findings of the DIDACT study were already applied, were assessed by means of a baseline questionnaire. Specialists were asked to rate the study design and the study results on a scale from 0–10 (1 = relevant; 10 = not relevant) if they were familiar with the study. Otherwise the study was briefly presented to them. A follow up questionnaire (2 months later) assessed the experience of the specialists with the use of DIDACT algorithm including rating, applicability and efficacy of the algorithm (1 = useful/ easy to apply/ efficacious; 10 = not useful/ difficult to apply/ not efficacious).

Results: 104 specialists of various fields (nephrology, surgery, hepatology, infectiology, cardiology and pneumology) were asked to participate to the SOP DIDACT. 98 (94%) specialists completed the baseline questionnaire and 71 (68%) specialists answered the follow up questionnaire. 65 specialists (62.5%) filled both questionnaires. **Baseline questionnaire:** 70.5% (69 out of 98) of participating specialists had either heard about or read the DIDACT study whereas 29.5% did not. 33.7% (33 out of 98) had already implemented the DIDACT algorithm. The study design was rated 2.9 ± 1.7 and the study result 2.7 ± 1.4 (mean ± SD). **Follow up questionnaire:** 72% (51 out of 71) of the specialists had applied the algorithm at least once since the baseline assessment and were included in the following analysis. The stepwise approach of the DIDACT algorithm was rated 3.1 ± 2.4 (n = 50), the practicability 2.5 ± 1.6 (n = 49), and the efficacy 2.7 ± 1.0 (n = 49). The following steps of the algorithm would be applied by the Swiss specialists in front of severe diarrhoea in transplant recipients: (1) withdrawal of diarrhoea-causing concomitant non-immunosuppressive medication, (2) microbiological stool examination, (3) exclusion of cytomegalovirus infection, (4) exclusion of bacterial overgrowth, (5) colonoscopy, (6) adaptation of the immunosuppressive therapy, and (7) empirical treatment.

Conclusion: The majority of the Swiss specialists was familiar with the DIDACT study and judged the results as relevant. Until the follow up assessment, 72% had applied the algorithm at least once. The algorithm was judged useful, easy to apply and efficacious. In contrast to the algorithm as presented by Maes, Hadaya et al [iii], the Swiss specialists preferred to adapt the immunosuppressive therapy only after having performed a colonoscopy. The DIDACT algorithm is accepted by the majority of the specialists who participated in the survey. The step-wise approach to investigate reasons for severe diarrhoea is perceived as being helpful to reduce unnecessary changes in the immunosuppressive therapy that could lead to higher rejection rates and lower graft survival.

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Thrombotic microangiopathy in renal transplantation: is single kidney transplantation an option for patients with hemolytic uremic syndrome caused by factor H gene mutation?

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Purpose: Hemolytic uremic syndrome (HUS) is a clinical syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. Pediatric cases are often caused by shiga-like toxin-producing *Escherichia coli*. However, atypical cases may occur, especially in adults, showing a tendency to relapse, to occur in families and to have a poor outcome. Mutations in the complement factor H gene account for about 10–30% of cases of

familial or recurrent HUS. Complement factor H is produced by the liver and is an important regulator of the complement cascade through alternative pathway by inactivation of C3b deposition on host cells. Patients with decreased levels of complement factor H or functional complement factor H deficiency fail to efficiently restrict complement deposition on endothelial cells, leading to microvasculature thrombosis and tissue destruction by uncontrolled complement activation. Plasma exchange therapy or plasma infusions can ameliorate the clinical symptoms of complement factor H deficiency-associated HUS, presumably by supplementing of complement factor H and the disease may transiently recover but in many cases recurs after complement factor H is cleared by the circulation and patients finally progress to end stage renal disease (ESRD). HUS also invariably recurs in the graft kidney and causes graft failure making the rationale of single kidney transplantation questionable. Given that complement factor H is mostly synthesized by the liver, transplantation of the liver or combined liver-kidney transplantation was postulated as rational option in the management of patients with HUS caused by complement factor H gene mutation. As cases of fatal outcome after combined liver-kidney transplantation have been reported double transplantation is no longer recommended. We report a case of successful single kidney transplantation combined with peri- and postoperative plasma infusions.

Methods and materials: On August 1999, following a prolonged upper respiratory tract infection with fever but no diarrhea, a 23 year old man developed an acute renal failure associated with signs of microangiopathic hemolytic anemia and thrombocytopenia, consistent with the diagnosis of HUS. He clinically presented with reduced general condition with elevated blood pressure, generalised edemas and nephrotic range proteinuria (7 g/day). He was treated with plasma exchange therapy and renal function mainly recovered with slightly elevated creatinine levels. A renal biopsy was performed, confirming thrombotic microangiopathy in the glomeruli and arterioles. The further clinical course was characterized by two relapses of HUS (one following an atypical pneumonia, the second one without an apparent trigger) and finally ESRD occurred. Chronic hemodialysis was started in November 2002. A comprehensive complement analysis provided normal complement factor C3, C4, B, I and H serum concentrations and activity of the *von Willebrand factor*-cleaving protease (ADAMTS 13) was normal. But genetic studies disclosed a heterozygous point mutation in the most C-terminal short consensus repeat 20 (translation of arginine to cysteine in aminoacid position 1210) of the complement factor H gene which has been previously identified in five pedigrees and 7 individual patients with atypical HUS, leading to concluding diagnosis of functional deficient complement factor H.

