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OC 01

Dietary intake of phosphate stimulates renal salt absorption and increases blood pressure (NCCR Project)

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Background: The thiazide-sensitive Na^+-Cl^- cotransporter NCC is critical for renal salt reabsorption and blood pressure control. High intake of dietary phosphate has been linked to increased cardiovascular morbidity and mortality in healthy subjects and patients with kidney diseases. We examined the regulation of NCC by dietary phosphate intake.
Methods: Mice were kept for 1–5 days on low (0.1%) or high (1.2%) phosphate (Pi) diets or received an acute bolus of phosphate by gavage. Plasma PTH, FGF23 and urinary aldosterone level were measured by ELISA. Systolic blood pressure was monitored by the tail cuff method. NCC abundance/phosphorylation was analyzed by western blot. Blood pressure in rats on high and low phosphate diets was measured by Telemetry.
Results: The high Pi diet increased plasma FGF23, PTH, urinary aldosterone and renal renin expression. Systolic blood pressure was elevated by high Pi diet and this effect was blunted by thiazide diuretics. Thiazide diuretics on high Pi diet increased urinary NaCl excretion more than on low Pi diet. Phosphate increased NCC abundance and phosphorylation within 1 hour after gavage. Similar to the high Pi diet in control mice, mice over expressing FGF23 or treated with recombinant FGF23 showed increased NCC abundance and phosphorylation. Also PTH stimulated NCC phosphorylation within 45 min. However, while the high Pi diet stimulated phosphorylation of SPAK, a positive regulator of NCC, isolated FGF23 overexpression or administration did not stimulate SPAK phosphorylation, suggesting that high Pi intake and FGF23 activate NCC by distinct pathways. However, genetic inactivation of SPAK prevented NCC phosphorylation. The expression of other Na^+ transporters like NHE3, NKCC2 and ENaC remained unchanged.
Conclusion: Dietary intake of Pi stimulates NCC activity and increases systolic blood pressure. The effect of Pi on NCC may involve several hormones such as PTH, FGF23 and aldosterone.

OC 02

Therapeutic efficacy and cost effectiveness of high cut-off dialyzers compared to conventional dialysis in patients with cast nephropathy

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Background: Multiple myeloma (MM) associated renal failure in cast nephropathy results from tubular precipitates of free light chains (FLC). High cut-off (HCO) dialysis filters are able to efficiently reduce FLC concentrations in the serum and may improve renal recovery. However, clinical trials which directly compare HCO dialyzers with conventional dialysis in cast nephropathy are lacking. The aim of this study was to assess clinical outcomes and economic impact of treatment with HCO dialyzers compared to conventional hemodialysis membranes in patients with cast nephropathy.
Methods: Multicenter retrospective analysis of patients treated for renal failure from FLC associated cast nephropathy after July 2005 with a follow-up until September 2014. Treatment consisted of Bortezomib and Dexamethasone in all patients, and hemodialysis with either HCO (n = 12) or conventional dialyzers (n = 7).
Results: At the end of follow-up, 4 patients treated with HCO dialyzers were still alive, while all patients in the control group had died (p = NS for Cox regression adjusted for age). With regard to recovery of renal function, a non-significant trend to higher independence of dialysis was seen in patients treated with HCO dialyzers. Moreover, trends towards better renal function at 12 months after diagnosis of MM as well as lesser time on renal replacement therapy were noted in the HCO group. Total treatment costs were CHF 193'000 ± 81'000 and 242'000 ± 179'000 (p = 0.421) in the HCO and conventional dialyzer group, respectively.
Conclusions: Hemodialysis treatment with HCO membranes for cast nephropathy tended towards faster and better recovery of renal function versus treatment with conventional dialyzers. However, no statistically significant survival benefit could be detected for the HCO treatment group. Total medical costs were not higher in the group treated with HCO dialyzers despite the higher product price of the high cut-off membranes.

OC 03

Long-term impact of cardio-renal involvement on adverse outcomes in patients with Fabry disease

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Background: Fabry disease (FD) is a rare X-linked lysosomal storage disease with a deficient activity of the enzyme alpha-galactosidase A which leads to progressive intralysosomal accumulation of globotriaosylceramide (GL-3) in different organs. We aimed to evaluate risk factors for the incidence of major cardiovascular complications and death in a prospective FD cohort.
Methods: A total of 104 genetically proven FD patients (mean age 45 ± 16; total males n = 40; on Enzyme replacement therapy (ERT) 88% males, 45% females) were annually followed up at the University

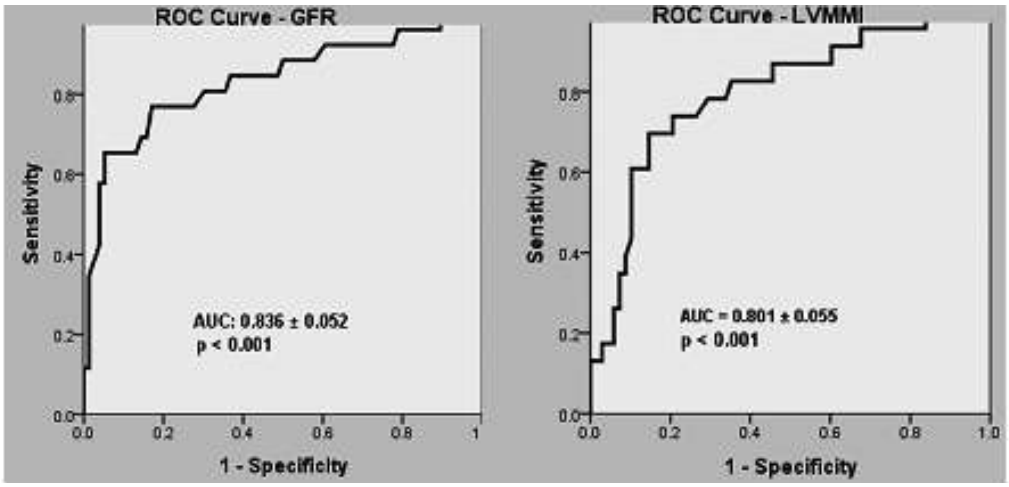

Figure 1: ROC-Curve of GFR an LVMMI to predict major cardiovascular events in patients with Morbus Fabry. GFR = glomerular filtration rate; LVMMI = left-ventricular myocardial mass index; AUC = area under the curve

Hospitals Zurich and Bern. The main outcome was a composite of incident renal replacement therapy (RRT), stroke and death. Glomerular filtration rate (GFR) and left ventricular myocardial mass index (LVMMI) where explored as the primary exposure variables.
Results: During a median follow-up of 9 [5–12] years, 28 new events occurred in 25 patients: 11 died, 4 received RRT, 11 developed strokes, 1 myocardial infarction. Baseline GFR (HR = 0.35; 95%CI 0.20–0.63; p <0.001) and LVMMI (HR = 2.00; 95%CI 1.17–3.44, P = 0.01) (both per SD) remained independent predictors of the adverse events composite after adjustments for age, gender, RRT, hypertension and cerebro-vascular disease. The accuracy of the events prediction by eGFR and LVMMI using receiver operating characteristic (ROC) analyses was moderate to high (fig. 1). Patients groups according to the best calculated cutoffs for GFR and LVMMI (fig. 2) better discriminated patients at low versus high risk than according to gender (fig. 3). We developed a new score containing the extent of cardiopathy and nephropathy as well as age and the presence of cerebrovascular disease. This score accurately predicts events occurrence (AUC = 0.88).
Conclusions: Although Fabry disease is transmitted in a X-linked pattern, cardio-renal involvement more than gender influences adverse clinical outcomes. A focus on cardio- and renoprotective therapies seems to be crucial. A new severity score accurately predicts the events occurrence.

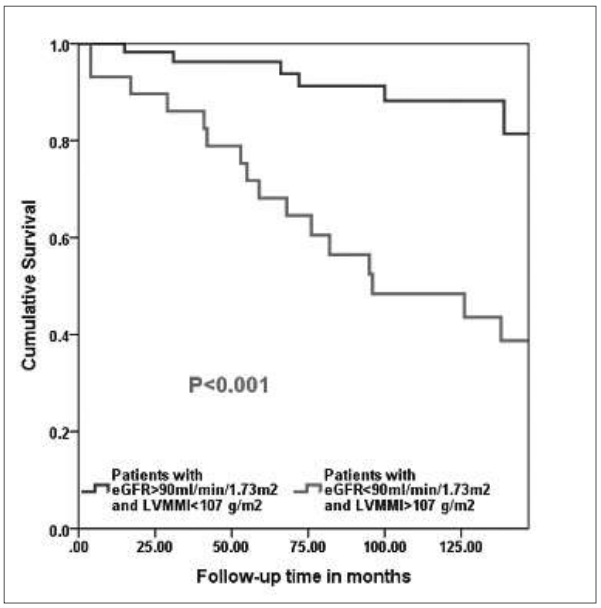

Figure 2: Long-term survival of Fabry patients grouped by the best calculated cutoffs for LVMMI and calculated eGFR at baseline.

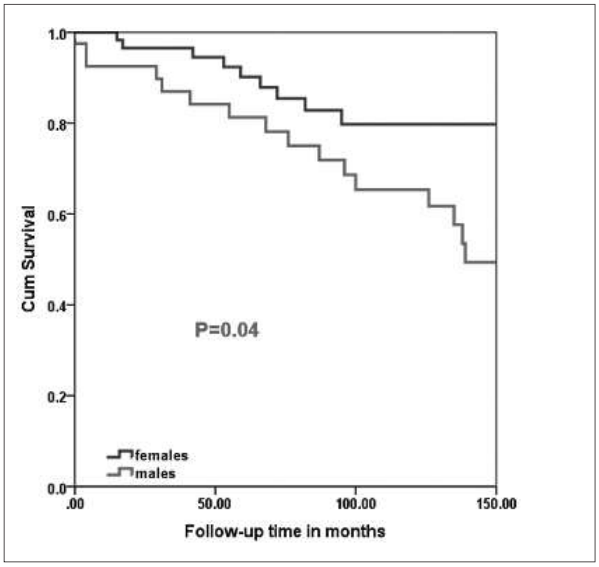

Figure 3: Long-term survival of Fabry patients grouped by gender.

OC 04

Survival after acute kidney injury in patients with acute dyspnea

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Background: Acute heart failure is one of the most frequent acute medical conditions warranting hospitalisation. Acute kidney injury (AKI) occurring during acute heart failure (AHF) has been termed the cardiorenal syndrome Type I (CRS I). CRS I has been suggested to carry prognostic importance in excess of AKI in other settings. Objectives: To compare the long-term mortality associated with AKI in 2130 dyspneic patients with and without AHF
Methods: Diagnosis of AKI was adjudicated by a board approved nephrologist after review of all medical records including prehospital, in-hospital and post-hospital serum creatinine values pertaining to the individual patient. Serum creatinine was measured throughout the hospitalization at prespecified timepoints: Admission, Day 2, 3, 4, 6, 8, 10, 12 and discharge. The final diagnosis underlying dyspnea was adjudicated by two independent internists.
Results: Baseline characteristics of the study population are described in table 1. The primary cause of dyspnea was AHF in 61% patients. The most common causes of non-cardiac dyspnea were

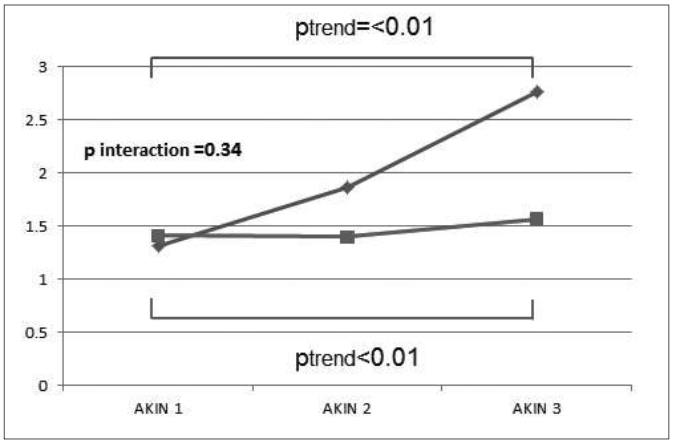

Figure 1: Multivariate hazard ratios for the impact of acute kidney injury severity on long-term survival according to the underlying cause of dyspnea (AHF red, non-cardiac dyspnea blue). Adjusted for age, comorbidities (coronary artery disease, arterial hypertension, diabetes, COPD, malignant diseases) laboratory parameters (haemoglobin, C-reactive protein, urea, albumin, BNP) and steady state renal function.

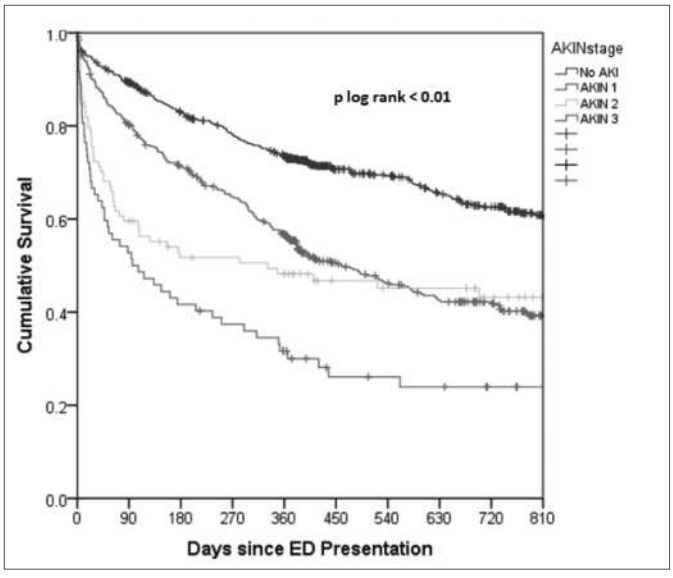

Figure 2: Kaplan Meier Curves for long-term mortality according to AKI severity.

Table 2: Medical characteristics of migrant patients.

Cause of ESRD	
HTN and DM	4
HTN	1
DM	1
Glomerulopathy	2
Unknown or other	4
Comorbidities	
DM	5
Smoke	4
Heart failure	1
Vascular disease	4
Alcohol abuse	1

obstructive pulmonary diseases, pneumonia and pulmonary embolism. Overall, 41% of patients experienced AKI; AKI was significantly more common (50% vs 26%; p <0.01) in AHF patients. The majority of AKI cases were graded as stage 1 (76%). The severity of kidney injury was similar in HF and non-HF patients (ptrend = 0.25). AKI was associated with a significant over-mortality independent of the underlying cause of dyspnea HRHF: 1.8; p <0.01; HRNON-HF: 2.2; p <0.01). A univariate interaction existed between AHF and AKI (HR 0.73; 95%CI 0.60–0.90; p <0.01). This interaction did not persist after multivariate analysis. The impact of acute kidney injury severity on survival is shown in figure 2.
Conclusions: AKI in patients with acute dyspnea is common and doubles the risk of long-term mortality. Importantly, the over-mortality associated with AKI is independent of the cause of dyspnea. CRS I does not carry additional prognostic importance.

OC 05

Specialised renal care in patients with CKD stage IIIb-IV: does it impact on mortality and RRT implementation?

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Background: Long-term prognosis of patients with CKD is poor and there is a need for the implementation of new strategies through collaboration between primary care physicians (PCP) and nephrologists. We undertook a prospective randomised trial to determine the impact of specialised care by nephrologists compared to guidelines-directed management by primary care physicians (PCP) on prognosis and planning of RRT in CKD patients.
Methods: Single center prospective randomised study. Inclusion criteria: CKD patients with an eGFR <45 ml/min and >15 ml/mn, aged 18–80 years old and enrolled during a hospitalization. Exclusion criteria: AKI or ESRD, estimated life expectancy <2 yrs, refusal or inability to sign writing consent and patients previously known by nephrologists. Patients were randomised in two arms: – Combined management PCP and nephrologists (4 nephrology visits/year) – Management by PCPs with the help of written instructions and consultations being provided by our unit if requested by PCPs. Patients who declined to participate in this study or previously known by nephrologists were followed on an observational basis.
Results: From November 2009 to the end of June 2013, 528 patients were identified of whom 242 patients were randomised. At the end of June 2015 (mean FU: 55 + 24 months), 26% of the patients in the combined management group were either dead or in RRT versus 25% in the PCP management group. During this time period, mortality rose to 31% and 27% in the groups of patients who declined to participate in this study (n = 139) or previously known by nephrologists (n = 147) respectively. Rate of RRT initiation was similar in patients randomized in the study and in those previously known by nephrologists
Conclusion: These results do not demonstrate a benefit of a regular renal care in terms of survival or RRT rate in patients with CKD stage IIIb-IV. ClinicalTrials.gov: NCT00929760

OC 06

FGF23 and markers of mineral metabolism in subjects with preserved renal function

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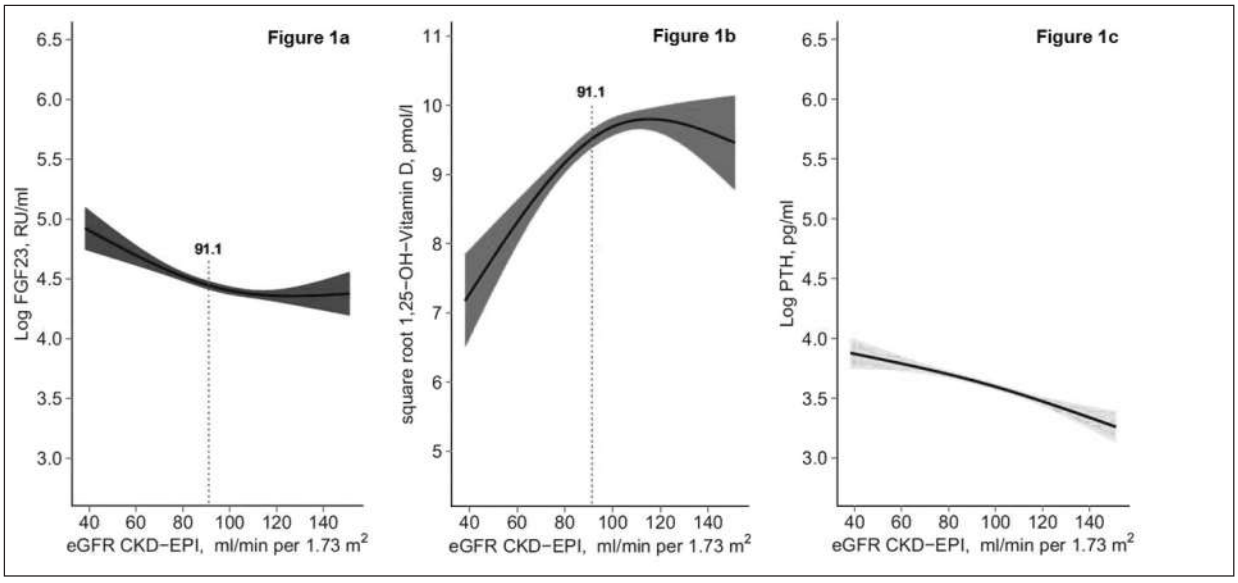
Background: Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphate homeostasis. FGF23 is elevated in CKD and independently associated with poor renal and cardiovascular outcomes and mortality in CKD patients. The study of FGF23 in



subjects with normal renal function has received little attention thus far.
Methods: We examined in a large family-based multicentric study with 1128 participants the associations of FGF23 with markers of diet, mineral metabolism and renal function.
Results: 1075 individuals were included in the final analysis. Mean CKD-EPI eGFR of the cohort was 96.7 ml/min per 1.73 m^2, median FGF23 levels were 79.6 RU/ml (IQR 63.7–105.1). Below an eGFR threshold of 91.1 ml/min per 1.73 m^2, FGF23 levels started to rise and were paralleled by a progressive decrease of 1,25-OH Vitamin D3 (fig. 1a and 1b). In contrast, PTH increased continuously with falling GFR without a threshold (fig. 1c). In multivariate analysis, FGF23 was negatively associated with 1,25-OH Vitamin D3 ($p < 0.001$), 24 h calcium excretion ($p < 0.001$) and fractional calcium excretion ($p < 0.001$) but not with plasma calcium or PTH. We observed a positive association of FGF23 with plasma phosphate ($p < 0.05$), no association with fractional phosphate excretion and, unexpectedly, a positive association with TmP/GFR.
Conclusions: In a large population with preserved renal function, PTH increases earlier than FGF23 when GFR declines. The rise of FGF23 occurs at a higher GFR threshold than previously reported and is closely associated with a decrease of 1,25-OH Vitamin D3. Furthermore, our analysis suggests that the main effect of FGF23 in the setting of preserved renal function is suppression of 1,25-OH Vitamin D3 rather than stimulation of renal phosphate excretion.