Results: The patient underwent kidney transplantation from a deceased donor in August 2007. To avoid HUS recurrence abundant perioperative plasma infusions of fresh frozen plasma (FFP) were given every 6 h for 48 h, once daily in the first week, twice a week for one month and thereafter weekly for a further month. Immunosuppressive therapy consisted of triple therapy with tacrolimus, mycophenolate and prednisone and basiliximab day 0 and 4. Two diagnostic graft biopsies (day 5 and 15) presented signs of acute tubular necrosis but no characteristics of a HUS relapse, so did the two protocol biopsies after three and six month. One-year-follow up showed stable graft function.

Conclusion: We conclude that single kidney transplantation with abundant peri- and postoperative FFP infusions, partly replacing the lack of functional complement factor H is a rational option for patients with atypical HUS associated with complement factor H gene mutation. It seems that extensive plasma infusion therapy during and after operation can prevent serious clinical complications by uncontrolled complement activation. However the follow up was short and further clinical observations are necessary.

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Prognostic potential of B-type natriuretic peptide in unselected hemodialysis patients

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Purpose: B-type natriuretic peptide (BNP) is universally increased in hemodialysis patients. Extracellular hypervolemia, concomitant heart disease and reduced renal BNP-clearance contribute to the high plasma concentrations. While BNP was shown to predict cardiac death in hemodialysis patients presenting with sinus rhythm and without known cardiac diseases, little is known about the prognostic potential of BNP in unselected dialysis patients.

Methods and materials: 113 consecutive, unselected, elective hemodialysis patients at the Kantonsspital Liestal were enrolled in a longitudinal study. All patients were over 18 years old and underwent at least three four-hour hemodialysis sessions per week. Patients were not excluded on the basis of co-existing illnesses or time on dialysis. The primary endpoint of this study was cardiac death.

Overall mortality as well as the composite of cardiac death, cardiothoracic surgery and percutaneous coronary intervention were assessed as secondary endpoints. The endpoints were prospectively assessed during follow-up.

Results: Detailed baseline characteristics of the study population are displayed in table 1. BNP values rose with patients' age ($r = 0.296$, $p = 0.002$), LVMI ($r = 0.448$, $p = 0.010$) and decreasing systolic ($rEF = -0.333$, $p = 0.016$) and diastolic ($rEA = 0.320$, $p = 0.03$) cardiac function. Of note, BNP values were significantly higher in diabetic patients (716 pg/ml [314–1300] vs. 340 pg/ml [147–726], $p = 0.004$), but not in patients with known cardiac ($p = 0.37$) or pulmonary ($p = 0.44$) diseases. Overall 23 patients reached the composite endpoint (17 cardiac deaths, 6 percutaneous interventions). The median follow-up period was 735 days [355–1455]. BNP values were equal in patients dying of cardiac causes and survivors (591 pg/ml vs. 431 pg/ml, $p = 0.37$). Similarly, patients reaching the composite endpoint (421 pg/ml vs. 466 pg/ml, $p = 0.72$) or dying of any cause (591 pg/ml vs. 415 pg/ml, $p = 0.44$) did not have higher BNP values. In a Cox regression analysis BNP failed to predict cardiac death (HR 1.00; $p = 0.23$), overall mortality (HR 1.00; $p = 0.20$) and the composite endpoint (HR 1.00; $p = 0.64$).

Conclusion: In unselected patients undergoing chronic hemodialysis BNP values fail to predict cardiac death as well as overall mortality or the need for coronary interventions.

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Validity of conventional scoring systems assessing nutritional status of hemodialysis patients

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Purpose: Malnutrition is a common problem among hemodialysis (HD) patients, and is associated with both increased morbidity and mortality. Unfortunately, nutritional assessment is cumbersome and frequently imprecise. Scores to assess nutritional status and/or risk for malnutrition are potential tools to routinely screen HD patients with reasonable effort. However, commonly available assessment tools, such as the NRS (nutritional risk screening), SGA (subjective global assessment), and MNA (mini nutritional assessment) have not been validated for a HD population. Thus, the aim of the present study was to evaluate conventional risk scores in maintenance HD and to validate them with a more extended assessment of nutritional status.

Methods and materials: A total of 56 patients were evaluated from a subset of participants from the *monitor!* trial, a prospective dynamic hemodialysis cohort study assessing a wide range of clinical, laboratory and anthropometrical parameters. Scores for every individual patient based on the 3 assessment tools NRS, SGA and MNA were calculated using the *monitor!* database. In addition, malnutrition was diagnosed by an extended assessment ("*monitor!* criteria"), rating 6 parameters including normalized protein catabolic rate (nPCR; <0.8 g/kg body weight), serum albumin concentration (<38 g/L), body mass index (BMI; <23 kg/m²), lean body weight (LBM; <10th percentile), weight loss over the preceding 3 months (>5% of body weight), and energy intake (calculated from dietary protocols; <75% of energy requirements). A risk score was calculated from the sum of criteria fulfilled. Patients with 0–1 points were rated as: "well nourished, no malnutrition detectable"; 2 points: "moderately malnourished"; and 3–6 points: "severely malnourished". Correlational analyses were performed using cross tables and the chi-square test by Pearson.