ORAL COMMUNICATIONS – BASIC SCIENCE / GENETICS / EXPERIMENTAL NEPHROLOGY

OC 07

An in vitro model of idiopathic membranous nephropathy reveals PLA2R- and complement-dependent pathways of podocyte injury

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Background: Idiopathic membranous nephropathy (iMN) is an autoimmune kidney disease that usually manifests as nephrotic syndrome through damage of podocytes. In a significant proportion of patients, the disease leads to progressive renal failure, with almost 40% eventually reaching end stage renal disease (ESRD). The hallmark of iMN is the deposition of immune complexes in the subepithelial space. Recently, the target antigen of autoantibodies in the majority of patients with iMN has been identified as the M-type phospholipase A2 receptor (PLA2R). The definitive proof for pathogenicity of PLA2R antibodies, however, is still lacking. Furthermore, mechanisms of podocyte injury remain elusive, although sublytic complement injury has been proposed to play a central role. In this study, we aim to develop an in vitro model for iMN to determine downstream mechanisms of anti-PLA2R-antibody mediated injury to podocytes.
Methods: PLA2R expression levels in conditionally immortalized human podocytes were modulated by infection with a lentivirus vector carrying FLAG-tagged full length human PLA2R or by shRNA-mediated knock down. These cells were then pretreated with sera from PLA2R-positive iMN patients or control sera and subsequently, human complement was added. Cell lysates were collected and analyzed by Western blotting, and the cells supernatants were analyzed for VEGF secretion.
Results: High-titer (1:1000) PLA2R antibody positive sera and sublytic complement concentration resulted in inhibition of Akt phosphorylation at both S473 and T308 sites, a decrease in synaptopodin expression, and increased VEGF production in podocytes overexpressing PLA2R. In contrast, control sera as well as sera with a lower antibody titer (<1:100) did not adversely affect Akt phosphorylation and synaptopodin expression, nor increase VEGF release.
Conclusion: iMN sera activate VEGF signaling and inhibit Akt phosphorylation in a PLA2R-dependent manner. Further studies will address the role of these pathways in mediating podocyte damage.

OC 08

MEMO1 deletion impairs renal FGF23 signaling in vivo (NCCR project)

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Background: Mediator of ErbB2-driven Cell Motility 1 (Memo) modulates fibroblast growth factor (FGF) signaling in vitro, but its physiological role is unclear. Memo KO mice showed premature aging, insulin hypersensitivity and a deranged mineral metabolism similar to what is observed in FGF23 KO and Klotho mutant mice (Haenzi B, FASEB J 2014). Here, we assessed Memo's role in mineral homeostasis in the kidney.
Methods: Exon 2 of MEMO1 was deleted in the full body of Memofl/fl mice using a tamoxifen-inducible Cre recombinase to obtain cKO mice. Littermates without Cre served as controls. 12 Memo cKO and 12 control mice were randomized to receive FGF23 or vehicle, and kidneys were studied by immunoblotting and qPCR. Memo cKO mice were treated with diets deficient in phosphate or vitamin D to assess disease-free survival. Inducible kidney-specific Memo KO mice were established using the PAX8-LC1 Cre recombinase (Traykova-Brauch M, et al. Nat. Med 2008).
Results: Memo cKO mice had impaired FGF23-induced ERK phosphorylation in kidney lysates. Moreover, the vitamin D inhibitory effect of FGF23 on the 24alpha-hydroxylase (CYP24A1) was absent in cKO mice. Neither dietary vitamin D3 nor phosphate deprivation prevented premature aging and death in Memo cKO mice. Kidney-specific Memo KO mice had normal life span despite abolished Memo expression in the kidney but not in other organs upon KO induction. Calcium transporters expressions in the distal nephron were increased in both mouse models, but this was prevented by a vitamin D3 deficient diet.
Conclusions: Memo is involved in the intracellular signaling response to FGF23. In addition, Memo modulates distal renal calcium handling by a mechanism involving vitamin D3. However, the results of Memo null phenotype rescue attempts are not congruent with those of klotho or FGF23 KO mice, suggesting an alternative or even broader physiological role of Memo.

OC 09

Higher serum galactose-deficient IgA1 level is associated with stronger mesangial inflammatory response and more severe histologic findings in IgA nephropathy

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Background: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide with extremely variable disease progression. Poorly galactosylated IgA1 (Gd-IgA1) is known to play a key role in the activation of mesangial cells. We aimed to evaluate, whether the serum level of Gd-IgA1 is associated with in vitro activation of mesangial cells in individual patient, and how this affects the clinical and histological parameters.
Methods: Serum sample and clinical data including MEST score were collected from IgAN patients in University Hospital Basel and Hammersmith Hospital London. Serum levels of IgA1 and Gd-IgA1 were measured by ELISA and lectin-binding assay using lectin Helix Aspersa (HAA). Primary human mesangial cells were stimulated with isolated IgA1 from serum of individual patient, and the concentration of monocyte chemoattractant protein-1 (MCP-1) was measured in cell culture supernatant by ELISA.
Results: Thirty-three patients with IgAN were enrolled in the study. A significant correlation was observed between the serum level of Gd-IgA1 and the concentration of MCP-1 in the culture supernatant in individual patient (Spearman $r = 0.5969$, $p = 0.0002$). The serum level of Gd-IgA1 did not correlate with eGFR or proteinuria. However, there was a significantly higher serum level of Gd-IgA1 in patients with segmental glomerulosclerosis (S0 vs S1, $p = 0.0245$) and tubular

atrophy/interstitial fibrosis (T0 vs T1&2, p = 0.0336). Patients with S1 & T2 had the highest serum level of Gd-IgA1 (p = 0.0269).
Conclusions: Our results suggest that patients with higher serum level of Gd-IgA1 have stronger glomerular inflammatory responses, leading to more pronounced chronic histologic changes. Due to the variable disease progression, a better identification of patients, who are most likely to have disease progression and need more effective therapy, is desired. The addition of serum level of Gd-IgA1 to the known clinical and histologic parameters may improve the assessment of prognosis in IgAN.

OC 10

Characterization of renal erythropoietin producing cells in vivo (NCCR Project)

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Background: The healthy adult kidney is an important sensor of molecular oxygen (O_2) and the PHD/VHL/HIF pathway is essential for the physiological response to reduced O2 supply. In order to unravel the mechanisms involved in hypoxia-induced erythropoietin expression a greater understanding of the nature of renal erythropoietin (Epo) producing (REP) cells is required.
Methods: We have developed a novel transgenic mouse model (Epo-CreERT2) with inducible Cre recombinase expression under the control of the 220 kb mouse Epo gene locus which when crossed with the Rosa26-loxP-Stop-loxP-tdTomato reporter allows us to permanently tag REP cells in response to an Epo inducing stimulus. We have investigated localization of REP cells within the renal cortex in normoxia, following 8% FiO_2 hypoxia (physiological stimulus) as well as following 0.1% CO (profound tissue hypoxia). Furthermore we have used RNAScope technology to localise Epo mRNA.
Results: 5 Epo-CreERT2 founder lines demonstrate a peritubular, interstitial localisation of tdTomato expressing REP cells in the juxtamedullary cortex. This localisation was further confirmed by the detection of Epo mRNA. We found that very few REP cells are required to maintain basal Epo expression in healthy normoxic mice. The number of cell which produced Epo in response to 8% FiO_2 and 0.1% CO is greatly increased. We predict that Epo production by as few as 2600 REP cells is sufficient for the physiological response to hypoxia in the mouse.
Conclusion: Our results demonstrate that REP cells are localised in the interstitium of the juxtamedullary cortex and that only few cells are needed to maintain Epo production under physiologic conditions. Furthermore, increased demand for Epo is likely to be met (at least partly) by an increase in the number of REP cells rather than by an increase in the Epo production rate within a specific population of renal cells in vivo.

OC 11

Paraneoplastic nephrotic syndrome in small cell lung cancer is closely related to the induction of c-mip in podocytes via a circulating factor

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Background: Paraneoplastic nephrotic syndrome (PNS) is a frequent complication associated with cancer. At the kidney levels, various histological lesions have been described. Although not well understood, some light has been shed on the link between neoplasia and PNS. In Hodgkin lymphoma-associated PNS, overexpression of the c-Maf inducing protein (c-mip) was shown to occur specifically in Reed Sternberg (RS) cells and podocytes of patients with nephrotic syndrome (NS). It is not known if c-mip is also involved in other cancer-associated NS.
Methods: A 76-year-old female presented with a nephrotic syndrome. A FSGS was found on kidney biopsy. In the context of previous history of cancer and smoking, we eventually found a small cell lung carcinoma (SCLC). One cycle of carboplatin – etoposide chemotherapy induced resolution of the proteinuria and radiologic reassessment after three cycles of chemotherapy showed a 50% reduction in the lung tumor size.
Results: C-mip was found to be overexpressed in podocytes and cancer cells of our patient while it was not in control normal kidney and in SCLC cells from 30 patients not harboring NS. To assess whether a circulating factor could induce c-mip overexpression in both cancer cells and podocytes, we analyzed the effect of the patient's sera (before and after the chemotherapy) on cultured podocytes. Patient's serum at diagnosis induced disorganization of the podocytes cytoskeleton, whereas this effect was not observed when the serum after chemotherapy was used.
Conclusions: We provide an extensive analysis of a case of SCLC associated PNS suggesting an important role for c-mip in the development of the renal lesions. As c-mip is confirmed as a key player in NS, its role in the development of a PNS in different histological pattern of cancer deserves further investigation. The potential role of c-mip in SCLC prognosis and treatment also deserves more studies.

OC 12

Mutation in the monocarboxylate acid transporter 12 gene affects guanidinoacetate excretion but does not cause glucosuria

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Background: A heterozygous mutation (c.643C>A; p.Q215X) in the monocarboxylic acid transporter 12 gene MCT12 (also known as SLC16A12) that mediates creatine transport was recently identified as the cause of a syndrome with juvenile cataracts, microcornea, and glucosuria in a single family. Whereas the MCT12 mutation cosegregated with the eye phenotype, poor correlation with the glucosuria phenotype did not support a pathogenic role of the mutation in the kidney.
Methods: In a stepwise approach to examine the role of MCT12 in the kidney, we conducted genotype-phenotype analyses in the index family, and functional studies in Xenopus oocytes, and cell-culture studies.
Results: We examined MCT12 in the kidney and found that it resides on basolateral membranes of proximal tubules. Patients with MCT12 mutation exhibited reduced plasma levels and increased fractional excretion of guanidinoacetate, but normal creatine levels, suggesting that MCT12 may function as a guanidinoacetate transporter in vivo. However, functional studies in Xenopus oocytes revealed that MCT12 transports creatine but not its precursor, guanidinoacetate. Genetic analysis revealed a separate, undescribed heterozygous mutation (c.265G>A; p.A89T) in the sodium/glucose cotransporter 2-encoding gene SGLT2 (also known as SLC5A2) in the family that segregated with the renal glucosuria phenotype. When overexpressed in HEK293 cells, the mutant SGLT2 transporter did not efficiently translocate to the plasma membrane, and displayed greatly reduced transport activity.
Conclusions: In summary, our data indicate that MCT12 functions as a basolateral exit pathway for creatine in the proximal tubule. Heterozygous mutation of MCT12 affects systemic levels and renal handling of guanidinoacetate, possibly through an indirect mechanism. Furthermore, our data reveal a digenic syndrome in the index family, with simultaneous MCT12 and SGLT2 mutation. Thus, glucosuria is not part of the MCT12 mutation syndrome.

OC 13

Overhydration is a strong predictor of mortality independently of cardiac failure in peritoneal dialysis patients

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Background: Overhydration is a recurrent problem in peritoneal dialysis population and has been shown to be correlated with mortality. However, it still remains unclear whether overhydration per se is predictive of mortality or whether it is mainly a reflection of underlying comorbidities. The purpose of our study was to assess overhydration in prevalent peritoneal dialysis patients using bioimpedance spectroscopy, to identify mortality predictors in this population and to investigate whether overhydration is an independant predictor of mortality.
Methods: We analyzed and followed 54 patients on peritoneal dialysis between June 2008 and December 2014 (up to 6.5 years follow-up). Patients were measured once with the BCM device (FMC) and divided into 2 groups: normohydrated and overhydrated. Overhydration was defined as an absolute overhydration/extracellular volume (OH/ECW) value >0.15. Simultaneously, clinical data and blood levels of CRP, cardiac biomarkers NT-proBNP and troponin, albumin as well as heamoglobin and heamatocrit were assessed. Survival of patients until December 31st was documented. Factors associated with mortality were identified and multivariable Cox regression model was used to identify independant predictors of mortality.
Results: There was no significant difference regarding gender, body mass index, comorbidities and cardiac medication between the 2 groups but for a higher daily peritoneal ultrafiltration rate in overhydrated patients. Overhydrated patients died earlier than euvolemic ones (fig. 1). In the univariate analysis, age, overhydration, low diastolic blood pressure, cardiac biomarkers troponin and NT-pro-BNP, hypoalbuminemia (<36 g/l), heart failure but not CRP were predictive of mortality. After adjustment, only overhydration, age and low diastolic blood pressure remained statistically significant in the multivariate analysis (table 1).
Conclusions: Overhydration is an independant predictor of mortality even after adjustment for heart failure in peritoneal dialysis patients and should therefore be actively looked for and managed in order to improve survival in this population.

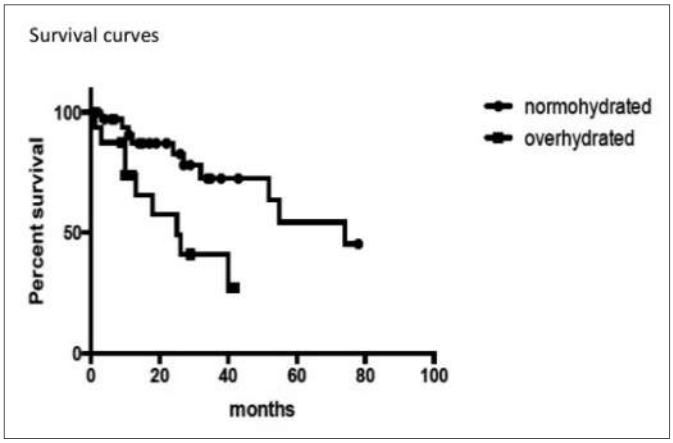

Figure 1

Table: Predictors of mortality 54 in patients on peritoneal dialysis.

	Univariate associations		Multivariate model	
	Relative hazard (95% confidence interval)	P value	Relative hazard (95% confidence interval)	P value
Overhydration, for 1 SD (0.11)	2.19 (1.35 – 3.54)	0.001	7.82 (1.10 – 29.07)	0.002
TNT, for 1 SD (0.0634)	2.30 (1.47 – 3.60)	<0.001	2.16 (0.86 – 5.39)	0.10
BNP, for 1 SD (24504)	1.48 (1.13 – 1.95)	0.005	1.95 (0.93 – 3.96)	0.066
C reactive protein for 1 SD (9.16)	1.31 (0.90 – 1.89)	0.16	0.75 (0.26 – 2.15)	0.60
Age (per year)	1.08 (1.03 – 1.12)	0.001	1.16 (1.07 – 1.27)	0.008
Heart failure (present vs absent)	5.12 (1.48 – 17.75)	0.010	1.33 (0.22 – 8.22)	0.76
Hypoalbuminemia (<36)	2.56 (1.01 – 6.50)	0.047	0.52 (0.07 – 3.63)	0.51
Diastolic BP, for 1 SD decrease (16.9 mmHg)	4.02 (1.97 – 8.19)	<0.001	8.10 (2.60 – 25.27)	<0.001

OC 14

Study of the possible physiological effects of antioxidants on some markers of neutrophil activation in chronic hemodialysis patients

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Background: Elevated oxidative status and reduced antioxidant defense systems are characteristic of end stage renal disease patients which may accelerate the prevalence of atherosclerosis and other chronic complications. The intradialytic activation and degranulation of neutrophils result in the release of neutrophil elastase together with reactive oxygen species, myeloperoxidase, and increased expression of CD 11b on granulocytes. The present study was designed to test the hypothesis that vitamin C supplementation might alleviate oxidative stress and modulate neutrophil activation markers in hemodialysis patients.
Methods: 30 patients maintained on hemodialysis were intravenously supplemented with vitamin C for 9 weeks and 15 age and sex matched subjects were used as controls. Plasma samples were stored at –80 °C until analysis. Three ml fresh whole blood samples were used for measuring CD11b. Plasma total cholesterol, HDL, and LDL levels were calculated using Friedewald formula. Neutrophil elastase and myeloperoxidase were estimated by enzyme linked immunoassay. CD11b expressed on neutrophils was measured by flow cytometry, and reactive oxygen species by fluorescent spectrophotometry.
Results: In our study, we reported a significant decrease of plasma neutrophil elastase, reactive oxygen species, myeloperoxidase, CD11b expression on neutrophils among vitamin C supplemented group compared to unsupplemented group. Plasma total cholesterol and low density lipoprotein was significantly decreased while high density lipoprotein was significantly increased in vitamin C supplemented

group compared to unsupplemented group. Collectively, the major finding of the present study was the strong association observed between vitamin C supplementation and reduction of all markers of neutrophil activation in hemodialysis patients.
Conclusions: We concluded that vitamin C supplementation was associated with the reduction of all markers of neutrophil activation in hemodialysis (HD) patients, also vitamin C supplementation improved lipid profile in HD patients as the results showed a significant decrease in total cholesterol and LDL levels with an increase in HDL.