Results: Extended evaluation of nutritional status based on the *monitor!* criteria found 41% of patients to be "well nourished", 34% "moderately malnourished", and 25% "severely malnourished". In contrast, rating by conventional assessment tools gave the following results and concordances with the *monitor!* score: Rating of nutritional status by different assessment tools

	«well nourished», %		«moderately malnourished», %		«severely malnourished», %	
	concordant		concordant		concordant	
<i>monitor!</i>	41	–	34	–	25	–
NRS	0	0	60.7	47.4	39.3	78.6
SGA	41	52.2	46.5	36.8	12.5	21.4
MNA	14.3	26.1	76.8	79	8.9	21.4

Statistical analysis revealed a positive correlation for the *monitor!* criteria with the NRS, but not with the SGA and MNA. Among the misclassified patients both the NRS and SGA scored 10% of "well nourished" subjects erroneously as "severely malnourished", whereas the SGA conversely misclassified 15% of "severely malnourished" patients falsely as "well nourished". Finally, the MNA attributed to

most of the patients a "moderately malnourished" status and missed the majority of both "well nourished" and "severely malnourished" subjects.

Conclusion: Our analysis confirmed the problem of malnutrition in a Swiss maintenance HD population, with more than 50% of patients being moderately or severely malnourished. Conventional assessment tools are not well suited to screen nutritional status of maintenance HD patients. Among the three tested scores the NRS fared best, especially with regard to detecting severely malnourished patients. The gold standard for nutritional assessment in our analysis consisted of a modified assembly of parameters as recommended earlier by the International Society of Renal Nutrition and Metabolism. This tool, however, awaits validation as a prognostic screening instrument.

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Decrease of time averaged B-type natriuretic peptide improves prognosis in unselected hemodialysis patients

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Purpose: B-type natriuretic peptide (BNP) is universally increased in hemodialysis patients. Extracellular hypervolemia, concomitant heart disease and reduced renal BNP-clearance contribute to the high plasma concentrations. The prognostic potential of BNP changes in unselected hemodialysis patients is presently unknown.

Methods and materials: 113 consecutive, unselected, elective hemodialysis patients at the Kantonsspital Liestal were enrolled in a longitudinal study. All patients were over 18 years old and underwent at least three four-hour hemodialysis sessions per week. Patients were not excluded on the basis of co-existing illnesses or time on dialysis. After enrolment BNP levels were measured every six months. Time-averaged BNP (TA-BNP) represents the average of every six-month period's BNP value. The primary endpoint of this study was four-year cardiac mortality. Overall mortality was assessed as the secondary endpoint. The endpoints were prospectively assessed during follow-up.

Results: Detailed baseline characteristics of the study population are displayed in table 1. Overall 35 died during the follow-up period (17 cardiac deaths, 18 other causes) and six patients underwent percutaneous coronary interventions. TA-BNP levels were significantly higher in patients dying of cardiac (1276 pg/ml [339–2312] vs. 487 pg/ml [254–887], $p = 0.03$) or any causes (890 pg/ml [296–1349] vs. 475 pg/ml [257–787], $p = 0.03$). In multivariate Cox regression analysis TA-BNP predicted cardiac (HR 1.08; 95% CI 1.03–1.13 for an increase in BNP of 100 pg/ml; $p < 0.01$) and overall mortality (HR 1.04; 95% CI 1.00–1.08 for an increase in BNP of 100 pg/ml; $p = 0.03$). TA-BNP tertiles were analyzed as categorical variables (fig. 1). In a subgroup analysis of 51 patients presenting with initial BNP values in the second and third tertial, a decrease of subsequent TA-BNP levels by at least one tertial significantly improved cardiac ($p = 0.05$) (fig. 2) and overall survival ($p < 0.01$).

Conclusion: In unselected patients undergoing chronic hemodialysis TA-BNP values powerfully predict cardiac death and overall mortality. A decline in TA-BNP over time significantly improves cardiac and overall survival.

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Quality of vascular access on chronic haemodialysis

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Purpose: Depending on patient characteristics, the quality of the native blood vessels, the preference, practice and know how of the surgeons and regional and national differences in patient management shunt survival on chronic haemodialysis varies considerably. On the basis of this background differences in respect of reported parameters of shunt quality and survival may not be easily transferable from one centre to another. The study aimed to collect data from a representative Swiss dialysis-unit about shunt survival depending on the type of vascular access and patients characteristics.

Methods and materials: We retrospectively enrolled all patients entering the chronic haemodialysis program of the University Hospital Basel between 01/1995 and 06/2006 and the affiliated Bethesda-Hospital since 09/2003 into a cohort study. The primary endpoint of this study was the time to any shunt-associated complication needing an intervention (complication free technical survival). A secondary endpoint was the time to first occlusion of the access (occlusion free technical survival). Kaplan-Meier analysis was used to calculate survival analysis. Comparisons were made using the log-rank test. A statistical significance level of < 0.05 was used.