OC 15

Preliminary results of dialysis study: accuracy of a single pool variable-volume calcium kinetic model with different calcium dialysate concentrations

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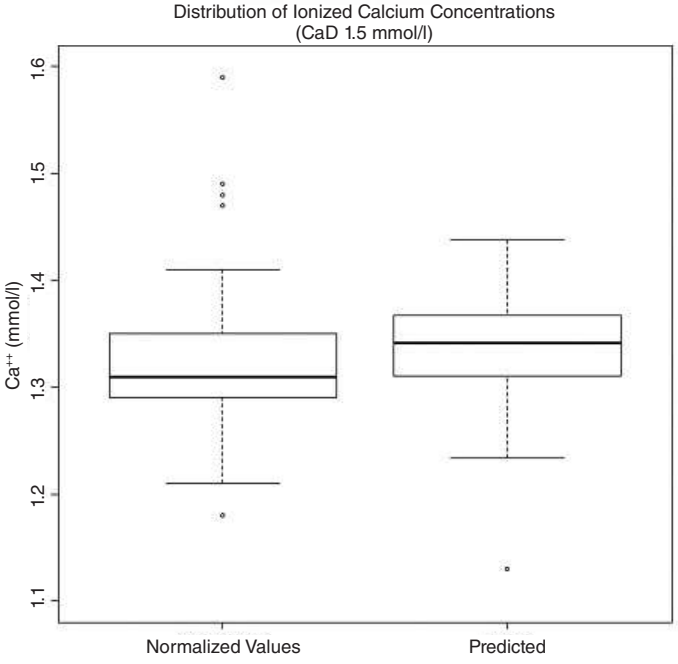
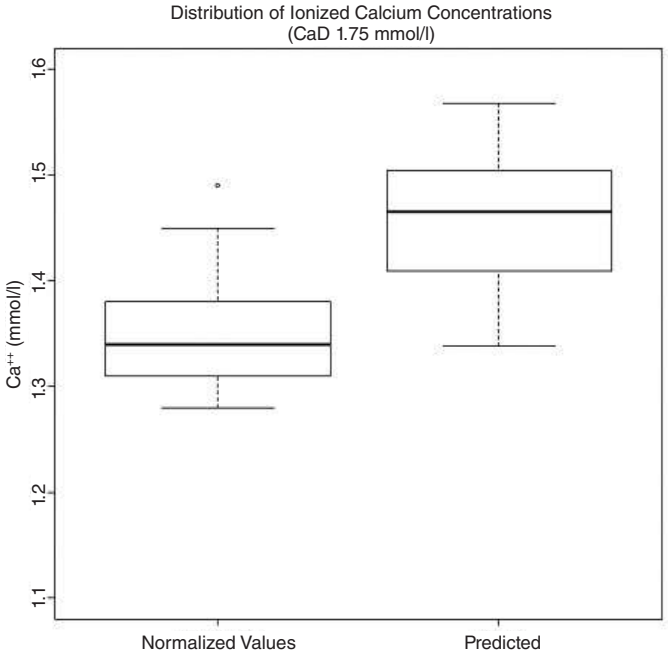
Background: The primary aim of the international study DialysIS (Dialysis therapy between Italy and Switzerland) is the increased personalization of hemodialytic treatments through a modellistic approach. Within the DialysIS study, we compare the accuracy of a single-pool variable volume calcium kinetic model (SPVV-CaKM) using two different dialysate calcium concentrations (CaD).
Methods: Pre- and post-treatment relevant variables of 34 patients treated with nominal CaD of 1.5 mmol/l (Group 1) and 22 patients with nominal CaD of 1.75 mmol/l (Group 2) were analyzed. The accuracy was evaluated determining the difference between predicted (Ca2+pwtP) and measured (Ca2+pwt) plasma water ionized calcium concentrations at the end of the dialysis sessions. To account for the changes in blood pH during dialysis session, which is known to affect plasma water ionized calcium concentrations, Ca2+pwt values were normalized at pH of 7.40.
Results: Fig. 1 indicate that the predicted values almost overlap t he normalized values for Group 1, while it's significantly higher for Group 2.
Conclusion: The SPVV-CaKM is accurate in Group 1 while it overestimates the Ca2+pwt Group 2. The Ca2+pwt of the two groups doesn't seem to account for the increased CaD. This suggests the presence of an additional compartment. Our hypothesis is that the administered calcium, predicted by our model, that doesn't appear in plasma could be deposited in bones and/or soft tissues. It is then theoretically possible to estimate the total calcium deposition or accumulation from the difference between predicted and measured post-treatment values.
Acknowledgments: Portions of this work were presented in abstract form at the Annual Meeting of the American Society of Nephrology in Philadelphia in November 2014 and the 52nd Congress of the ERA-EDTA.

	Ca^{2+}D [mmol/l]	Ca^{2+}pw start [mmol/l]	Ca^{2+}pwt [mmol/l]	Ca^{2+}pwtP [mmol/l]
Group 1	1.25 (1.16÷1.35)	1.17 (1.00÷1.43)	1.30 (1.16÷1.41)	1.32 (1.23÷1.42)
Group 2	1.47 (1.31÷1.67)	1.19 (0.98÷1.45)	1.43 (1.28÷1.63)	1.57 (1.40÷1.77)





OC 16

Benefits of Transonic® access flow measurement and percutaneous angioplasty

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Background: Thrombosis is the primary cause of access failure in arteriovenous graft and fistula. Intervention is largely limited to maximizing patency by detecting culprit lesions early and intervening with angioplasty or surgical revision. Regular access flow (AF) monitoring e.g. by Transonic® ultrasound dilution technique, the gold standard AF measurement, can predict dysfunction and reduce the risk for thrombosis. Despite convincing results concerning accuracy and prognostic value AF measurement it is not widely used in Switzerland yet.
Methods: We performed a retrospective analysis of the AF measurements routinely done with the Transonic® device. A total of 84 patients and 3115 patient-months were examined and analysis included AF decline leading to angiographic access evaluation, detection of an underlying stenosis and AF increase after percutaneous angioplasty. Furthermore we examined the number of

Table 1: Intervention related AF changes and shunt complications.

Patients with peripheral vascular access (n=59)	Mean	SD
AF decline leading to intervention (%)	50	24
AF decline leading to intervention (ml/min)	427	264
AF increase after intervention (%)	153	147
AF increase after intervention (ml/min)	409	387
Intervention interval (d)	639	486
Total intervention per patient-month	0.08	0.10
PA intervention per patient-month	0.05	0.07
Shunt thrombosis per patient-month	0.03	0.07

AF=access flow; PA=percutanous angioplasty; d=days, SD=standard deviation

Table 2: Shunt patency and complications in grafts and fistulas.

Patients with peripheral vascular access	Graft n=27		Fistula n=32		p-value
	Mean	SD	Mean	SD	
AF baseline (ml/min)	806	445	1064	568	<0.05
Intervention interval (d)	301	240	438	293	<0.01
Shunt patency (d)	988	765	2109	1535	<0.01
Total intervention per patient-month (n)	0.12	0.19	0.05	0.06	<0.01
PA intervention per patient-month (n)	0.07	0.08	0.02	0.04	<0.01
Shunt thrombosis per patient-month (n)	0.05	0.10	0.01	0.02	NS

AF=access flow; PA=percutanous angioplasty; d=days, SD=standard deviation

shunt complications and interventions per patient-month as well as access patency. Included were all patients of the Kantonsspital Liestal dialysis unit who had been dialyzed in august 2015 over a peripheral vascular access for at least 6 months.
Results: 59 patients (74%) had a peripheral vascular access, whereof 32 (54%) had a fistula and 27 (46%) had a graft. Mean AF decline leading to radiographic shuntogram was 50% (427 ml/min). In 94% an underlying stenosis was found followed by percutaneous angioplasty, which was performed without complications. Mean AF increase was 153% (409 ml/min). Mean intervention rate per patient-month was 0.08, vascular access thrombosis occurred in 0.03, respectively (table 1). The comparison between graft and fistula are summarized in table 2.
Conclusion: Transonic® access flow measurements highly predicted underlying vascular access stenosis (94%) if AF decline was more than 40% (200 ml/min) of baseline value. Angioplasty was nearly always successful with mean AF increase of more than 150% (400 ml/min), ensuring vascular access patency.

OC 17

A new method to personalize dialysis therapy

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Background: Health conditions and quality of life of uremic patients treated with hemodialysis could be improved by tailoring the treatment on each patient, whereas dialysis is usually based on standard not patient-specific parameters.
This work aims at adapting a mathematical model, describing fluid and solutes kinetics to single patient's characteristics, in order to simulate the patient reaction to the therapy and allow the clinician an offline evaluation of the settings and prescriptions to improve the treatment outcomes.
This work is part of the Project DialysIS, founded by a Cross-border Cooperation Programme (INTERREG IT/CH 2007–2013).
Methods: A multi-compartment model was adopted and data from 70 patients (recorded both at Regional Hospital of Lugano, Switzerland and at Alessandro Manzoni Hospital, Lecco, Italy) were used to estimate each patient's parameters. A sensitivity analysis was performed on the parameters.
The parameters are related to the mass exchange across the patient-specific cellular and capillary membranes and to the dialyzer membrane efficiency.
Parameters were computed using a constrained non-linear optimization algorithm (CNLO).
Results: Solutes concentrations and volume profiles simulated in about 400 dialysis sessions by the kinetic model optimized through the CNLO method, show to better fit clinical data than using the non-optimized model. The effects of different parameter settings are highlighted in terms of different molecules removal efficiency.
The simulation error of the model, estimated in the preliminary tests, comparing the output to the clinical trends, is always below 6 ± 0.7% for the solute concentrations (urea and the main plasmatic electrolytes were considered) and 0.2 ± 0.2% for the blood volume trend.
Conclusions: the kinetic model, coupled with a robust method to identify patient-specific parameters, allows a better prediction of electrolytes and fluid transfer during dialysis, and the possibility of evaluating the effects of different therapy settings. These results will be beneficial to improve dialysis therapy planning.

OC 18

Changing trends in end-stage renal disease patients with diabetes in the canton of Vaud between 2009 and 2014

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Background: Diabetes has become the most common cause of end-stage renal disease (ESRD) in most countries and the total cost of renal replacement therapy (RRT) has considerably increased due to the high prevalence of diabetes. We therefore carried out this study in the Canton of Vaud to determine the trends in incidence and clinical care characteristics of ESRD patients with diabetes from 2009 to 2014.
Methods: With the cooperation of dialysis facilities of the Canton of Vaud, we summarise sociodemographic, clinical, laboratory and health care characteristics of ESRD patients with diabetes between 2009 and 2014.
Results: There was a 156% increase in newly diagnosed diabetic patients with ESRD during the 5y study period with a total of 274 diabetic subjects requiring RRT. The estimated annual incidence of dialysis in diabetic patients was 1.4/1000. The 5y mortality rate was 61.7%. In 2009, 100% of diabetic patients with ESRD underwent hemodialysis decreasing to 96.2% in 2014 with 3.8% on peritoneal dialysis. The following clinical care characteristics were examined and compared in diabetic patients on RRT at the end of 2009 and 2014. There was no difference in age, sex, body mass index, type of diabetes, duration of diabetes, cause of ESRD, dialysis duration, dialysis frequency, vascular access, and HbA1c level. Hemoglobin level was decreased from 117.9 ± 10.9 g/L to 112.3 ± 11.6 g/L ($p < 0.001$). There was no difference in insulin, statin or erythropoietin treatment. Calcium containing phosphate binders and angiotensin-converting enzyme inhibitor treatments significantly decreased while iron therapy significantly increased with time.
Conclusions: The growing incidence of diabetic patients on dialysis therapy in canton of Vaud emphasizes that preventing chronic kidney disease and its progression should be a public health priority. From these results, we extrapolate an annual incidence of 364 diabetic patients undergoing renal replacement therapy in Switzerland.

OC 19

Influence of hip position on oxygenation and perfusion of renal transplants: The bent knee study – a pilot study

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Background: Interstitial fibrosis/tubular atrophy (IFTA) determines long-term kidney graft survival and is considered multifactorial. Iliac flow restrictions with kinking are described in cyclists secondary to fibrous fixation of the iliac bifurcation. In renal transplantation, a fibrous perigraft reaction develops soon postoperatively. Functional kinking due to tethering of iliac arteries by adjacent fibrotic tissue may occur in graft recipients when sitting and in turn lead to repetitive graft hypoperfusion. The purpose of this study is to test the hypothesis that perfusion and oxygenation of renal transplants are reduced during hip flexion compared to the stretched position by employing MRI techniques.
Methods: This prospective pilot study enrolled five renal transplant recipients. MRI including blood oxygenation level-dependent (BOLD) and diffusion tensor imaging (DTI) was performed in neutral hip position and in maximally achievable hip flexion. The perfusion fraction (FP), the apparent diffusion coefficient (ADC) and the fractional anisotropy (FA) were determined in cortex and medulla from DTI; BOLD yielded the relaxation rate (R2*), which is inversely related to the oxygenation status.
Results: The cortical perfusion fraction was significantly lower during hip flexion as compared to the stretched position (p = 0.0006) (fig. 1). There were no significant changes in ADC and FA. Cortical R2* significantly increased during hip flexion (p = 0.04) indicating reduced oxygenation (fig. 2). Medullary diffusion and BOLD parameters did not change significantly (table 1).
Conclusions: MRI of renal transplants was successfully performed during hip flexion and extension in five patients. Hip flexion lead to a marked decrease in cortical FP and was paralleled by an increase of cortical R2*, both supporting the hypothesis of position-dependent reduced blood supply in renal grafts. However, more subjects are needed to validate this initial finding. As expected, there was no significant influence on ADC and FA. Medullary parameters showed no changes in this pilot study.

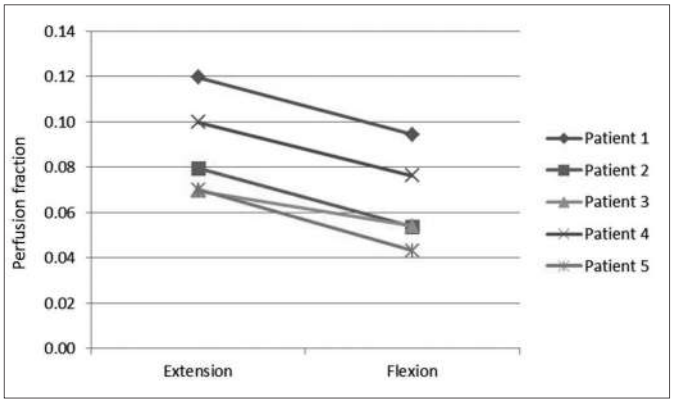

Figure 1: Perfusion fraction as measured by DT-MRI.

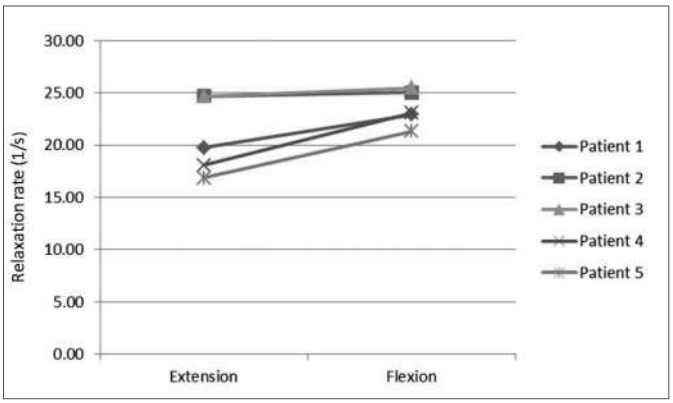

Figure 2: Relaxation rate (R2*) measured by BOLD-MRI.

Table 1: Diffusion and BOLD parameters during hip flexion and extension. Values are expressed as mean with standard deviation. P = patient; p = p-value (t-test).

		Perfusion fraction		ADC [10-5 mm2/s]		Fractional anisotropy		Relaxation rate [1/s]	
		Extension	Flexion	Extension	Flexion	Extension	Flexion	Extension	Flexion
Cortex	P1	0.12±0.05	0.09±0.06	242±18.04	248±12.11	0.30±0.09	0.27±0.08	19.75±2.32	22.90±4.16
	P2	0.08±0.04	0.05±0.06	202±9.40	208±9.68	0.22±0.08	0.24±0.05	24.68±3.57	25.03±2.58
	P3	0.07±0.06	0.05±0.07	206±9.37	217±13.15	0.15±0.05	0.24±0.08	24.68±3.57	25.47±2.49
	P4	0.10±0.05	0.08±0.04	218±10.03	199±11.2	0.25±0.05	0.30±0.10	18.05±2.39	23.05±3.80
	P5	0.07±0.03	0.04±0.12	222±9.57	228±17.8	0.23±0.07	0.30±0.10	16.84±2.54	21.28±2.90
	p		0.0006		0.7		0.19		0.04
Medulla	P1	0.13±0.09	0.09±0.07	242±15.6	250±23.2	0.33±0.09	0.31±0.10	23.52±3.17	25.34±5.13
	P2	0.02±0.06	0.04±0.06	206±10.1	209±9.3	0.25±0.09	0.24±0.07	24.35±5.10	25.00±3.68
	P3	0.01±0.09	0.08±0.09	199±12.3	225±12.4	0.18±0.05	0.30±0.09	31.36±3.90	28.36±7.45
	P4	0.06±0.10	0.04±0.05	221.2±10.2	199±7.3	0.30±0.10	0.20±0.10	25.10±4.68	25.13±6.63
	P5	0.05±0.07	0.06±0.10	217±13.0	232±16.9	0.25±0.07	0.40±0.09	19.60±3.70	21.80±3.90
	p		0.72		0.5		0.3		0.36

OC 20

Belatacept-treated patients had superior graft survival compared with cyclosporine-treated patients: final results from BENEFIT

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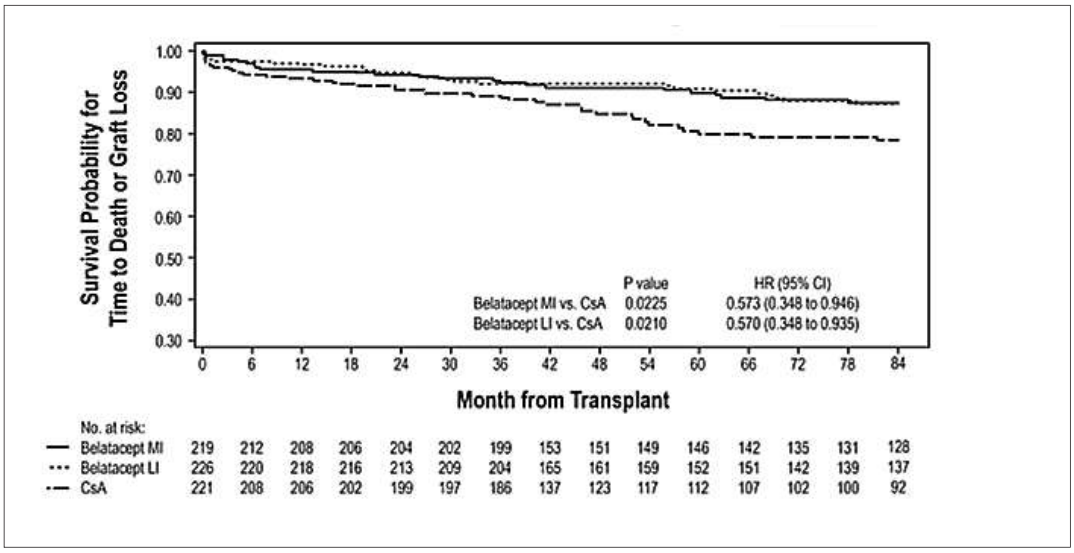
Background: No prospective, phase 3, randomized studies of immunosuppressive regimens have shown a survival advantage over cyclosporine-based regimens. In prior analyses of BENEFIT, renal function was improved in belatacept-treated vs cyclosporine-treated kidney transplant recipients. We report final 7-year results from BENEFIT.
Methods: Patients were randomized to more (MI) or less intense (LI) belatacept-based or to cyclosporine-based immunosuppression. Outcomes were assessed for all randomized, transplanted patients at year 7. In a prospective analysis, time to death or death-censored graft

loss was compared between regimens using Cox regression. Presence of donor-specific antibodies (DSAs) was determined centrally. Kaplan–Meier estimates were calculated for the cumulative rate of de novo (DN) DSA development.
Results: 153/219 belatacept MI-treated, 163/226 belatacept LI-treated, and 131/221 cyclosporine-treated patients were evaluable for death/graft loss at year 7. Hazard ratios comparing time to death/graft loss were 0.573 for belatacept MI vs cyclosporine (P = 0.02) and 0.570 for belatacept LI vs cyclosporine (P = 0.02)–a 43% risk reduction in death/graft loss for belatacept (MI or LI) vs cyclosporine. Mean MDRD estimated GFR (as observed, ANOVA) at month 84 for belatacept MI, belatacept LI, and cyclosporine was 74, 78, and 51 mL/min/1.73 m^2, respectively. Cumulative event rates for DN DSAs at years 3, 5, and 7 were 1.18%, 1.86%, and 1.86% for belatacept MI; 3.40%, 4.64%, and 4.64% for belatacept LI; and 8.72%, 16.19%, and 17.81% for cyclosporine, respectively. The rates of serious AEs were similar across regimens (71%, belatacept MI; 69%, belatacept LI; 76%, cyclosporine). PTLD occurred in 3 belatacept MI-treated, 2 belatacept LI-treated, and 2 cyclosporine-treated patients; all PTLD cases in belatacept-treated patients occurred before month 24.
Conclusions: At 7-years post-transplant in BENEFIT, belatacept conferred statistically better graft survival and renal function, with a reduced incidence of DN DSAs vs cyclosporine. The belatacept safety profile was consistent with prior reports.