Results: Overall 282 patients entered the chronic haemodialysis program during the study period. Thirteen patients were dialysed by a temporary access and therefore excluded; three patients had to be excluded due to incomplete data. As first access, 226 patients (85%) received a native arteriovenous (AV) fistula, 16 patients (6%) a synthetic graft and 24 patients (9%) a double-lumen tunnelled cuffed catheter. 142 patients (53%) had at least one access-associated complication. Thrombosis ($n = 50$, 35.2%) and stenosis of the access ($n = 45$, 31.7%) were the most common complications. The one-, three- and five year rates of complication free technical survival were 57%, 39%, 33% respectively. In diabetics compared to non-diabetics ($p = 0.02$) and in women compared to men ($p = 0.007$) complication free technique survival was significantly poorer. In 71 patients (27%) an occlusion of the access was observed. The one-, three- and five-year rates of occlusion free technical survival were 77%, 61% and 56%. The occlusion free technical survival for synthetic grafts was significantly inferior to native AV fistulas ($p < 0.0001$). Median occlusion free technical survival of radiocephalic fistulas were 15 (Tabatière) and 5.1 (Cimino) years, respectively. The median time of occlusion free technique survival of synthetic grafts was 5.4 (forearm) and 1.4 (upper arm) months, respectively.

Conclusion: Our data with a high percentage of native AV fistulas as primary access suggest that the guidelines for chronic haemodialysis access can be achieved with satisfying outcome. However, to further improve the outcome of the access in chronic haemodialysis prospective studies are essential which compare different approaches in creation of fistula based on predefined criteria.

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Altered proteasome activity plays a key role in CD4+/CD25+ Treg apoptosis in patients with end-stage kidney disease

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Purpose: The ubiquitin-proteasome system is responsible for the turnover of intracellular polyubiquitinated proteins. The key regulators of cell survival and apoptosis, including members of the Bcl-2 family, some caspases, and inhibitor of apoptosis proteins, have all been recognized as substrates of the proteasome. The role of proteasome pathway in CD4+ T cell immune dysfunction of patients with ESKD remains unclear. In this study, we emphasized the key role of the proteasome in the regulation of CD4+/CD25+ regulatory T cell (Treg) apoptosis in 10 chronic HD patients, 10 CKD (non-HD) patients and 10 healthy control subjects.

Methods and materials: The activity of the cytosolic 20 and 26 S proteasomes, the induction of the cyclin-dependent kinase inhibitor p27Kip1, the accumulation of the pro-apoptotic protein Bax, the amount of the anti-apoptotic molecule Bcl-xL, the percentage of annexin V positive cells and the DNA fragmentation of CD4+/CD25+ Treg were determined.

Results: The 20 and 26S proteasomes activity was significantly down-regulated (–43% and –51%, respectively) in CD4+/CD25+ Treg from patients with ESKD compared with CD4+/CD25+ Treg proteasomes activity in non-HD CKD patients and control subjects ($p = 0.001$, ANOVA). This was accompanied by the up-regulation of the proteasome-related protein p27Kip1, the accumulation of Bax and the decrease of the Bcl-xL amount (p from 0.02 to 0.001). In parallel, percentage of annexin V positive CD4+/CD25+ Treg was significantly higher in patients with ESKD ($p = 0.003$). This was confirmed by the increased DNA fragmentation. This raised the possibility that p27Kip1 and Bax are targeted for degradation by the 26 S proteasome. The enhanced stabilities of these molecules and the low activity of Bcl-xL may be responsible at least in part for the higher CD4+/CD25+ Treg apoptotic rate in patients with ESKD.

Conclusion: These data suggest that uremia and chronic HD stimulate CD4+/CD25+ Treg apoptosis by altering proteasome activity. This response could contribute to the CD4+ T cell immune dysfunction associated with ESKD.

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Incidence of catheter-related bloodstream infections (CR-BSI) in patients treated with hemo(dia)filtration in intensive care units

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Purpose: Today, continuous hemo(dia)filtration is the modality of choice for patients suffering from acute renal failure in intensive care units (ICU). Patients with renal failure are at high risk for CR-BSI, but few data are available on the incidence of this complication. A metanalysis of hemodialysis patients with temporary nontunnelled hemodialysis catheters (16 studies, 5,184 catheter days) revealed a rate of 4.8 CR-BSI per 1000 catheter days. But this result might not be extrapolated for a population of ICU patients treated with a continuous renal replacement therapy. Therefore, the study goal was

to assess the incidence of CR-BSI the incidence of CR-BSI in this specific population.

Methods and materials: Prospective cohort study of all patients treated with continuous hemo(dia)filtration from March 1st 2003 to May 1st 2007, admitted to either surgical sICU or medical ICU (mICU). The temporary vascular access was inserted by the treating intensive care physician. All patients requiring continuous hemofiltration were screened for nasal colonization with *Staphylococcus aureus*. Positive cases were decolonized with mupirocin nasal ointment. In addition, standard catheter care was supplemented with mupirocin at the insertion site. The definitions established by the Centers for Disease Control and Prevention (CDC) were used throughout the study. Catheters were cultured by the roll-plate and sonication technique.

Results:

Patient number (n)	173
Age (years)	
median	68.6
range	18.9–87.8
Male/female (%)	63/37
ICU (n)	
OICU	104
MICU	69
Days of catheter	
mean	9
range	1–60
total catheter days	1595
Insertion site	
Subclavian vein	81
Jugular vein	67
Femoral vein	19
unknown	6
Positive nasal screening	50 (28.9%)
Risk factors for infection (n; %)	
Diabetes mellitus	52 (30.1%)
Immunosuppression	35 (20.2%)
Antibiotic therapy at time of onset	132 (76.3%)
Preexisting skin disease	17 (9.8%)
Outcome	
CR-BSI (n; %)	6 (3.5%)
CR-BSI per 1000 catheter days	3.8
Causative organism	coagulase-negative Staphylococci in all cases
Death during hemo(dia)filtration	86 (49.7%)
Attributable mortality due to CR-BSI	0

Conclusion: The risk of CR-BSI in critically ill patients with temporary nontunneled vascular access and continuous renal replacement therapy was not higher than in hemodialysis patients with nontunneled catheter despite of the enhanced risk profile. All observed CR-BSI in this study were caused by coagulase-negative staphylococci. No *S. aureus* CR-BSI was observed, usually the most frequently encountered pathogen in this setting. Good infection control coupled with routine decolonization of *S. aureus* carriers with mupirocin succeeded to eliminate *S. aureus* CR-BSI in this study.