OC 21

Chronic transplant vasculopathy in renal allografts: a result of undiagnosed rejection and suboptimal treatment strategies

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Background: Chronic rejection – including chronic transplant vasculopathy – is a major cause of renal allograft failure. The aim of this study was to assess the risk factors associated with the development of chronic transplant vasculopathy.
Methods: A cohort of 552 kidney transplantations performed between 2004 and 2013 with different HLA-risk (AB0-compatible without pre-transplant HLA-DSA: n = 405, with HLA-DSA: n = 99, and AB0-incompatible: n = 48) was studied. Using the Banff chronic vascular (cv) lesion score, recipients biopsies (protocol or indication) performed >300 days after transplantation were classified as cv-negative (cv score = 0) or cv-positive group (cv score ≥1). Multivariate logistic regression analysis was performed to assess independent risk factors for transplant vasculopathy.
Results: Eighty-seven (16%) kidney allograft recipients developed chronic vasculopathy: cv1 in 57 (66%), cv2 in 21 (24%), and cv3 in 9 (10%). In 54/87 (62%) of cases no acute arteritis was detectable in previous biopsies, performed < 300 days after transplantation. The strongest independent risk factors for chronic transplant vasculopathy were: the presence of preformed HLA-DSA (odds ratio (OR) 4.2, p = 0.02) and acute rejection episodes within the first year after transplantation (OR 2.4, p = 0.01 for AMR; and OR 4.0, p <0.001 for TCR). In contrast, the use of an induction therapy (including Interleukin-2-receptor antagonist or T-cell depleting agents) or anti-rejection treatment was not protective (p = 0.9 and p >0.3, respectively) for chronic transplant vasculopathy.
Conclusions: The association of chronic transplant vasculopathy with preformed HLA-DSA and acute rejection strongly indicates an immune-mediated pathogenesis for chronic transplant vasculopathy. Currently used treatment protocols are suboptimal to prevent its development. A considerable proportion of patients with chronic transplant vasculopathy showed no acute vascular lesions in previous biopsies. They may represent a sub-group with underdiagnosed low-grade inflammatory processes.

OC 22

2222 kidney transplantations at the University Hospital Basel: a story of success and new challenges

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Background: The aim of this study was to investigate changes in kidney allograft recipient/donor characteristics and long-term outcomes over a period of almost 50 years of kidney transplantation at our center.
Methods: We retrospectively reviewed all 2222 kidney transplantations performed between 1967 and 2015. The population was divided into four eras according to major changes in immunosuppression and pre-transplant risk stratification: (i) 1967–1980 (n = 231), (ii) 1981–1997 (n = 883), (iii) 1998–2004 (n = 437), (iv) 2005–today (n = 671).
Results: We observed a continuous increase of the median recipient (45 yrs, 48 yrs, 52 yrs, 55 yrs; p <0.0001) and donor (26 yrs, 46 yrs, 51 yrs, 54 yrs; p <0.0001) age. Notably, the frequency of expanded criteria donors – defined as donor age >60 years – increased dramatically (<1%, 10%, 28%, 40%; p <0.0001). Death-censored graft survival at 1 year (73%, 88%, 94%, 98%), 5 years (60%, 81%, 85%, 93%), and 10 years (53%, 70%, 73%, 89%) significantly improved (p <0.0001). In the current era, we observed a remarkable increase of death-censored graft survival among deceased donor transplants, which

almost matches the results of living donor transplants. Patient survival improved also significantly and remained stable at a high level within the last three eras (1 year: 98%; 5 years: 90%; 10 years: 80%). The proportion of patients dying with a functioning graft increased in the most recent era (51%, 49%, 42%, 62%; p = 0.009).
Conclusions: Despite increasing donor and recipient age, short- and long-term outcomes improved, documenting ongoing progress in kidney transplantation. A major new challenge is to match the functional capacity of the donor organ with the anticipated lifespan of the recipient.

OC 23

Six-month urinary CCL2 and CXCL10 levels predict long-term renal allograft outcome

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Background: Early prognostic markers that identify high-risk patients could lead to more intensive post-transplant surveillance, personalized immunosuppression and improved long-term outcomes. The goal of this study was to validate 6-month urinary CCL2 as a non-invasive predictor of long-term allograft outcomes and compare it to 6-month urinary CXCL10.

Methods. A prospective, observational renal transplant cohort (n = 185) with a 6-month surveillance biopsy/corresponding urine sample, and a minimum 5-year follow-up was evaluated. The primary outcome was a composite of allograft loss, renal function decline (>20% decrease eGFR between six months and last follow-up), and biopsy-proven rejection after six months. Urinary CCL2 and CXCL10 were measured by ELISA.
Results. Fifty-two patients (52/185, 28%) reached the primary outcome at a median 6.0 years and their urinary CCL2:Cr was significantly higher compared to patients with stable allograft function [median (IQR) 38.6ng/mmol (19.7–72.5) vs. 25.9 ng/mmol (16.1–45.8), p = 0.009]. Low urinary CCL2:Cr (≤70.0 ng/mmol) was associated with 88% 5-year event-free survival compared to 50% with high urinary CCL2:Cr (p <0.0001). In a multivariate Cox-regression model, the only independent predictors of the primary outcome were high CCL2:Cr [HR 2.86, 95%CI 1.33–5.73] and high CXCL10:Cr levels [HR 2.35, 95%CI 1.23–4.88; both p = 0.009]. Urinary CCL2:Cr/CXCL10:Cr AUCs were 0.62 (p = 0.001)/0.63 (p = 0.03), respectively. Time-to-endpoint analysis according to combined high or low urinary chemokines demonstrates that endpoint-free survival depends upon the overall early chemokine burden (fig. 1).
Conclusions. This study confirms that 6-month urinary CCL2:Cr is an independent predictor of long-term renal allograft outcomes. Urinary CCL2:Cr and CXCL10:Cr alone have similar prognostic performance, but when both are elevated this suggests a worse prognosis. Therefore, urinary chemokines may be a useful tool for timely identification of high-risk patients.

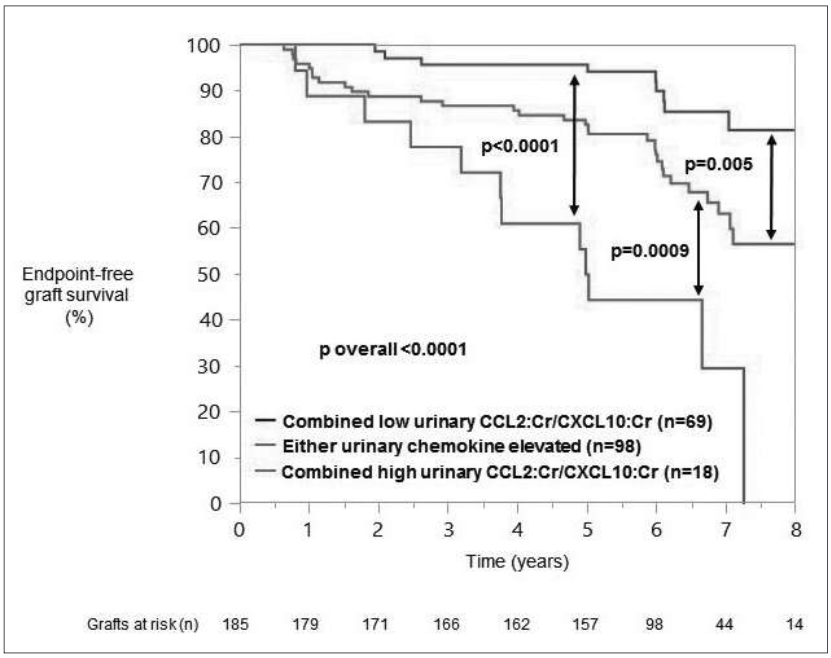

Figure 1: Endpoint-free graft survival of patients stratified according to their levels of 6-month urinary CCL2:Cr and CXCL10:Cr. The intermediate groupe was defined as a single elevated urinary chemokine.

OC 24

The kSORT assay in kidney transplant recipients: first experience in Switzerland.

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Background: Noninvasive diagnostic assays may improve the diagnostic accuracy of graft acute rejection (AR) and provide a non invasive alternative to protocol biopsies. When cell infiltrates suggesting a borderline T-cell mediated rejection (bTCMR) are seen in a protocol biopsy of a recipient without graft dysfunction, the benefit: risk ratio of methylprednisolone pulses is not obvious. We evaluated the use of a validated blood quantitative real-time PCR (QPCR) assay in the context of inconclusive biopsy results from kidney transplant recipients in Geneva University Hospitals.

Table 1: Patient's results and AR score according to kSAS scale.

Patient #	Sample date	AR risk score	Prognosis
1	1.22.15	-13	No Rejection Predicted
2	2.18.15	-13	No Rejection Predicted
3	7.1.15	-9	Indeterminate
3	8.7.15	-13	No Rejection Predicted

Methods: From November 2014 to April 2015, 3 patients (p1, p2 and p3) underwent a posttransplant protocol biopsy at 3, 15 and 1 years respectively, leading to bTCMR diagnosis. They had no renal dysfunction at the time of the biopsy. Gene expression was assessed by QPCR (Sarwal's Lab, UCSF, San Francisco, USA). A 17-gene set, the Kidney Solid Organ Response Test (kSORT) was analyzed for each patient. A numerical AR risk score was obtained to classify patients as high risk versus low risk for AR. Blood samples were received within 48 hours and results delivered within 10 days.
Results: 2 patients (p1 and p2) had a low risk score (–13) and p3 had an intermediate score (–9) requiring a retest which came back as low risk (–13). P2 underwent a second graft biopsy 6 months later that has not found any infiltrate. No patient was treated for AR and the three patients had a stable functioning graft (follow up from to 5 to 10 months).
Conclusions: The kSORT is of high interest when histopathological results are inconclusive or are not consistent with clinical and biology. It might avoid overimmunosuppression. It also highlights the importance of a better understanding and characterization of currently unexplained graft infiltrates.

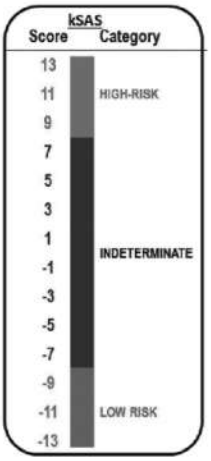

Figure 1: kSAS scale for scoring the risk of rejection.

POSTER PRESENTATIONS – CLINICAL NEPHROLOGY / HYPERTENSION / MINERAL / ELECTROLYTES

P 01

Probability of Renal Stone Formation in obese patients before gastric bypass surgery

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Background: Prevalence of obesity has massively increased over the last decades worldwide, and consequently so did the number of gastric bypass procedures over the last years (ca 100 procedures/yr in our center). Gastric bypass is known to lead to metabolic disorders that dramatically raise the risk of renal stone formation. We wanted to estimate the stone risk of a cohort of obese patients naïve of nephrolithiasis scheduled for gastric bypass surgery
Methods: A standard urinary metabolic work-up was performed in obese patients scheduled for gastric bypass surgery in our center in the following month. To estimate the stone risk we calculated the probability of stone formation (PSF) according to Robertson: the method applies the Bayes' Theorem on the frequency distributions of traditional stone risk factors measured in a 24h urine sample among idiopathic stone formers and controls. PSF can be calculated for uric acid (UA), calcium oxalate (CaOx), calcium phosphate (CaP) or mixed crystals, and tightly correlates with the incidence of nephrolithiasis.
Results of the first 6 patients prospectively enrolled: All females, aged 35.3 ± 9.0 yrs, weighing 120.8 kg ± 19.4 with BMI of 46.6 kg/m^2 ± 5.9 (all means ± SD). Results of the 24h urine analyses are depicted in table 1 and the plot of PSF values in fig 1, respectively. Four patients had a severe risk of CaOx stone formation and one of them (patient 4) simultaneously had a moderate risk of UA stone formation.
Conclusions: Obese patients without history of nephrolithiasis scheduled for a gastric bypass are already at high risk of CaOx stone formation formation prior to surgery, a fact which is largely underestimated by most surgical teams. We are currently carrying out a prospective randomized study assessing the benefit of a dedicated preventive strategy aiming at reducing the stone risk after bypass surgery.

Figure 1: Preoperative probability of stone formation (PSF).

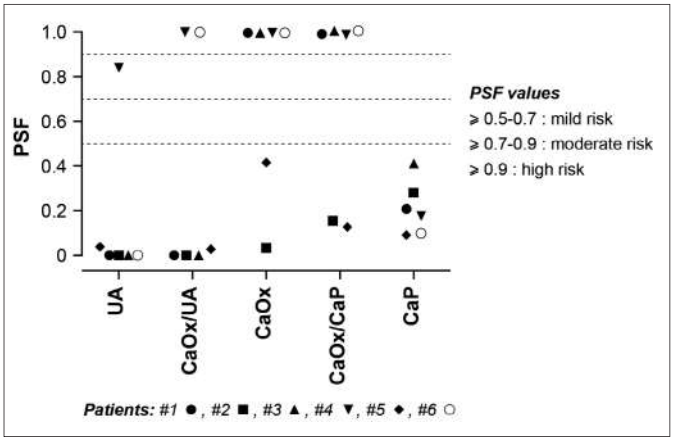

Table 1: 24h urine collection analysis.

	#1	#2	#3	#4	#5	#6
volume (ml/24h)	1180	2550	1430	880	1500	800
pH	6	6.5	6	5.5	5.5	5.5
creatinine (mmol/24h)	16.0	11.5	13.7	10.3	15.6	16.9
Na (mmol/24h)	136	153	342	141	164	168
K (mmol/24h)	72	84	54	41	40	79
Ca (mmol/24h)	6.08	1.76	9.55	6.44	4.58	3.13
phosphate (mmol/24h)	25.1	26.0	45.5	29.5	27.2	34.2
urea (mmol/24h)	367	160	535	384	390	362
uric acid (mmol/24h)	4.33	4.21	5.71	3.67	4.67	2.02
Mg (mmol/24h)	5.25	5	4.98	3.89	2.64	4.87
citrate (µmol/24h)	4347	4287	5764	2895	2768	6976
oxalate (µmol/24h)	523	507	635	383	278	734

P 02

Parathyroid hormone is critical for the acute adaption to oral or intravenous phosphate loading (NCCR Project)

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Plasma phosphate (Pi) is kept within a narrow range by balanced intestinal absorption, bone resorption/deposition, and renal reabsorption. These processes are controlled mainly by PTH, 1,25-dihydroxy-vitamin D3 (VitD), FGF-23, and extracellular Pi. The aim of this study was to analyze the effect of rapid Pi loading in rats upon intravenous or intragastric application (gavage). Rats were fed for 5 days with low Pi diet, and after 12 hours fasting, were infused intravenously or gavaged with either sodium-phosphate (Pi) or saline. Over the next 4 hours, blood and urine was collected at different time points and at the end of the experiment several tissues were harvested.
We found that intravenous Pi infusion resulted in a rapid increase in plasma Pi concentration, and that this increase was fully normalized two hours post-infusion. The increase of plasma Pi was associated with a rapid elevation of PTH levels, increased phosphaturia, reduced uptake of 32Pi into renal brush border membrane vesicles and reduced expression of renal Na/Pi-cotransporters NaPi-IIa and NaPi-IIc. No change in FGF-23, VitD, and insulin was detected over 4 hrs whereas dopamine increased in the infused animals. The excretion of the phosphate load was delayed in gavaged animals but both infused and gavaged animals excreted approximately 50% of the load over the 4 hrs period. To test the role of PTH, parathyroidectomized (PTX) rats were infused or gavaged. The phosphaturic response was blunted in PTX rats, the animals developed sustained hyperphosphatemia, and FGF-23 levels were increased; however, renal uptake of 32Pi and expression of NaPi-IIa and NaPi-IIc did not change in these animals.
Taken together, our experiments demonstrate a rapid normalization of plasma Pi upon acute Pi loading as well as a prominent role of PTH in this process.

P 03

Outcome of "double positive" anti GBM disease: a case report

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Background: Anti-glomerular basement membrane (anti-GBM) disease and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis both could cause rapidly progressive glomerulonephritis (RPGN). The coexistence of anti-GBM and ANCA antibodies known as "double positive" are seen in up to 30% of patients diagnosed as anti-GBM disease and showing poorer outcome than anti-GBM antibodies positive only patients. We here describe a case of a "double positive" patient.
Case: A 68-year old man was referred to our clinic with a history of acute onset of anuric renal failure. The patient was complaining about general malaise, subfebrile temperature, a non-productive cough without hemopthysis since three weeks prior to presentation. His medical history was remarkable for an ongoing heavy smoking and a subsequent COPD complicated by an interstitial pneumopathy. On clinical examination the patient presented with subfebrile temperature (38.2 °C), high blood pressure (165/79 mm Hg) and oxygen saturation of 93% on pulseoxymetry with 2L oxygen. The initially measured creatinine was 977 µmol/l, and CRP of 339 mg/l. The Anti-GBM titers were initially very high at >680U/ml. ANCA Titers were slightly positive at 1:40, with anti-MPO at 15 U/ml and negative anti-PR3 values. Renal biopsy revealed an anti-GBM disease. An induction therapy with cyclophosphamide and initially high dose methylprednisolone parallel to plasmaexchange was initiated. This regimen led to a considerable decline in Anti-GBM titers, which remained detectable at 3 months. The patient was reluctantly recovering diuresis up to 1500 ml per day but unfortunately without relevant recovery of renal function and patient remained dialysis dependent.
Conclusion: In "double positive" patient with anti-GBM disease presenting with renal failure and initially dialysis dependency are showing poor renal prognosis despite treatment.