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Optimizing peritoneal dialysis (PD) outcome with a tungsten-containing “self-locating” PD catheter

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Purpose: Peritoneal dialysis (PD) catheter displacement is one of the major causes of PD dysfunction. The «self-locating» PD catheter is similar to the Tenckhoff catheter, but it includes a small tungsten cylinder (weight 12 g) at the distal end to prevent dislocation. Catheter displacement may be less frequent with the «self-locating catheter» than with other types of PD catheters. This study was performed to analyze the functionality, the complication profile and the utility of the self-locating PD catheter in our PD program.

Methods and materials: Retrospective analysis of 26 implanted “self-locating” catheters at our center from September 2005 until August 2008, analyzing dislocations and complications.

Results: Included in this study were 24 patients with 26 self-locating catheters (11 females, 13 male patients, mean age 48.5 ± 26.5 yrs). The catheter survival rate was 92.4% at 1 year. During 282 PD months there was only one catheter dislocation, occurring shortly after implantation. We observed 3 leakages which were successfully corrected by surgery. One catheter had to be exchanged due to a hernia. 5 catheters were removed due to transplantation, 1 was removed after improved kidney function and 1 was replaced due to omental capture. We observed 6 peritonitis episodes, one exit site infection and one tunnel infection (1/35 patient-month). *Staphylococcus aureus* was the most common cause of infection. One of these infections necessitated a catheter removal and a switch to hemodialysis.

Conclusion: In our experience, the use of “self-locating” PD catheters was very successful. Catheter migration and dislocation were rare. In our program «self-locating» catheters seem to be associated with fewer removals due to malfunction compared with conventional Tenckhoff catheters. Infection rates were low, in accordance with other studies with the “self-locating” catheter. The use of the “self-locating” catheter could help to improve the results of existing PD programs.

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Patient survival on chronic haemodialysis: a retrospective analysis from the Basel Dialysis Unit 1995–2006

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Purpose: Patient survival on chronic haemodialysis varies considerably among different countries and healthcare systems. So far, the mortality rates of Swiss dialysis patients have not been analysed separately.

Methods and materials: We retrospectively enrolled all patients entering the chronic haemodialysis program of the University Hospital Basel between 01.01.1995 and 30.06.2006 into a cohort study. Patient survival on chronic haemodialysis was the primary endpoint of this study. Cumulative survival was calculated using Kaplan-Meier analysis. Comparisons were made using the log-rank test. A statistical significance level of 0.05 was used.

Results: Overall 269 patients entered the chronic haemodialysis program during the study period. Three patients had to be excluded from the analysis due to incomplete data. The median age of the 266 remaining patients was 64.5 [range: 15.2–89.6] years. Diabetic nephropathy (17%), vascular nephropathy (15%) and glomerulonephritis (13.5%) were the most common causes of end stage renal disease requiring dialysis. The most common co-morbidities were cardiovascular disease (72%), diabetes mellitus (34%) and malignant diseases (26%). The one-, three- and five-year survival rates on hemodialysis were 88%, 68% and 46% respectively. Survival rates were equal in women and men ($p = 0.34$) and among diabetic and non-diabetic patients ($p = 0.41$). Until the end of the observation period 91 (34%) patients died, 69 (26%) patients underwent kidney transplantation and three (1%) patients changed to peritoneal dialysis. In 23 patients the termination of dialysis contributed to their death. The median survival after termination of dialysis was 12 [range: 2–381] days.

Conclusion: Patients entering the chronic dialysis program at the University Hospital Basel were older and included more diabetic patients than previous foreign cohort studies. Nonetheless, Swiss survival rates compared favourably to the European and American averages.

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Interferon-release assays vs. tuberculin skin testing for detecting latent tuberculosis infection in hemodialysis patients

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Purpose: Efficacy of Interferon-release assays (IGRA) for detecting latent tuberculosis infection (LTBI) in chronic hemodialysis (HD) patients is yet undetermined. We aimed to determine the performances of IGRA versus the tuberculin skin testing (TST) in a group of hemodialysis patients.

Methods and materials: Prospective study of HD patients: simultaneous sampling of T-SPOT.TB (Oxford Immunotec, UK) and QuantiFERON-Gold in tube (QFT, Cellestis, Australia), TST; Diagnosis of LTBI was based on patients' clinical, epidemiological and radiological data.