P 04

Community-acquired enterococcal urinary tract infection

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Introduction: Community-acquired febrile urinary tract infection (UTI) is common in children, causing substantial morbidity and accounting for many hospitalizations particularly in infants and younger children. Most causal pathogens are gram-negative enterobacteria: The predominant pathogen is E. coli, whereas only ≤5% of UTI are caused by Enterococci, mainly E. faecalis. All enterococci are resistant to cephalosporins. We report a case series of children with febrile UTI caused by E. faecalis.
Patients and methods: We retrospectively collected data from patients presenting with febrile UTI between January 2013 and December 2014 caused by isolated growth of Enterococci. Urine was obtained either by transurethral bladder catheterization or midstream urine.
Results: A total of 8 episodes of febrile UTI were observed in 7 boys. Median age was 0.75 years (range 0.1–5.1). Median fever duration at diagnosis was 2 days (0.5–4) and median CRP 118 (5–372 mg/l. Urinalysis showed mild leucocyturia (6–10 / high power field) in only one case. Initial empiric antibiotic therapy consisted of cephalosporin in 5 (switched to amoxicillin after urine grew E. faecalis), and amoxicillin in one; in 2 episodes, amoxicillin was started only when urine culture became positive. 5 patients had an underlying malformation: Ectopic kidney, duplex kidney, solitary kidney with megaureter, hydronephrosis and complex bilateral renal and ureteral malformation.
Conclusion: Febrile UTI with enterococcal monoculture is rare. In addition, the often inconspicuous urinalysis is a diagnostic challenge leading to underdiagnosis. It's suggested that boys, in particular with un-derlying malformation of kidneys and urinary tract, are more prone to enterococcal UTI. Standard empiric antibiotic therapy with cephalosporins often fails to resolve symptoms, and switch to amoxicillin is required. This study is also meant to raise the awareness of enterococcal UTI, in par-ticular in children with persistent fever without other symptoms and normal urinalysis.

P 05

Nephrologic psychiatry: hyponatremia in a depressive woman – a case report

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Background: A somnolent but easily arousable 51-year old woman with cough, vomiting and fatigue was admitted without prior blood sampling from a psychiatric unit with a suspicion of pneumonia. She had been treated for a moderate depression with escitalopram and chlorprothixen. She had a gastrostomy-tube since 2012 due to dysphagia after surgery and radiation of a squamous cell carcinoma of the rhinopharynx. The afebrile patient was slightly hypovolemic at initial presentation.
Methods: History and clinical examination was taken and we performed a chest x-ray, urinary tract ultrasound as well as longitudinal blood and urinary testing. Therapeutic adaptions were regularly performed according to blood and urinary test results during 12 days of hospitalization.
Results: The suspected pneumonia was confirmed. Surprisingly, we found a severe hyponatremia of 118 mmol/L, a low plasma osmolality of 243 mmol/L, a very low urine sodium of <10mmol/l with a normal estimated GFR. After ruling out hypocortisolism and hypothyroidism, in-deep history revealed a daily consumption of 5 litres of water because of a dry throat since radiotherapy. Initial intravenous followed by oral sodium substitution together with a reduced daily fluid intake of 3 litres rapidly resulted in a distinctivly better mental state. At discharge, sodium levels were at 133 mmol/l. After 2-months the psychiatric outcome was still very satisfying under escitalopram in combination with salt tablets.
Conclusions: We diagnosed a severe hyponatremia due to excessive intake of hypo-osmolar fluids because of salivary gland dysfunction after radiotherapy. Dysphagia aggravated the explicit imbalance between salt intake and excretion despite a normal renal function. The current treatment with escitalopram as well as acute pneumonia might have negatively influenced sodium levels, we found no signs of SIADH or other hormonal dysregulations. We propose a broad history and electrolyte testing to rule out confounding factors in depressive psychiatric patients.

P 06

Nephrogenic Diabetes insipidus due to Sevoflurane administration

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Background: In the 1970s the toxicity of inorganic fluoride ions on renal cells was studied and described first. Since the 1990s the inhalative anaesthetic agent Sevoflurane has been used worldwide and has been favored because of its low solubility in blood and tissue, which allows rapid recovery after general anaesthesia. However, Sevoflurane has been implicated in the damage of renal cells because of the production of compound A and the breakdown of sevoflurane into inorganic fluoride ions. In 1999 Morita et al compared serum and urine concentrations of Arginine Vasopressin (AVP), Acquaporin 2 (AQP2) and osmolar changes during sevoflurane and propofol anaesthesia in 30 patients and suggested that nephrogenic diabetes insipidus (nDI) associated with sevoflurane was caused by impairment of the AQP2 response to an increase in AVP during surgery.
Method: We describe 6 patients in an ICU setting who developed DI after initiation of sevoflurane sedation.
Results: 5 male and 1 female patient developed polyuria and hypernatraemia within 2–4 days after starting of sevoflurane sedation. Each patient had an impaired urine concentration permitting diagnosis of DI. 3 out of 6 patient furthermore had a negative desmopressin-test confirming diagnosis of nDI.
Conclusion: Polyuria due to sevoflurane has been described as rare complication but may be missed because of its transient character, making it difficult for identification of less severe forms. After stopping of sevoflurane all patients had spontaneous cessation of polyuria. However, hypernatraemia, the risk of delirium and fluctuations in fluid status and hemodynamics should be kept in mind as a consequence of nDI as a potential side effect of sevoflurane.

P 07

Neolymphangiogenesis is related to worse clinical outcome in lupus nephritis

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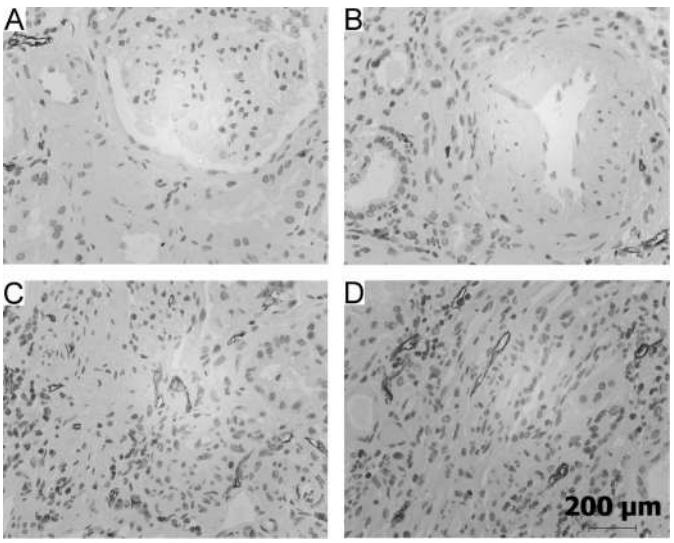
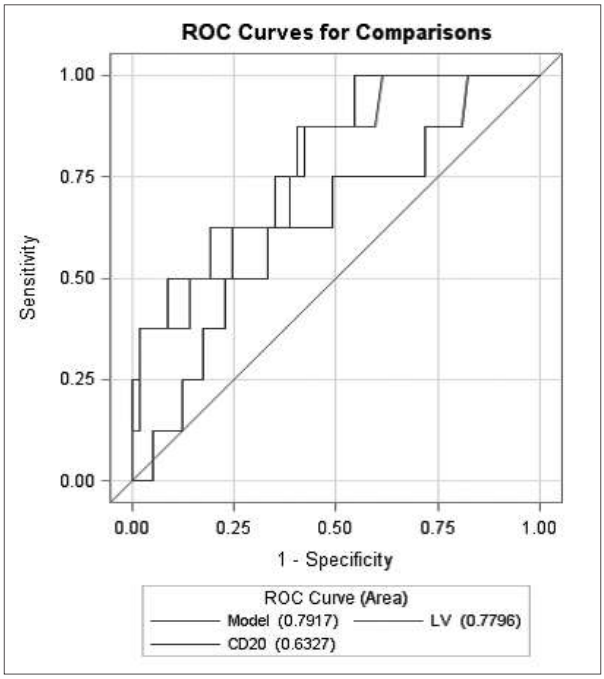
Background: Defective apoptosis and clearance of postapoptotic cell debris are much discussed etiological factors in systemic lupus erythematosus. Whereas the mechanisms of defective apoptosis are not known, lymphatic vessels have been shown to play a role in exit routes in many physiological and pathological conditions. The objective of this study was therefore to analyze lymphatic vessels in lupus nephritis (LN) and their pathophysiological and clinical significance.
Methods: Sixty seven renal biopsies from patients with LN and 13 from healthy allograft donors as controls were used. The slides were immunohistochemically stained for D2-40, CD20, CD3 and CD68. Analysis of lymphatic vessels and cellular infiltrates was performed by using a rigorous morphometric with a computer assisted stereological system.





Results: The mean LV length density in LN was significantly higher than in control biopsies (14.1 mm^{-2} vs 0.56 mm^{-2}, p <0.001). The LV length density was comparable among all histological classes of LN (p <0.73). Logistic regression analysis identified a statistically significant correlation between high proteinuria (≥500 mg/mmol creatinine) and LV length density (OR 0.83; 95% CI, 0.70 to 0.98; p <0.035). The mean follow up time was 150.92 months. A total of 8 patients (12%) developed ESRD. Logistic regression analysis revealed that LV length density (p<0.01) and the volume fraction of CD20 (p <0.05) both predicted ESRD.
Conclusions: This study is the first to show neo-lymphangiogenesis in LN, based on the analysis of a representative number of patients and a long follow-up time. Higher LV density did not correlate with fibrosis but with high proteinuria, and was predictive of worse renal prognosis.

P 08

Contrast-enhanced Ultrasound (CEUS) of the kidney – a prospective evaluation of its value in the detection and risk stratification of pyelonephritis

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Background: Contrast-enhanced ultrasound (CEUS) has been described as a promising method for detecting acute pyelonephritis and its complications. Here we evaluated its value in diagnosis and risk stratification in the setting of a randomized controlled trial (RCT).
Methods: Immunocompetent adults with community-acquired urinary tract infection (UTI) were enrolled in the emergency department of the Kantonsspital Aarau. Decisions about initiation and duration of antibiotic therapy and about site of care were made according to biomarker-assisted algorithms or current guidelines (Drozdov et al. Trials 2013). Outcomes included antibiotic exposure, duration of therapy, persistent infections and recurrences/rehospitalizations.
In a prespecified substudy all hospitalized UTI patients with fever and/or flank pain were scheduled to undergo CEUS in addition to gray-scale and Doppler ultrasound of both kidneys within 72h after admission, looking for signs of pyelonephritis (PN), such as triangular hypoechogenic hyoperfused areas in the medulla.
Results: Of 70 UTI study patients hospitalized with fever and/or flank pain, 41 (59%) underwent the ultrasound study. Dropout reasons included missing consent (5), early discharge (6) or technical (18). Examined and non-examined patients did not differ significantly in baseline characteristics or outcomes. Findings suggestive of PN were found in 5/41 (12%). In 3 patients, this was evident in greyscale/Doppler already, in 2 additional patients, critical findings were only present in CEUS. Thus, the detection rate for PN findings was almost doubled by CEUS (12% versus 7%). Presence or absence of

sonographic signs for PN was not associated with any specific baseline characteristic or outcome.
Conclusions: Ultrasound evidence of pyelonephritis is rare in patients hospitalized for UTI with fever or flank pain. The addition of CEUS to the early ultrasound exam may substantially increase the number of positive findings.

P 09

Postpartum anuric renal failure in a Jehovah's witness with catastrophic antiphospholipid syndrome

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The differential diagnosis of postpartum acute renal failure includes severe preeclampsia, thrombo-tic microangiopathy, anti-phospholipid syndrome and acute tubular injury due to sepsis. We descri-be a patient with a dramatic presentation whose management was complicated by her religious beliefs.
A 25-year-old healthy primigravida presented at 324/7 weeks' gestation with preeclampsia. Ten days previously she had developed generalized edema and on admission her blood pressure was 150/92 mm Hg. The creatinine was 67 umol/l, thrombocytes, liver enzymes and LDH were normal. Urinanalysis revealed nephrotic-range proteinuria. Lung maturation was induced and a cesarean section performed on day 3. The 1620 g neonate needed oxygen therapy but was otherwise healthy. On day 5 the patient's condition worsened rapidly with tachycardia, tachypnea, acrocya-nosis and livedo reticularis. She became icteric, anuric and her concious level worsened. Within 24h her platelet count fell to 22 giga/l with DIC and activation of fibrinolysis (d-dimers >120 000 ng/ml). Scant fragmentocytes were identified. The creatinine rose rapidly until hemodiafilt-ration was started on day 7. LDH increased to 5345 U/l with moderately elevated liver enzymes and direct hyperbilirubinemia (263 umol/l). CRP increased to 329 mg/l and Klebsiella oxytoca was identi-fied in one blood culture. Severe thrombocytopenia (<20 giga/l) persisted for 4 days with a purpuric rash and bleeding from IV-lines, large bullae appeared on both legs. Hemoglobin decreased to a nadir of 66 g/l. Transfusions of erythrocytes and platelets were repeatedly refused. TTP/HUS was ruled out due to preserved ADAMTS 13 activity. An anti-beta 2-glycoprotein IgG-titer of 72 U/l (normal range <17.7 U/l) led instead to the diagnosis of catastrophic antiphospholipid syndrome. Treatment with IV methylprednisolone and IVIG was performed. A skin biopsy was consistent with the diagnosis, showing diffuse fibrin thrombi in dermal capillaries. The patient's condition improved rapidly and she was discharged on phenprocoumon and prednisolone on day 23. One week later her creatinine was 92umol/l and the skin lesions were slowly healing.

P 10

Long-term renal outcome in lithium-treated patients: experience of a single swiss centre

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Background: Lithium salts are widely used in the treatment of bipolar disorders and may result in various side effects such as nephrogenic diabetes insipidus and nephrotoxicity. Lithium–induced nephropathy is a well-established complication occuring after several years of lithium exposure and accounts for 0.2% of the dialysis population. The underlying histological pattern is consistent with a tubulo-interstitial disease, Although only a small percentage of patients reach end-stage renal disease (ESRD), the outcome is variable among patients. The aim of this retrospective study was to analyse the progression of the nephropathy in relationship to lithium exposure time and to concomitant renal disorders in our nephrology centre.
Methods: Clinical and laboratory data of all patients attending our outpatient clinic and treated with lithium salts were reviewed.
Results: Overall we identified 6 caucasian patients treated with lithium (4 male and 2 female), aged 71 + 7.5 (SD) yrs (range 60–83). The mean duration of lithium therapy for bipolar disorder was 20.2 + 11.4 yrs (SD), range (3–34). Serum lithium was kept in therapeutic range, but 3 (50%) patients developed an episode of acute lithium toxicity. Overall, 3/6 (50%) of the patients exposed to lithium salts developed stage G5A2-A3 renal disease. Among 4 patient with treatment time >20 yrs, 2 developed ESRD. One patient with a pre-existing nephroangioslerosis and short term-treatment developed stage G5A3 nephropathy after only 3 yrs of lithium exposure.
Conclusion: Long-term treatment with lithium salts may favour the development of ESRD. However, short term exposure to lithium may accelerate the course of an underlying nephropathy. Careful assessment of potential renal disease should be performed before initiation of lithium therapy. Close monitoring is mandatory for long-term lithium-treated patients.

P 11

Wunderlich syndrome in a chronic kidney disease patient on hemodialysis: a case report

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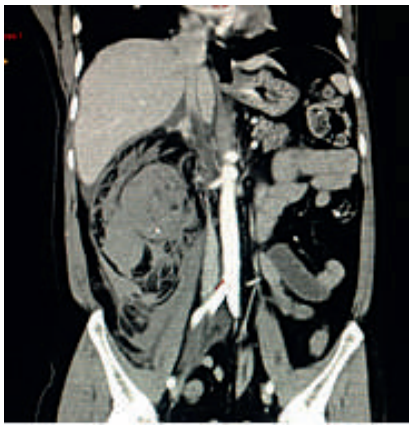
Background: We report a case of a man who presented with sudden onset of right upper quadrant pain, who upon being subjected to a Computed Tomography (CT) scan of the whole abdomen with contrast, revealed a large hematoma on the right kidney.
Case presentation: A 46 year old male, Filipino, a known case of Chronic Kidney Disease (CKD) Stage V, maintained on renal replacement therapy, presented with sudden onset of right upper quadrant pain. Aside from a previous history of urinary tract infection, he had no history of renal trauma, urolithiasis, recent percutaneous instrumentation, hematologic disorders and was not taking any anti-platelet medications. CT Scan of the whole abdomen with iodinated contrast revealed a large right renal capsular, para-renal and right para-psoas retroperitoneal hematoma accumulation. He underwent nephrectomy of the right kidney, which stopped the bleeding and relieved his symptoms.
Conclusion: Wunderlich Syndrome (WS) is a rare condition in which spontaneous renal hemorrhage occurs into the subcapsular and perirenal spaces. The most frequently associated etiologies include renal tumors, vascular lesions and renal infection. Management is mainly expectant, although endovascular or surgical interventions may be required in cases of massive hemmorhage or persistent hemodynamic instabilility.



P 12

Effect of enzyme replacement therapy on fabry nephropathy progression

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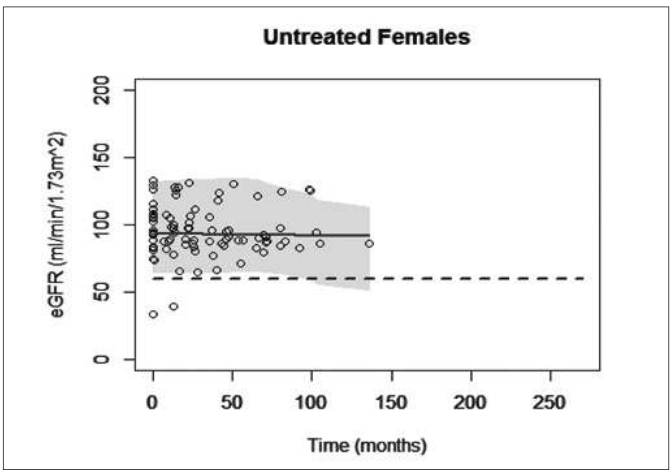
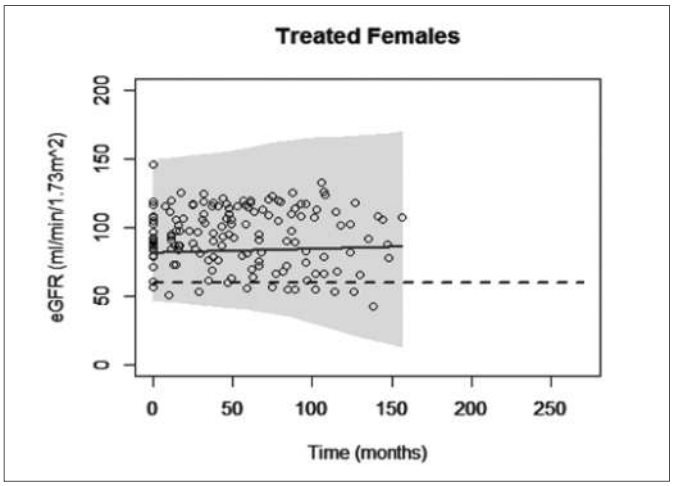
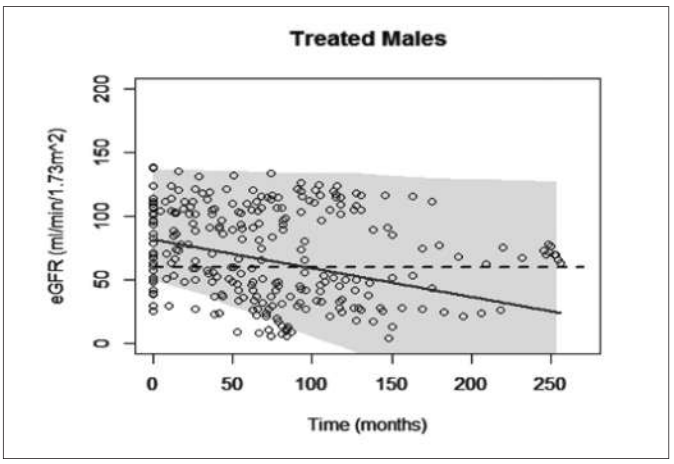
Background: Fabry disease (FD) is a rare inherited lysosomal storage disease with common and serious kidney complications. Enzyme replacement therapies (ERT) with agalsidase-α and -β were investigated to determine their therapeutic effect on renal function in a prospective cohort of FD patients.

Methods: In total, 84 FD patients (median baseline age 36 years, median follow-up time 7.2 years) not on renal replacement therapy and with more than 1 creatinine measurement were included into the dynamical analysis. Data of 49 females (25 on ERT) and 35 males (31 on ERT) were included.
A model, first to characterize the time course of estimated glomerular filtration rate (eGFR) and second, to investigate the therapeutic effect of ERT on kidney function, was developed.
Results: Change of eGFR over time was best described by the linear model eGFR(t)=eGFR (base)+eGFR (slope)·t where eGFR (base) is the eGFR baseline value and eGFR (slope) the slope.
Female patients without ERT had an eGFR slope of –0.17 ml/min/1.73 m^2 (fig. 1); with ERT a slope of 0.35 ml/min/1.73 m^2 (fig. 2) per year. Individual slopes in untreated and treated female patients did not differ. Male patients with ERT showed an eGFR slope of –2.7 ml/min/1.73 m^2 (fig. 3) per year.







No difference in treatment effect between agalsidase-α and -β was found; there was no significant effect on individual eGFR slope.
Conclusions: No significant effect of ERT on the kidney function in female patients was found. The decline of kidney function in treated male FD patients seems faster than in published data in normal population. Further investigations need to clarify, wither earlier ERT treatment and/or higher doses of ERT can preserve kidney function in FD patients.

P 13

Effect of acute hyperglycemia on renal tissue oxygenation as measured with BOLD-MRI in overweight individuals and persons with impaired glucose tolerance

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Background: Diabetic nephropathy affects 30% of diabetics, and its development has been linked to poor glycemic control. Animal studies have suggested that hyperglycemia induces transient renal hypoxia and thus kidney damage, yet this has not been previously tested in humans. In this interventional study we assessed the effect of hyperglycemia on renal tissue oxygenation as measured with blood oxygenation level-dependent MRI (BOLD-MRI).
Methods: Nineteen healthy overweight volunteers (age 37 ± 10 years, BMI 28.9 ± 3 kg/m², HbA1c 5.4 ± 0.3%, 57.9% women) were recruited and underwent an oral glucose tolerance test. Two had impaired glucose tolerance, none had diabetes. On a separate day, BOLD-IRM was performed under standard hydration conditions before, and after the intravenous administration of 0.15 g/kg of glucose in a 20% solution. R2* maps were analyzed using the concentric objects technique, a semi automatic procedure which divides the kidney parenchyma in twelve equal layers at increasing depth. R2* is a measure of local desoxyhemoglobin concentrations, with high R2* values corresponding to low oxygenation.
Results: The mean glycemia rose from 4.5 ± 0.3 mmol/l to 9.0 ± 0.9, 8.9 ± 0.7, 7.7 ± 0.6 and 6.8 ± 0.8 mmol/l respectively 1, 10, 20 and 30 minutes after IV glucose administration, whereas circulating insulin levels increased. The corresponding mean R2* values decreased significantly in all kidney layers (see fig.), irrespective of glucose intolerance suggesting an improvement of renal oxygenation.
Conclusion: These findings indicate that glycemia influences the R2* signal and should be measured before each BOLD-MRI. Hyperglycemia lead to an increase, not a decrease, of renal tissue oxygenation as measured with BOLD-MRI in healthy, obese volunteers. Whether this glucose-induced increase in oxygenation is due to alterations in renal perfusion or a decrease in oxygen consumption due for example to an acute osmotic diuresis or both, and whether this also occurs in patients with diabetes needs further study.

P 14

Metabolic acidosis stimulates calcium and magnesium excretion via OGR1

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Background: Hypercalciuria is a common feature of patients facing metabolic acidosis. However, the sensing mechanisms responsible for the decreased calcium reabsorption during acidosis are still unknown. Knockout mice for the Ovarian cancer G-protein coupled receptor 1 (OGR1) are resistant to develop the acid-induced hypercalcuria and hypermagnesuria. This work aimed to identify which calcium reabsorption pathways are insensitive to the normal response to chronic metabolic acidosis in an OGR1-deficient mouse model.
Methods: Wild type (OGR1+/+) and an OGR1-deficient mouse model (OGR1–/–) were subjected to metabolic acidosis (2% NH4Cl in food) or non-acidotic control condition for 1 and 7 days and basic physiological parameters were collected from blood and urine. Several organs were isolated such as kidneys, intestine, brain, heart, etc. in order to extract RNA and perform RT-PCR/real time PCR. Kidneys were also used for protein extraction/western blotting.

Results: OGR1 mRNA was found in many organs such as kidney, spleen, brain and lungs. No acid-base modifications were observed in OGR1–/– mice, except for a higher plasma pH in the 1 day metabolic acidosis group (7.20 ± 0.04 vs 7.12 ± 0.03, p <0.05). As was expected, metabolic acidosis caused an increase in calcium and magnesium excretion in OGR1+/+, but this was not observed in OGR1–/–. The mRNA levels of proteins involved in Ca2+ and Mg2+ reabsorption like Calbindin-D28k, TRPV5/6, TRPM6/7 and Claudins 16 and 19 were not altered in OGR1–/–. The expression levels of the key proteins for calcium reabsorption in the distal convoluted tubule (DCT), TRPV5, Calbindin-D28k and NCX1 were respectively increased by 2.4, 2.0 and 3.5 fold in OGR1–/– under metabolic acidosis. This may explain the lower calcium excretion in these mice.
Conclusion: OGR1 is involved in the hypermagnesuria and hypercalciuria developed during metabolic acidosis, by a mechanism that may involve the transcellular reabsorption pathway of calcium in the DCT.

P 15

Acute tubular necrosis – a rare side effect of dabigatran?

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Background: Dabigatran is a direct thrombin inhibitor approveded for the risk reduction of arterial thromboembolism due to non-valvular artrial fibrillation. Yet- Dabigatran is not known to cause interstitial nephritis.
Case: (instead of Methods and Results): We report a case of an 83 year old women with a chronically moderate renal impairment (eGFR (CKD-EPI) 40–45 ml/min) who developed unexplained rapid decline in renal function 8 weeks after starting dabigatran (eGFR (CKD-EPI) 13 ml/min). The only other drug she was on was lisinopril (for several years). Urine analysis showed mild glomerular hematuria and proteinuria (600 mg/d). Renal biopsy showed in addition to a nonproliferatively chronic IgA nephropathy an acute interstitial nephritis. Dabigatran was stopped and replaced by phenprocouman, lisinopril was paused (for 4 weeks) and a prednisolone therapy was started (0.5 mg/kg bodyweight, tapered off over 3 months). Kidney function improved and reached an eGFR of 32 ml/min after three months of prednisolone therapy and afterwards remained stable. Because in the literature there is no relation known between interstitial nephropathy and dabigatran the Swiss pharmacovigilance was informed.
Conclusions: In view of this course, absence of another new drug, without any histopathological signs of proliferation of the chronic IgA nephritis and without signs of infection or autoimmune disease a dabigatran caused acute interstitial nephritis leading to kidney failure remains possible.

P 16

A case of membranoproliferative glomerulonephritis associated with hypocompementemic urticarial vasculitis in Fribourg Switzerland

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Hypocomplementemic urticarial vasculitis (HUV) is often associated with systemic diseases (SD) as same as lupus erythematous, primary Sjögren syndrome ,myeloma and other hematologic disorders, drug hypersensitivity. Without SD , HUV is so idiopathic and represent a rare auto immune disorder called HUV syndrome or McDuffie syndrome. To better define this clinicopathology entity, Schwartz et al. proposed criteria including 2 major criteria (chronic urticarial exanthema and hypocomplementemia) associated with at least 2 minor criteria (leukocytoclastic vasculitis, arthralgia an arthritis, uveitis or episcleritis or conjunctivitis, glomerulonephritis, abdominal pain , positive C1q antibody).
Renal injury associated with HUVS has not been well studied and the gold standard strategy for treating HUV has yet to be defined. We report a case of membranoproliferaitve glomerulonephritis associated with HUVS.

P 17

Type 2 primary hyperoxaluria – an unusual cause of nephrolithiasis and renal failure

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Background: Primary hyperoxaluria (PH) is a rare cause of nephrolithiasis and nephrocalcinosis. PH type 1, the most common form, is caused by mutations in the AGXT gene which encodes alanine-glyoxylate aminotransferase. Early terminal renal failure is common in these patients. PH type 2, due to mutations in the GRHPR gene (encoding glyoxylate reductase/hydroxypyruvate reductase), accounts for only 10% of primary hyperoxaluria. Renal outcomes are thought to be much better.
We present a case of PH type 2 found in a patient with nephrolithiasis and CKD4.
Case report: The 56 year old patient was sent to our clinic for evaluation of declining kidney function. He had had recurrent nephrolithiasis since the age of 15. Because of chronic pyelonephritis his then nonfunctioning left kidney had been removed at 45 y. Evaluation by different nephrologists had shown markedly elevated levels of urinary oxalate excretion (>1500 umol/d) with normal glycolate levels. Measurement of L-glycerate had not been done and was unavailable to us. Since nephrectomy, his kidney function had deteriorated at a rate of 3–6 ml/min/1.73 m^2 per year. At a current GFR of 18 ml/min/1.73 m^2 his plasma oxalate levels were stable at around 17 umol/l. Ultrasound of his right kidney showed multiple twinkling artifacts adjacent to the pyramids suggestive of small stones without clear signs of nephrocalcinosis.
Two of his four older siblings had suffered from renal stones before age 20. None allegedly showed impairment of kidney function.
Sanger Sequencing of the AGXT gene was unremarkable, but a well described homozygous frameshift mutation (c.103delG) was found in the GRHPR gene, leading to a protein chain termination at position 35 (p.Asp35Thrfs*11).
This confirmed the diagnosis of a primary hyperoxaluria type 2.
Conclusion: Sequence analysis made the diagnosis of this very rare syndrome possible. Due to his rapidly deteriorating kidney function our main concern now is the prevention of systemic oxalosis.

P 18

A case of unusual discoloration of urine

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Case report: A 75 year-old male patient was admitted in the geriatric ward for a decline of his general condition. His medical history includes type 2 diabetes, hypertension and a stroke in 2011. He suffers from urinary incontinence of unclear origin for which an indwelling urinary catheter was placed in 2013. His urinary tract is colonized with an

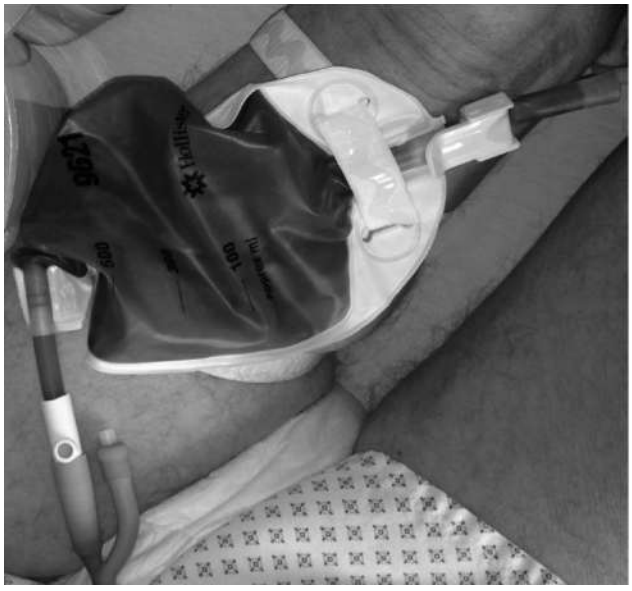

Figure 1: Purple discoloration of the urinary bag and catheter.

ESBL Klebsiella pneumoniae. During his hospitalization, his urine color turned purple (fig. 1). The patient declared no other new symptoms and there was no relevant physical finding. Blood tests revealed no leukocytosis or inflammatory syndrome and renal function was unchanged. Urinary analysis showed the following: non-measurable pH due to the urine color, leukocytes 10/µl, non-glomerular erythrocytes 20/µl, bacteria 3+, and struvite crystals 2+. Urine culture came back positive for Citrobacter koseri and Klebsellia pneumoniae.
Diagnosis: A purple urinary bag syndrome (PUBS) with a urinary tract infection was diagnosed. The urinary catheter was removed. No antibiotherapy was introduced and the urine color rapidly normalized.
Discussion: PUBS is a rare presentation of urinary tract infection associated with urinary tract catheterization that is more frequently observed in female elderly patients. Purple discoloration of the urine is due to metabolic end-products of the amino acid tryptophan eventually leading to the breakdown of indoxyl into indigo and indirubin, appearing blue and red, respectively, by bacterial enzymes catalyzed in alkaline urine (fig. 2). Such enzymes are found in Klebsiella, Citrobacter, some Enterobacter, Morganella, Proteus, Providencia and Pseudomas species.
Conclusion: PUBS is a rare entity but its prevalence is probably underestimated. Most patients are asymptomatic and have a benign course. There is no specific treatment other than removing the urinary catheter and antibiotics are not primarily recommended. This case illustrates the importance of regularly questioning the indication and management of long-term urinary catheter, particularly in frail patients.

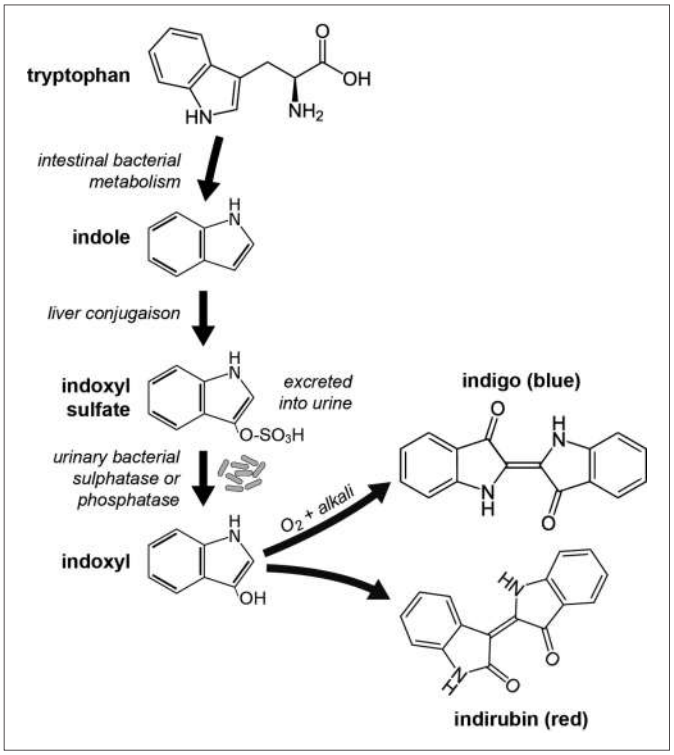

Figure 2: Tryptophan metabolism into indigo and indirubin.

P 19

Recurrent catastrophic antiphospholipid syndrome treated with eculizumab in a peritoneal dialysis patient

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Background: Catastrophic Antiphospholipid Syndrome (CAPS) is a severe variant of Antiphospholipid Syndrome (APS), a systemic autoimmune disease characterized by multiple arterial and/or venous thromboses in presence of elevated titers of antiphospholipid antibodies (aPL). These autoantibodies, promote thrombosis by activating endothelial cells and platelets.
We describe a case of clinical remission in recurrent CAPS via inhibition of terminal complement with Eculizumab in a Peritoneal Dialysis (PD) patient.
Case report: A 48-year-old man has shown recurrent CAPS characterized by diffuse arterial thromboses in the heart, kidneys, liver and lungs, confirmed by positivity of aPL. Angiography revealed a bilateral subclavian arterial thrombosis, a right iliac arterial stenosis that was treated with a stent and a left renal arterial occlusion. The patient's renal function decreased until ESRD, secondary to chronic thrombotic microangiopathy. We decided to start peritoneal dialysis, because it was impossible to obtain a vascular access. During 14 months, our patient presented 8 recurrent episodes of disease with pulmonary involvement characterized by multiple alveolar hemorrhages in concomitance with liver necrosis (biopsy proven) and miocardial ischemia.
The patient was treated with high-dose pulse corticosteroids (methylprednisolone 500 mg/day for 3 days) followed by prednisone (1 mg/Kg/day), plasma exchange (5 series with a total of 74 sessions), IV immunoglobulin (400 mg/Kg/day for 5 days), IV Rituximab (initial therapy and maintenance after 6 months), clopidogrel, aspirin and anticoagulation. Despite this standard therapy, we did not observe a sustained remission.
After a review of the literature, we decided to administer Eculizumab, a monoclonal antibody against complement C5, that blocks and prevents the generation of the prothrombotic and proinflammatory molecules C5a and membrane attack complex C5b-9.
Conclusions: Eculizumab induced sustained remission in refractory CAPS for 1 year of follow-up. Peritoneal capillary, probably, were not involved by thrombotic microangiopathy. PD allowed a satisfactory Kt/V and fluid balance.