Results: 62 patients (16F, 46M, aged 65 ± 15 years, 50% foreign-born, 10% from high incidence countries, 5 with previous TB) were included; LTBI was diagnosed in 13 patients. TST was >5 mm in 12 (19%), >10 mm in 9 (14%); T-SPOT.TB was positive in 18 subjects (29%, 7 indeterminate), and QFT: in 13 cases (21%; 5 indeterminate). Agreement between IGRA was 73% (kappa: 0.52). Agreement between TST (>5 mm) and both IGRA was low (kappa: 0.32 for

T-SPOT.TB and 0.16 for QFT). In multivariate analysis, a positive QFT was predictive of LTBI (OR: 4.4; 95% CI: 1.1–17.6; $p = 0.032$); trend was not significant for T-SPOT.TB (OR: 1.2; 95% CI: 0.3–4.8) and for TST >5 mm (OR: 1.7; 95% CI: 0.3...8.5). Among five patients with definite prior TB, TST and T-SPOT.TB were positive in 1 and QFT, in 2. **Conclusion:** Our results suggest that, in our population, QFT was superior to TST testing and T-SPOT.TB for detecting LTBI, but both IGRA and TST have important limitations. Whether QFT is clearly superior to T-SPOT.TB in this population should be confirmed by further studies.

Efficacy of intravenous CERA administered once monthly compared with epoetin beta administered once weekly in patients with end-stage kidney disease on hemodialysis: a randomized trial

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Purpose: Erythropoiesis-stimulating agents (ESAs) are standard therapy for patients with renal anaemia and are associated with improved survival of patients with chronic kidney disease (CKD). However, traditional ESAs have relatively short intravenous (IV) half-lives and require frequent administration. Current guidelines recommend maintenance of hemoglobin (Hb) levels at ≥ 110 g/L. In addition, various guidelines specify an upper limit of 130 g/L for patients with cardiovascular disease or diabetes. Despite these guidelines, many patients still fail to achieve minimum Hb targets. The use of current ESAs at extended administration intervals has been examined in several studies in patients who already had stable Hb levels at administration intervals of at least once weekly. CERA, a continuous erythropoietin receptor activator, is a novel agent that provides correction of anaemia and stable control of Hb levels at extended administration intervals. Preclinical and Phase I and II studies demonstrate that CERA has unique pharmacologic properties, acting differently than epoetin at the erythropoietin receptor level, with a long serum half-life and low clearance.

Methods and materials: The purpose of this open-label, randomized study was to determine the efficacy and the safety of IV CERA administered once monthly (QM) for Hb maintenance in patients with end-stage kidney disease (ESKD) chronically hemodialyzed (HD) who converted directly from epoetin beta (EPO) once weekly (QW). Adult patients with ESKD on HD receiving stable IV EPO QW were randomized (1:1) to receive IV CERA QM ($n = 19$) or continue their current EPO regimen ($n = 15$) for 24 weeks. Doses were adjusted to maintain Hb levels within ± 10 g/L of baseline and between 110 and 130 g/L. The primary endpoint was the mean Hb change between baseline and the evaluation period (every 4 weeks). No patient presented inflammation, infection or uncontrolled hyperparathyroidism. They were on stable EPO treatment without Hb modification or blood transfusion 3 months before entering the study.

Results: Eighty percent of patients in the CERA group did not require a dose change (either increase or decrease) during the course of the study (0.59 mg/kg/week). However, a significant drop of the Hb level (-6.9 ± 3.4 g/L) was observed in this patients' group after the switch at 4 weeks. At that time, Hb response rates (intent-to-treat population) were 93% with CERA and 100% with EPO. Peak mean Hb levels were 114 ± 8 g/L with CERA and 121 ± 10 g/L with EPO ($p = 0.02$). Mean change in Hb levels from baseline to the end of the correction period (8 weeks) were 4.3 ± 2.5 g/L with CERA and 3.8 ± 2.7 g/L with EPO ($p = \text{NS}$). The mean \pm SD difference between CERA and EPO in the primary endpoint was 2.0 ± 0.3 g/L within a pre-defined non-inferiority limit. CERA was clinically non-inferior to EPO ($p = 0.002$) in maintaining Hb levels at 24 weeks. Both treatments were well tolerated.

Conclusion: After a short significant but non-clinically relevant drop, Hb levels were successfully maintained in patients with ESKD chronically HD directly converted to IV CERA QM from EPO QW. These features have the potential to provide an advance in the management of anaemia by minimizing renal unit workload during the correction of anaemia.

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regimens used in Swiss dialysis units and the achievement of KDOQI targets.

Methods and materials: In this observational chart review, an analysis was carried out on 748 unselected dialysis patients from 21 participating sites localized in geographically distinct parts of Switzerland, (representing about 25% of the Swiss hemodialysis population). Information on baseline characteristics, laboratory values and concurrent medications was collected at the sites. These results were then compared with the DOPPS II (2002–2004) and COSMOS (2005–2008) data.

Results: 61.8% of the 748 patients were male, mean age (SD) was 66.5 (14.0) years and mean weight (SD) was 73.8 (16.9) kg; 93.0% received HD and 7% were on CAPD.

Of 748 patients, 54.4% were treated with vitamin D sterols (vs DOPPS: 52.2%; COSMOS: 48.0%) and 81.0% received at least one phosphate binder (vs DOPPS 81.1%; COSMOS 81.4%). Calcimimetics were used in 24.1% of the Swiss collective (vs DOPPS no data; COSMOS 6.2%).