P 20

The V-ATPase B1 subunit polymorphism p.E161K is associated with impaired urinary acidification in recurrent stone formers

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Background: Mutations in the V-ATPase B1 subunit gene ATP6V1B1 cause autosomal-recessive distal renal tubular acidosis (dRTA). We previously identified a single nucleotide polymorphism (SNP) in the human B1 subunit (c.481G>A; p.E161K) that displayed greatly diminished pump function in vitro.
Methods: To investigate the impact of this SNP on urinary acidification, we conducted a genotype-phenotype analysis of recurrent stone formers in the Dallas and Bern kidney stone registries.
Results: 32 of 555 (5.8 %) of the patients examined were heterozygous for the p.E161K SNP, the remaining 523 patients (94.2%) carried two wild-type alleles. Adjusted for sex, age, BMI and dietary acid and alkali intake, p.E161K SNP carriers had a tendency to higher urinary pH on a random diet (6.31 versus 6.09; p = 0.089). Under an instructed low calcium and sodium diet, urinary pH was higher in p.E161K SNP carriers (6.555 versus 6.005; p <0.005). Kidney stones of p.E161K carriers were more likely to contain calcium phosphate than stones of wild-type patients. In acute ammonium chloride loading, p.E161K carriers displayed a higher trough urinary pH (5.34 vs 4.89; p = 0.01) than wild-type patients. 14.58 % of wild-type patients and 52.38% of p.E161K carriers were unable to acidify their urine below 5.3 and thus can be considered to have incomplete distal renal tubular acidosis.
Conclusions: Our data indicate that recurrent stone formers with the V-ATPase B1 subunit p.E161K SNP exhibit a urinary acidification deficit with an increased prevalence of calcium phosphate containing kidney stones. The burden of E161K heterozygosity may be a forme fruste of distal renal tubular acidosis.

P 21

Polyvinylpyrrolidone storage disease in a drug addicted patient - a lesson from Norway

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Background: A 23 year old man with an 8 year history of i.v. heroin and methadone consumption was referred for renal biopsy because of renal insufficiency. He had no proteinuria or hematuria, was HCV positive, and denied the use of herbal medicines or anabolic steroids.
Methods: Case report. The kidney biopsy was evaluated by light microscopy, immunofluorescence and electron microscopy.
Results: Light microscopy showed peculiar bluish vacuoles in macrophages within glomeruli and the tubulo-interstitium. The material stained with congo red, but was negative in congo red fluorescence and showed no birefringence in polarized light. By electron microscopy, these deposits were empty vacuoles or contained lipid like material and could partly be located to lysosomes. Clinical follow-up, the recognition of more such cases within Norway, and a thorough literature search resulted in the identification of polyvinylpyrrolidone (PVP) as the stored substance. PVP is widely used in oral medications, including oral drugs in the opioid maintenance treatment (OMT) program, to improve dissolution rate and bioavailability. High molecular PVP is not harmful when taken orally. However, some opioid addicted patients inject their OMT medications illicitly. Then high molecular PVP may accumulate in the body resulting in PVP storage disease. This can affect multiple organ systems (e.g., bone marrow, synovia, GI tract, liver).
Conclusion: Paying attention to details matters. Always think of drugs in case of unexplained biopsy findings. As a result of these observations, methadone containing high molecular PVP was withdrawn from the European market.

P 22

Postpartal thrombotic microangiopathy – HELLP or HUS?

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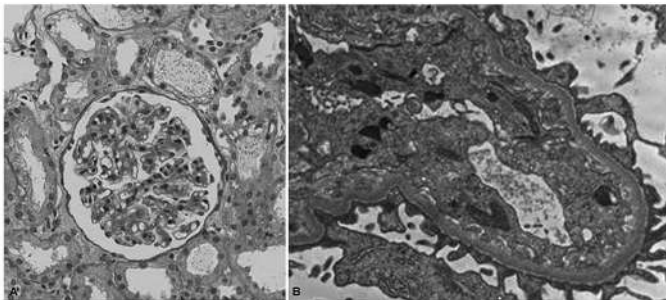
Background: Complications in pregnancy are challenging; diseases and consecutive treatment decisions bear risks for the mother and/or the offspring. Maternal adaptations may in rare cases trigger previously subclinical effects of genetic abnormalities, for example atypical hemolytic uremic syndrome (aHUS). Because of possible devastating consequences of thrombotic microangiopathy (TMA), identification and appropriate treatment of the underlying disease is imperative.
Case presentation: A 31-year-old previously healthy pregnant patient was hospitalized due to new onset edema, hypertension and proteinuria at the end of the third trimester. Because of progressive preeclampsia with uncontrolled hypertension and pathologic reflexes, cesarean section was performed. Despite magnesium sulfate, the patient developed eclampsia and was intubated. Progressive microangiopathic hemolytic anemia (MAHA) and elevation of liver enzymes occurred. Direct Coombs Test was negative and schistocytes were detected in the blood smear. HELLP-syndrome was diagnosed. Because of progressive acute kidney injury (AKI) in the context of TMA, kidney biopsy was performed.
Results: Biopsy revealed endotheliosis and acute tubular injury, without evidence of fibrin thrombi. Due to the histological diagnosis of endotheliosis, treatment with plasma exchange was not considered necessary. Further course during hospitalization was favorable. The patient recovered from HELLP-syndrome after giving birth to a healthy child. One month after dismissal kidney function recovered completely.
Conclusions: HELLP is a consequence of maternal immune maladaptation to the invading trophoblast leading to abnormal placentation. Anti-angiogenic factors induce endothelial dysfunction with consecutive hypertension and glomerular endotheliosis. Activation of the endothelium leads to MAHA. TMA and circulating hepatotoxic factors cause hepatocyte necrosis. In combination with underlying genetic defects pregnancy can trigger uncontrolled complement activation and result in severe organ damage.
In the case of advanced AKI in combination with HELLP, kidney biopsy is essential to differentiate secondary from atypical HUS and avoid unnecessary plasma exchange.

Table 1: Laboratory examinations (*cesarean section).

	normal	Admission	Day 4*	Day 5	Day 10
Hemoglobin, g/dl	12 – 15.4	12.5	11.4	8.6	7.4
Thrombocytes, 10^9/l	150 - 370	215	182	32	90
Creatinine, µmol/l	45 - 84	53	55	181	473
GPT/ALAT, IU/l	< 33	7	33	314	29
LDH, IU/l	< 214	216	295	2361	353
Total Bilirubin, µmol/l	< 21	4		292	188
Uric acid, µmol/l	143 - 339	350			
Complement C_3, g/l	0.9 – 1.8				0.86
Fibrinogen, mg/dl	150 - 450		257		
INR	0.85 – 1.15	0.84	1.20	1.08	
Urine protein	*negative*	*(+)*	*++*		*+*
Urine erythrocytes, cell/VF	*< 5*	*0 - 2*	*0 - 2*		*3 - 10*

Figure 1: Kidney biopsy.



A) Light microscopy: Glomerulus with swollen endothelial cells and mildly corrugated basement membrane. Acute tubular injury. (PAS, original magnification ×20). B) Electron microscopy: Glomerular capillary loop with swollen endothelial cells (TEM, original magnification ×3000).

P 23

Successful management of severe hypernatraemia, rhabdomyolysis and acute kidney injury (aki) with hyper-osmolar dialysate solutions in continuous renal replacement therapy (crrt)

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Background: Severe hypernatraemia causes hyperosmolarity and cellular dehydration. Rhabdomyolysis is characterized by muscle necrosis and leakage of muscle constituents into the plasma and it may lead to AKI.
Case report: A 69-year-old woman was admitted to the hospital for hypernatraemia combined with rhabdomyolysis and AKI. Initially for hydration and to correct slowly hypernatraemia, 0.9% sodium chloride was given intravenously. The serum sodium level

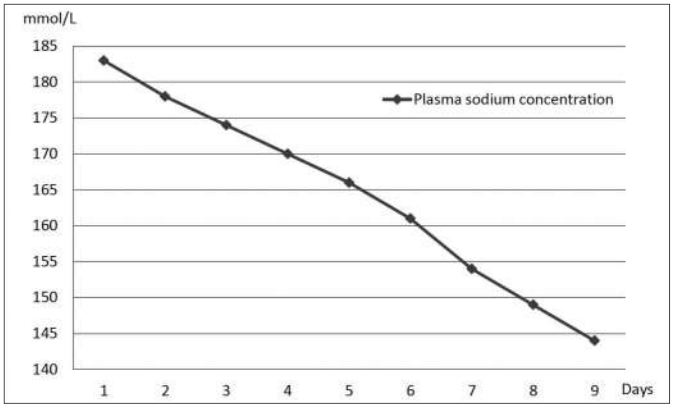

Figure: Plasma sodium concentration during CVVHD in the time.

increased from 179 mmol/L to 183 mmol/L in the first 12h. The patient was oliguric at admission and progressed up to anuria.
To gradually correct serum sodium concentration, we decided to start CRRT, choosing a diffusive therapy (CVVHD) with an high cut-off filter. A commercial solution for CVVHD, with sodium concentration [Na] of 140 mmol/L was adjusted by adding 11.7% NaCl. We obtained a [Na] of 178 mmol/L in the dialysate solution. During the first 48h we performed CVVHD sessions for 8h daily in order to gradually reduce blood osmolality. Serum sodium level decreased from 183 mmol/L to 176 mmol/L after 24h. Successively, we extended the time of CRRT and we adjusted dialysate [Na] with a 4 mmol/L targeted reduction of serum [Na] every 12h. This resulted in progressive and slow correction of hypernatraemia 9 days later (figure), according to current standard recommendations, without neurological sequelae.
Conclusions: CRRT can be considered a feasible strategy for treatment of severe hypernatraemia associated to AKI. In our case, the choice of CVVHD as treatment modality has been also due to the objective of reducing albumin loss which is related to higher mortality risk in intensive care patients. According to other recent reports, this treatment solution can be efficient also in rhabdomiolysis. CVVHD with high cut-off membrane can be a successful therapeutic compromise between myoglobin removal, albumin loss and diffusive correction of hypernatraemia.

P 24

Uromodulin modulates the effect of salt on blood pressure in the general population

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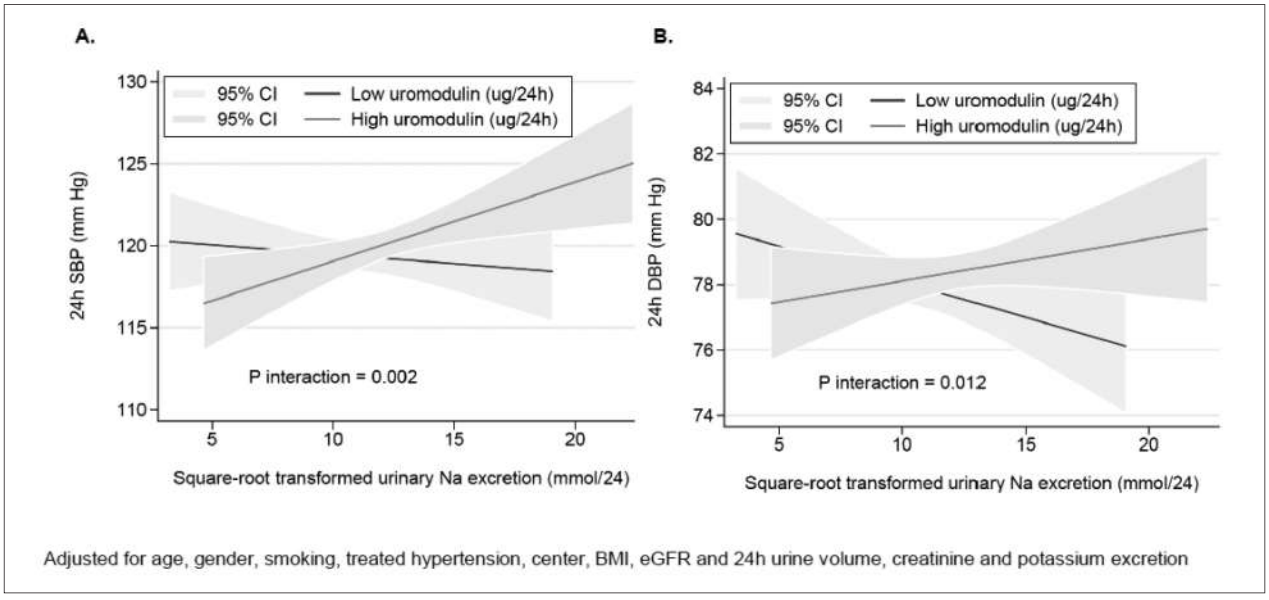
Background: Genome wide association studies have shown that the gene encoding for uromodulin (UMOD) is associated with hypertension. Recently, animal studies have demonstrated that UMOD modulates NaCl reabsorption driven by NKCC2. We hypothesised that the NaCl effect on blood pressure may be modulated by UMOD levels in the general population.

Methods: Urinary UMOD levels were measured in 994 participants of the SKIPOGH population-based study who completed 24h blood pressure monitoring and 24h urinary collection. We used mixed linear regression models to determine the association between 24h sodium excretion and systolic (SBP) or diastolic (DBP) blood pressure. Age, gender, smoking, treated hypertension, center, BMI, eGFR and 24h urine variables (volume, creatinine, potassium) were entered as covariates in the models. There was an interaction between sodium and UMOD excretion for SBP (p = 0.002) and DBP (p = 0.012), we divided UMOD levels into low or high according to the median and stratified the analyses by UMOD groups.
Results: Participants mean age was 47.5 ± 17.5 years; 51.8% were women. The mean 24h SBP and DBP were 119.9 ± 13.9 and 78.2 ± 8.7 mm Hg. Median 24h sodium excretion was 136.0 mmol (IQR 100.4–177.5) and median UMOD 40.1 mg (IQR 28.0–56.2). In multivariate analysis, sodium excretion was not associated with SBP in the lower UMOD group [n = 495; coef –0.21 (95%CI –0.74 to 0.32), p = 0.44] but was strongly associated in the higher one [n = 499; coef 0.87 (95%CI 0.36 to 1.38), p = 0.001]. Regarding DBP, we observed no significant association in the higher UMOD group [coef 0.21 (95%CI –0.10 to 0.51), p = 0.19] although there was an inverse one in the lower group [coef –0.39 (95%CI –0.73 to –0.04), p = 0.027].
Conclusion: These data show that the association of NaCl with blood pressure is modified by urinary UMOD levels. This is consistent with animal studies demonstrating that UMOD modulates NKCC2 activity and sodium reabsorption by the renal tubule.

Figures: Association between 24h sodium excretion and 24h mean SBP (A) and DBP (B) according to UMOD group.



P 25

C-terminal fragment of agrin (CAF) predicts acute kidney injury and long term mortality after acute myocardial infarction – A cohort study

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Background: Acute kidney injury (AKI) occurs frequently after acute myocardial infarction (AMI) and contributes to increased mortality and morbidity, while available renal biomarkers have considerable limitations in AKI prediction. We explored the predictive value of pre-interventional plasma and urine levels of C-terminal agrin fragment (CAF) as a novel AKI biomarker after AMI.
Methods: Plasma and urinary samples from 436 adults with AMI and without previous renal disease were obtained at admission. Levels of CAF, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18) and cystatin-C were measured. The incidence of AKI was assessed by AKIN, RIFLE and KDIGO criteria during hospitalization, while all-cause mortality was assessed after 2 years.
Results: The incidence of AKI was 6.7–14.6% depending on criteria used and increased across quartiles of urine CAF (uCAF) (x2:10.99, p <0.001). Both uCAF and plasma CAF (pCAF) correlated strongly with plasma creatinine at all time-points (baseline: r = 0.233, p <0.001; r = 0.175, p<0.001 / at 48h: r = 0.263, p <0.001; r = 0.226, p <0.001), as well as with plasma and urine concentrations of cystatin-C (r = 0.267, p <0.001; r = 0.292, p <0.001). The predictive accuracy for AKI of uCAF was good (AUC:0.630, 95%CI:0.552–0.708) and better compared to urine NGAL (AUC:0.616, 95%CI:0.540–0.692), whereas that of pCAF was moderate (AUC:0.587, 95%CI:0.509–0.666). ROC analysis suggested a uCAF cut-off value of 1044pM for AKI prediction with 37% (95%CI:25–51) sensitivity and 85% (95%CI:81–89) specificity (table 1). Univariate and multivariate logistic regression showed an independent association of uCAF with AKI (OR:1.45, 95%CI:1.15–1.82, p = 0.002 and OR:1.35, 95%CI:1.05–1.74, p = 0.001) and of pCAF with mortality (OR:4.1, 95%CI:1.7–9.7; p = 0.001 and OR:2.5, 95%CI:1.02–6.2; p = 0.044).
Conclusions: CAF strongly correlates with established renal biomarkers and accurately identifies patients who develop AKI after AMI. Furthermore, elevated plasma CAF at admission is associated with 2-year all-cause mortality after AMI. Thus CAF could serve as a novel prognostic and diagnostic biomarker in AKI.

Table 1: Discriminating ability for acute kidney injury of CAF and other biomarkers.

	AUC	95% CI	P value	Sensitivity	Specificity	PPV	NPV
Urine							
IL-18	0.538	0.450-0.626	0.35				
NGAL	0.616	0.540-0.692	0.004	75	45	19	91
Cystatin-C	0.573	0.489-0.657	0.07				
CAF	0.630	0.552-0.708	0.001	37	85	30	89
Plasma							
IL-18	0.530	0.440-0.619	0.47				
NGAL	0.522	0.438-0.606	0.6				
Cystatin-C	0.571	0.492-0.650	0.08				
CAF	0.587	0.509-0.666	0.03	71	47	19	90

AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value

P 26

C-terminal fragment of agrin (CAF) is associated with GFR and proteinuria and predicts progression of kidney disease in type 2 diabetics

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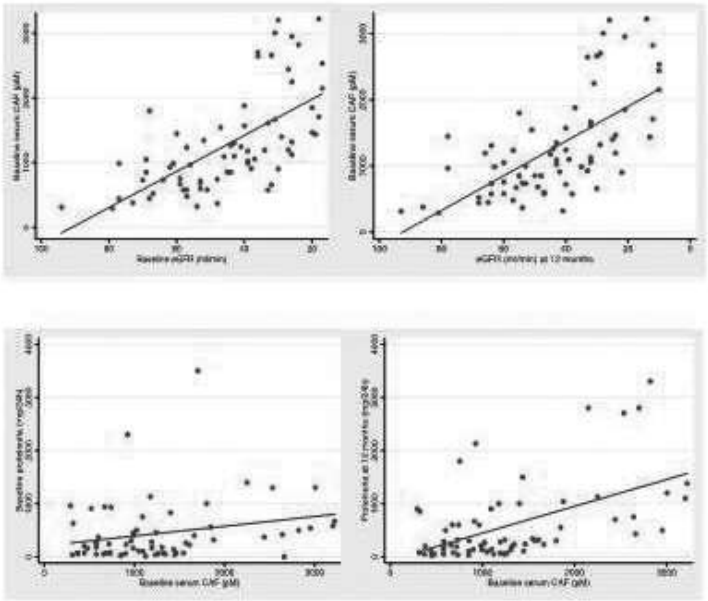
Background: Diabetes is the leading cause of chronic kidney disease (CKD) in the industrialized world. We and others have shown that C-terminal fragment of agrin (CAF) is a novel kidney function and injury biomarker. Here we investigated whether serum CAF predicts progression of kidney disease in type 2 diabetics.
Methods: Serum CAF levels were measured in 71 elderly patients with diabetic nephropathy using a newly developed commercial ELISA kit (Neurotune®). Estimated glomerular filtration rate (eGFR) and proteinuria in spot urine were assessed at baseline and after 12 months follow-up. The presence of end stage renal disease (ESRD) was evaluated after 24 months follow-up. Correlation and logistic

Table 1: Correlation analysis of CAF levels with variables of laboratory and clinical significance and scatterplots of CAF with GFR and proteinuria.