Table 1

Percentage of patients within NKF/KDOQI targets

	DOPPSN = 6864	COSMOSN = 4500	SWISS averagen = 748
corr Ca (2.1–2.4 mmol/L)	42.5	50.5	68.3
P (1.13–1.78 mmol/L)	44.4	51.5	56.6
CaxP (<4.5 mmol/L ²)	61.4	68.6	77.4
iPTH (16.5–33.0 pmol/L)	26.2	29.1	32.1
PTH & CaxP within targets		22.3	26.5
All 4 parameters in targets	5.5	9.0	15.7

Conclusion: This benchmark analysis shows that KDOQI target levels are difficult to achieve. A total of 15.7% of Swiss patients achieved all 4 KDOQI parameters, which is about 3-fold higher compared with DOPPS in 2004. Despite variations in baseline characteristics of the studied populations, reasons for the better findings in Switzerland could be a considerable awareness of guideline recommendations and the enhanced integration of new therapies compared with DOPPS and COSMOS.

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Effect of L-carnitine administration on post-dialysis symptoms in erythropoietin era

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Purpose: L-carnitine plays an essential role in the beta-oxidation of fatty acids by catalyzing their transport into the mitochondrial matrix. A functional deficiency that occurs with kidney disease and is magnified by dialysis is a disturbance in the homeostatic control of carnitine. Originally described as carnitine deficiency, the disorder that develops in dialyzed patients differs from the classic genetic or primary carnitine deficiencies in that it represents a functional deficiency that can be corrected with pharmacologic doses of L-carnitine. This dialysis-related carnitine disorder (DRCD) manifests itself as a syndrome of clinical problems and symptoms including anemia that is hyporesponsive to erythropoietin therapy, intradialytic hypotension, cardiomyopathy, and skeletal muscle dysfunction manifested as generalized fatigability. Numerous studies investigating whether L-carnitine supplementation will alleviate several dialysis-related symptoms, such as intradialytic hypotension, heart failure, muscle weakness, low exercise capacity, and anemia, have reported conflicting results. The purpose of this study was to examine the effects of carnitine replacement on DRCD in chronic hemodialysis (HD) patients.

Methods and materials: This non-interventional investigation, which lasted 3 months, was multicenter and open labelled. Patients had to have at least two of the following symptoms of DRCD: intradialytic hypotension, muscle cramping, lack of energy, muscle weakness or post-dialysis asthenia in order to qualify for treatment with 1 g i.v. carnitine after each HD session. Patients that started carnitine treatment were eligible for the investigation. Clinical parameters and dialysis related symptoms were recorded at baseline and thereafter monthly until 24 months. Improvement of DRCD was compared each month with baseline values (V0 to V24). One hundred and two stable long-term HD patients completed the investigation (mean age 68 y; range 34 to 90 y).

Results: Improvement in post-dialysis asthenia, fatigue and muscle cramps were statistically reduced during the follow-up compared with the baseline evaluation (V4 vs. V0; $p < 0.001$). Carnitine was well tolerated, and no drug-related adverse effects were identified.

Conclusion: Thus, intravenous L-carnitine in chronic HD patients appears to be associated with a decrease in post-dialysis asthenia, fatigue and muscle cramps, with an improvement in exercise capacity and sense of well being.

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Management of secondary hyperparathyroidism in 21 Swiss dialysis units and the achievement of NKF/KDOQI targets: A benchmark analysis with international data

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Purpose: Secondary hyperparathyroidism (sHPT) is a common complication of chronic kidney disease in dialysis patients, and is associated with adverse clinical outcomes. With conventional therapies only a small proportion of dialysis patients with sHPT achieve and sustain control of the recommended KDOQI targets for PTH, P and Ca. This ongoing project analyzes sHPT therapeutic

Efficacy of pegylated epoetin-beta (Mircera) in peritoneal dialysis patients

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Purpose: Pegylated epoetin-beta (Mircera) is a continuous erythropoietin receptor activator with a long half life (approximately 130 h) which allows to extend the dosing interval in patients with renal anemia. This study was performed to evaluate the efficacy and safety of Mircera administered monthly in patients on peritoneal dialysis (PD).

Methods and materials: We studied 14 stable PD patients (9 males and 5 females, mean age 49.9 ± 16.6 yrs) with a mean time on PD of 31.4 ± 19.5 months, and a baseline Hemoglobin (Hb) of 10.5 ± 2.0 g/dL. At the time of conversion to Mircera, 2 patients were erythropoiesis-stimulating agents (ESAs) naive, 10 patients were on darbepoetin alfa (mean dose 81.5 ± 88.9 mg weekly, median dose 40.0 mg weekly), and 2 patients were on epoetin beta (mean dose 8000 ± 2828 IU weekly, median dose 8000 IE weekly) for the previous 3 months. The PD patients were switched from weekly or bi-weekly sc darbepoetin alfa or weekly sc epoetin beta to iv Mircera monthly.

Results: The mean Hb value after 3 months was 10.8 ± 0.9 g/dL with a mean Mircera dosis of 195 ± 205 mg monthly (median dose 103 mg monthly).

Conclusion: We conclude that the conversion from epoetin beta or darbepoetin alfa to Mircera administered monthly effectively maintains stable Hb levels in patients on PD. The drug tolerance was excellent. The extended dose intervals allowed the administration of Mircera during regular outpatient visits, ensuring optimal patient compliance.

Development of dose and costs after conversion to CERA in hemodialysis patients

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Purpose: CERA (Mircera®) is a new Erythropoiesis-Stimulating Agent (ESA) that allows treatment of renal anemia with a once monthly dosing interval. The aim of this study was to evaluate the development of CERA doses and cost of treatment after conversion of patients from epoetin beta.

Methods and materials: In a Swiss center all patients were converted from epoetin beta (Recormon), two to three times per week, to once monthly CERA according to the label in February of 2008. We retrospectively analyzed hemoglobin values of these patients from three months before conversion to five 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 the five months after conversion (11.81 g/dl vs. 11.79 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 five month after conversion was 228 mg/month and 169 mg/month at month five. Cost calculations using the list prices for Switzerland resulted in mean costs of CHF 1251 per patient and month on epoetin beta. During the five months after conversion to CERA the average monthly cost per patient was CHF 921. At month five the cost for ESA had decreased to CHF 685. The values for Ferritin (153 vs. 388 mg/l; p = 0.02) and Transferrin saturation (14 vs. 29%; p < 0.001) were significantly higher after conversion as compared to before conversion.

Conclusion: The experience in this single center shows significant cost savings after the conversion of patients from epoetin beta to CERA. Average monthly costs for the ESA treatment in the five months post conversion decreased by 26%. Costs decreased by 45% from conversion to month 5. This decrease in cost of ESA therapy might be partially explained by differences in iron parameters. However the findings of this analysis confirm cost savings seen in Phase III trials after conversion from epoetin to CERA independent of iron status.

The real important key in phosphate-binding therapy is adherence. A single centre observation

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Purpose: Phosphate-binding therapy is one of the most important concerns of rounds in hemodialysis units. The increased incidence of cardiac disease in patients with ESRD has been associated with hyperphosphatemia, making phosphate control an important goal of treatment.

Methods and materials: All patients (n = 27) on hemodialysis in our unit were monitored in respect of prescription and covering with phosphate-binding therapy over 12 months. 23 (85%) of this patients obtain all of their medicaments above our pharmacy. In these patients the amount of phosphate-binding therapy was registered by counting the pills, which they demanded. 4 (15%) of patients purchased their drugs somewhere else. Phosphorous serum-levels were monitored monthly. The reliance on percentage of demanded vs. prescribed phosphate-binding therapy and the phosphate serum levels were done with the Pearson test.

Results: Only 62% (range 13–117%) of the prescribed tablets were called of the patients. The phosphate-serum level correlated with the percentage of demanded vs. prescribed phosphate-binding therapy (marker of compliance) on coefficient of 0.77, whereas with the whole amount of phosphate-binding therapy only of 0.53. The patient gets a prescription in mean of 7.8 (0–26.2) tablets of phosphate-binding therapy per day.

Conclusion: The adherence in phosphate-binding therapy in this single-centre study is bad, but comparable with studies in other hemodialysis populations. The serum phosphate level correlates better with the adherence than with the prescribed amount of phosphate-binding therapy. Concepts of proving the adherence in this field for example by patient education or other kind of phosphate therapy with minor quantity of pills (i.e. lanthanum) should be proofed.

Bariatric surgery in a chronic hemodialysis patient

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Purpose: Obesity has a negative impact on graft-and patient-survival after kidney transplantation. Weight loss is thus recommended for dialysis patients with a Body Mass Index (BMI) ≥ 35 kg/m² to be eligible for kidney transplantation. However, bariatric surgery is generally contra-indicated in the dialysis population, because of the risk of malnutrition.

Methods and materials: We report the case of a 45-year old woman, on hemodialysis due to autosomal dominant polycystic kidney disease, who also suffers from morbid obesity (dry weight 147 kg, BMI 50.6 kg/m²). A low-calorie diet was introduced and resulted in a weight loss of 15 kg, but was followed by stagnation which still contra-indicated transplantation. In order to overcome this, gastric banding was performed, without major complications. Zinc and vitamins were prescribed, and an exercise-program initiated.

Results: In the months following the intervention, an additional weight loss of 19 kg was obtained. Actually, 14 month later, she weighs 113 kg (BMI 39 kg/m²). Her lean body mass is intact. She tolerates well her actual diet. She feels saturated after her meals, which helps her to avoid snacking. Biological parameters are as follows: Haemoglobin 132 g/l, urea 26 mmol/l, creatinine 1014 µmol/l, total protein 79 g/l, albumin 44 g/l, Calcium 2.16 mmol/l, Phosphate 1.73 mmol/l, intact PTH 72 ng/l, Vitamine B12 >1000 pmol/l, folic acid >45 nmol/l, Zinc 13 µmol/l, Vitamine B1 66 nmol/l, Vitamin B6 756 nmol/l (all: pre-dialysis values).

Conclusion: Bariatric surgery is a modern and efficient treatment for morbid obesity. Nevertheless, this treatment is rarely used for patients with end stage renal disease, and even considered as a contra-indication by many, mainly due to the fear of inducing or worsening protein malnutrition in this at risk-population. In our patient, however, this treatment was well tolerated, did not lead to protein malnutrition, and has opened the gate to kidney transplantation. We believe that several factors have contributed to the success in this case: 1) The application of gastric banding instead of a gastric bypass, which limited the risk of malabsorption. 2) The addition of an intense physiotherapy-program, which helped to preserve her lean muscle mass. 3) The prescription of vitamin- and oligo-elements prevented a deficit of these micronutrients. 4) The multidisciplinary approach including nephrologists, nutritionists, surgeons and physiotherapists. One should consider the possibility of bariatric surgery in dialysis patients with morbid obesity who are otherwise good candidates for kidney transplantation. Gastric banding appears to be a good bariatric surgical option, since this technique limits the risk of malabsorption.

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