CAF levels (pM)	r	p
Age	,032	0.79
Body Mass Index	,118	0.32
HbA1c	-,098	0.42
Duration of T2DM	,035	0.77
Creatinine T0	,705[b]	<0.001*
Creatinine T1	,644[b]	<0.001*
Estimated GFR T0	-,698[b]	<0.001*
Estimated GFR T1	-,677[b]	<0.001*
Proteinuria T0	,287[a]	0.02*
Proteinuria T1	,449[b]	<0.001*
End Stage Renal Disease	,314	0.008*
Δ-Proteinuria T0-T1	,340	0.004*



Values represent Spearman's correlation coefficients. *Significance at the 0.05 level (2-tailed). Δ-Proteinuria: Increase of proteinuria (≥500 mg/day) during the first year follow-up.

Table 2: Association between GFR-decline with serum CAF and additional clinical regressors.

		GFR decline at 1 year ≥ 1 ml/min		
		OR	CI	P
Model A	CAF levels (log-transformed)	4.18	1.2-14.5	0.024*
	eGFR at baseline	1.03	0.99-1.08	0.102
	Proteinuria at baseline	1.0002	0.99-1.0006	0.299
Model B	CAF levels (log-transformed)	4.09	1.16-14.4	0.028*
	eGFR at baseline	1.03	0.98-1.08	0.161
	Proteinuria at baseline	1.0002	0.99-1-0007	0.342
	Age	0.99	0.93-1.07	0.950
	Body Mass Index	0.96	0.88-1.05	0.438

OR, odds ratio; CI, 95% confidence interval, *significance levels at 0.05

regression analyses were carried out to explore the associations of serum CAF levels with GFR, proteinuria, GFR loss and incident ESRD.
Results: We found a strong association of serum CAF levels with eGFR and a direct association with proteinuria both at baseline ($r = 0.698$, $p < 0.001$ and $r = 0.287$, $p = 0.02$) as well as after 12 months follow-up ($r = 0.677$, $p < 0.001$ and $r = 0.449$, $p < 0.001$), respectively) (table 1). Furthermore, in multivariate analysis, serum CAF levels predicted eGFR decline at 12 months follow-up after adjusting for known risk factors (eGFR, baseline proteinuria) [OR(95%CI) 4.2(1.2–14.5), $p = 0.024$] (table 2).
Conclusions: Serum CAF levels reflect renal function and are highly associated with eGFR and proteinuria at several time points. CAF was able to predict subsequent loss of renal function irrespective of baseline proteinuria in diabetic nephropathy. This finding may open new possibilities for clinical trial design, since CAF may be used as a selection tool to identify high-risk patient with diabetic nephropathy.

P 27

Food intake assessed by food dairy and PRODI6 analysis in Swiss Kidney stone formers: comparison to 24 hour urine excretion. NCCR project

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Kidney stones are highly prevalent in Western countries and are associated with type and quantity of food intake. Food assessments for one given individual are difficult to obtain and rely mainly on analysis of food diaries or food frequency questionnaires. We evaluated the food intake in the Swiss Kidney Stone Cohort and compared it with urine 24h excretion.
We instructed 27 recurrent Swiss stone formers to fill out a 5 days food diary. During the last two days, patients collected 2 × 24h urine. Food diaries were reviewed by a specialized dietician with the patients and then analyzed using PRODI6 software (NutriScience GmbH, Hausach, Germany), allowing micronutriment analysis. We compared protein, sodium, potassium, phosphate, calcium, magnesium and liquid intake with 24h urine excretion of the same metabolites for the same day. Protein was evaluated by 24h urea excretion. Food intake variability was assessed by comparing 1 day food intake to the mean of the 5-day food intake.
We found that food intake assessed by food diary and PRODI6 correlated with 24h urine excretion with R2 coefficient of 0.41 for the liquids, 0.21 for the protein, 0.24 for potassium, 0.13 for sodium, 0.11 for phosphate, 0.17 for calcium and 0.38 for magnesium. Correlations between one day and the mean of the 5-day food diary were: R2 0.76 for the liquid, 0.35 for protein, 0.62 for potassium, 0.33 for sodium, 0.50 for phosphate, 0.49 for calcium and 0.48 for magnesium. Overall, even if some correlation between intake and output was found for liquid and potassium, food assessment by food diary followed by analysis by PRODI6 performed poorly. Discrepancies might be explained by incomplete indication of food content, only partial reporting of ingredients used and by imprecise quantity assessment. New methodologies should be explored.

P 28

Swiss Kidney Stone Cohort: first description of Swiss stone formers in 2014-2015. NCCR Project

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Kidney stones are one of the most frequent diseases of the urinary tract, cause excruciating pain to the patient and represent a significant burden to the Health system. In addition, kidney stones are associated with cardiovascular mortality, renal insufficiency and osteoporosis, conditions that are highly prevalent in the population. The mechanisms leading to stone formation are still poorly understood and new treatment possibilities are needed. The NCCR Kidney.CH launched the Swiss Kidney Stone Cohort in 2014 in order to foster research in this field. We now report on the first 150 patients included to date in the Swiss Kidney Stone Cohort (SKSC).
Adult patients were recruited in five University Clinics of Nephrology (Basel, Bern, Geneva, Lausanne and Zurich) if they were recurrent stone formers or had a single episode, but with pre-determined risk factors. Investigations were standardized between the five centers, including 2 × 24h urine collection, food and activity questionnaires, food diary and cristalluria measurements. Samples of urine, blood and DNA were stored in a biobank. All lab analysis were centralized. Follow-up visits are organized at 3 months and then annually.
Between May 2014 and August 2015, 156 patients were recruited, 48 females and 108 males. Mean age was 46.6 ± 15.1 years. Mean BMI was 26.4 ± 4.7 Kg/m^2. The type of stones was available in 37% of the cases: 31 mainly whewellite, 11 weddelite, 9 apatite, 2 struvite, 4 uric acid, 1 cystine, 1 other. Mean 24h urine volume was 1732 ± 812 ml/24h. Hypercalciuria, defined as urinary calcium >7.5 mmol/24h in men and >6.5 mmol/24h in women was present in 30% of cases. Mean oxaluria was 172 ± 90 umol/24h and hyperoxaluria (>400 umol/24h) was encountered in 1.5% of cases. Thirty-five percent had sodium excretion >200 mmol/24h.
This first description of the Swiss stone formers population will allow further research and open new avenues for intervention.

P 29

Impact of Renin-Angiotensin-Aldosterone blocking drugs in patients with Chronic Kidney Disease and superimposed community-acquired Acute Kidney Injury

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Introduction: Due to their long-term nephroprotective effect, ARBs and ACEIs are widely used in patients with CKD despite their association with an increased risk of superimposed AKI. We aimed to better define its occurrence in relation to use of these drugs
Methods: Prospective observational study within the Emergency Department of a University Hospital, screening for any patient >16 years admitted with an eGFR <60 ml/mn. Patients with CKD (previously known for an eGFR <60 ml/mn) were included in this

analysis and superimposed AKI was defined as a decline in eGFR compared to previous values according to KDIGO AKI criteria.
Results: From May 1st up to June 21st 2013, there were 8464 admissions of whom 361 (4%) had a eGFR <60 ml/mn and were known to have previous CKD. Use of ACEIs, ARBs, diuretics, was respectively found in 19, 23, and 37% of patients. Low and medium-high doses were found similarly in 30 and 70% in patients treated with ACEIs and in those with ARBs. Diuretic use and its dosage was similar in the 2 groups. AKI was superimposed in 102 (28%) CKD patients. Etiology was mainly prerenal (73%). Multiple logistic analysis showed that occurrence of AKI was associated with male gender (OR 2.03; 95%CI:1.23–3.35, p = 0.005) diuretic use (OR 1.61; 95%CI:1–2.60, p = 0.05) and ARBs use (OR 1.61; 95%CI:1–2.60, p = 0.05) . ACEIs use was found to be slightly nephroprotective (OR 0.49; 95%CI:0.25–0.96, p = 0.04)
Conclusion: Community-acquired superimposed AKI in elderly CKD patients is more frequently encountered in male patients and those treated with diuretics and ARBs, but not ACEIs. Although ARBs and ACEIs are supposed to have a similar impact on renal hemodynamics, further clinical trials should be implemented in CKD patients to examine whether ARBs are more detrimental than ACEIs in terms of risk of superimposed CA-AKI.

P 30

Endocrine abnormalities predisposing autism spectrum disorders to arterial hypertension

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Background: Autism spectrum disorders are positively linked to arterial hypertension. The reason for this close relationship is elusive. It might be secondary to an increased psychosocial secondary stress response, alternative causes must be considered. A strong regulatory impact of steroid hormones such as aldosterone on blood pressure is known for long. Thus, we hypothesized that a primarily disturbed and/or secondary response to a heightened stress response might be causative.
Methods: Urine samples of an otherwise healthy cohort of young children with autism spectrum disorders (boys n = 46, girls n = 16) and a matched case control group were analyzed for steroid hormone metabolites by gas chromatography-mass spectrometry. Steroid hormone excretion was corrected for urinary creatinine.
Results: Urinary excretion of mineralcorticoid, glucocorticoid and androgen metabolites was elevated in autistic children as compared to controls for boys (2.1 ± 0.2 vs. 1.5 ± 0.1 µg/mmol, p <0.00 for tetrahydroaldosterone; 11.5 ±1 .6 vs. 7.2 ± 0.7 µg/mmol, p <0.00 for cortisol; 2.8 ± 0.5 vs. 1.1 ± 0.2 µg/mmol, p <0.00 for testosterone) and girls (2.2 ± 0.5 vs. 1.3 ± 0.1 µg/mmol, p <0.05 for tetrahydroaldosterone; 6.3 ± 0.7 vs. 4.5 ± 0.6 µg/mmol, p <0.04 for cortisol; 0.8 ± 0.1 vs. 0.6 ± 0.1 µg/mmol, p <0.01 for testosterone), respectively, all of them capable of increasing systemic blood pressure.
Conclusion: the steroid hormone pattern is strikingly disturbed in children with autism comparable to induced stress responses with a substantial stimulation of cortisol and androgen production. Unexpected and yet to be explained, urinary tetrahydroaldosterone excretion was also elevated in affected children suggesting a disturbed adrenal regulation beyond a simple stress response.

P 31

Devastating anti-MPO glomerulonephritis 14 years after autologous stem cell transplantation for progressive systemic sclerosis

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Background: Autologous stem cell transplantation is occasionally followed by secondary autoimmune disease. ANCA disease has been described very rarely.
Case report: This 38 year old patient of Asian origin presented to the emergency room with hemorrhagic pulmonary edema and severe acute renal failure (creatinine 870 µmol/l). Based on a glomerulonephritic sediment and high titers of anti-MPO ANCA (417 IU/ml, normal <7), a diagnosis of ANCA-associated RPGN was made. This was confirmed on day 12 by a renal biopsy. Despite prompt treatment with 4 sessions of plasmapheresis, steroids and cyclophosphamide, the patient remained dialysis dependent to this day. At the age of 24, she had undergone autologous stem cell transplantation for severe progressive systemic sclerosis as part of the ASTIS trial protocol, which included a cumulative dose of 5.4 g of cyclophosphamide. The disease was judged as inactive after this treatment and annual checkup examinations were performed at the study center. 4 months before this hospitalisation, one examination showed a creatinine increase to 96 µmol/l as well as proteinuria/microhematuria which however were not further investigated.
The sera which had been collected during the annual followup examinations were thawed and assayed for anti-MPO ANCA. The patient was ANCA negative both before and during the first 7 years after stem cell transplantation. Anti-MPO antibodies first became detectable (with rather high titers >100 IU/ml) 8 years after stem cell transplantation. Thereafter, they remained around 50 IU/ml, but increased to very high levels (>140) in the last year.
Conclusions: This is the second documented case of ANCA vasculitis after autologous stem cell transplantation. The long time period during which anti-MPO were detectable without apparent clinical disease highlights the requirement for a second trigger for ANCA disease to occur. Relevant autoantibodies such as ANCA should be prospectively measured after autologous stem cell transplantation.

P 32

Liver origin of erythropoietin during chronic kidney disease

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Introduction: Anemia of chronic kidney disease (CKD) is generally thought to be related to impaired renal erythropoietin (Epo) production. The glycosylation pattern of Epo is dependent on its synthesizing cell, thereby indicating its origin. Epo glycosylation is also know to modify its interaction to its receptor. Here we tested the hypothesis that synthesis of Epo from non-kidney cells is increased to compensate for insufficient renal Epo production in patients with moderate CKD.
Methods: We determined plasma [Epo] levels and Epo glycosylation patterns in 19 stage 3 and 4CKD patients and compared these to values obtained in healthy volunteers and other controls.Glycosylation pattern was determined by studying the migration of Epo on a specific strip (MAIIA kit).
Results: Despite higher Epo levels (15.75 (11.3–24.2) IU/L) compared to healthy controls (8.4 (7.56–8.98) IU/L, p <0.01), CKD patients were moderately anemic ([Hb]: 113 ± 11 g/dl). Glycosylation was increased in CKD patients (34 ± 12%; measured as percent migrated isoform) when compared to healthy controls (8.6 ± 1%; p <0.01), whereas the pattern did not differ from umbilical cord plasma (55 ± 10%, p >0.05) which is known to contain mainly liver derived Epo. There was a clear correlation (R = 0.8, p <0.01) between the eGFR and the percent of migrated isoform indicating that the lower the renal function, the higher the proportion of highly glycosylated liver derived Epo.
Conclusion: These results suggest that 1) moderate CKD patients exhibit preserved Epo levels despite declining renal function 2) this may be achieved by increasing liver Epo synthesis and 3) Epo originating from liver seems less erythropoietic consistent with the fact that it is more glycosylated. These obervations may modify the understanding of anemia in CKD and may also influence future therapies.

P 33

Rituximab in steroid- and calcineurin-inhibitor dependent minimal change disease in adults: report of two cases

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Background: Treatment of minimal change disease (MCD) in adults remains a challenge since steroid dependence, steroid resistance and relapsing course are often observed leading to high cumulative steroid doses. The necessity to use alternative, steroid-sparing immunosuppressive agents like calcineurin-inhibitors also includes potential toxic side effects restricting their long-term use. There is increasing evidence that Rituximab (RTX), a monoclonal antibody targeting CD20, is a feasible option in the treatment of recurrent and/or refractory MCD.
Cases: We treated two patients (24 and 21 years of age) with frequent relapsing (patient 1 with 44 relapses, patient 2 with 17 relapses),

steroid- and calcineurin-inhibitor dependent MCD with one course of RTX (375 mg/m^2). Both patients were on maintenance therapy with steroids and calcineurin-inhibitors (patient 1 tacrolimus, patient 2 cyclosporine) and suffered a relapse after stopping steroids. Remission was achieved three weeks after RTX in patient 1 and tacrolimus was stopped four weeks later. Patient 2 received steroids (1 mg/kg body weight/day) for four weeks and achieved remission before receiving RTX. Thereafter steroids were stopped after two more weeks and the calcineurin-inhibitor another three weeks later. Patient 2 remained in remission without any maintenance therapy 12 months later. His CD20/CD19 lymphocyte count was undetectable during follow-up. Patient 1 suffered her 45th relapse 11 months after RTX. She was retreated with steroids (1 mg/kg body weight/day) and a second course of RTX and achieved remission four weeks later and steroids were again stopped thereafter. At time of relapse her CD20/CD19 lymphocyte count had recovered to normal values (214 cells/μl).
Conclusion: RTX is a feasible treatment option in steroid-and calcineurin-inhibitor dependent MCD. Data on long-term outcome, safety and timely retreatment with RTX as maintenance therapy are still lacking.

P 34

SWIDINEP: a Swiss cohort of patients with diabetes and nephropathy. Baseline characteristics

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Background: Diabetic nephropathy is the leading cause of ESRD. Why some patients continue to progress to ESRD despite considerable improvements in therapy needs further exploration.
Methods: SWIDINEP (Swiss Diabetic Nephropathy cohort) is a prospective cohort. Its goal is to recruit 250 diabetic subjects with CKD stage 1–5 and to follow them over 5y and study the clinical, vascular, biochemical and DNA factors involved in renal function decline.
Results: Baseline data from the first 100 individuals recruited for this cohort were examined. Mean ± SD age was 63.1 ± 10.6y, 74.5% were men and 83.5% were Caucasian. Estimated GFR was 61.2 ± 27.7ml/min and urinary albumin/creatinine ratio was 45 ± 101 mg/mmol. 96.2% had type 2 diabetes of 15 ± 9y duration. HbA1C was 7.8 ± 1.3%. Hypertension was reported in 99% of cases and mean ambulatory diurnal and nocturnal systolic/ diastolic BP were resp. 130 ± 17/77 ± 9mmHg and 120 ± 21/70 ± 10 mm Hg. Office BP goal attainments were 58%/89% for SBP <140 mmHg/DBP <90 mm Hg. The majority of subjects were on RAS blockade. BMI was 31.7 ± 5.3 kg/m^2. LDL cholesterol was 2.2 ± 0.9 mmol/l with 70.5% on a statin and 43% reaching <2.6 mmol/l. Smoking was active in 19.8% of cases, 71.9% were on aspirin and only 2.2% were taking a NSAID. Kidney resistance indexes were 0.77 ± 0.13 (>97th percentile from an age-matched normal population), femoral pulse wave velocity (PWV) was 11.8 ± 3.1 m/s (>90th pecentile) and left carotid intima media thickness was 0.78 ± 0.2 mm (>75th percentile). Regression analysis showed that age, systolic blood pressure, pulse pressure, kidney resistance index, femoral PVW and left carotid artery intima media thickness were all significantly and inversely correlated with eGFR.
Conclusions: The baseline renal and vascular characterization in patients enrolled in the SWIDINEP cohort demonstrates a fairly good control of CV risk factors. Indirect markers of vascular damage are clearly linked with eGFR. Whether these vascular markers are involved in the accelerated renal function decline will be investigated at the 2 and 5y follow-up.

P 35

Defect of complement regulatory proteins in a patient with HELLP syndrome and renal involvement

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Background: The HELLP syndrome represents a severe form of preeclampsia, which shares several clinical and biologic features with thrombotic microangiopathy (TMA). A common pathophysiologic mechanism, such as complement dysregulation may therefore underlie both conditions.
Results: We report a case of a 36 year-old female who developed partial HELLP syndrome with renal involvement after spontaneous delivery of healthy non-identical twins. Four weeks prior to the delivery preeclampsia was diagnosed. During the immediate postpartum period, she developed severe hypertension, haemolytic anaemia (Hb 62 g/l), elevated liver enzyme (AST 142 U/l) and severe thrombocytopenia (18 × 109/l). In addition, an anuric renal failure was observed (max. creatinine 389 μmol/l). She recovered gradually under supportive treatments and was discharged 13 days after delivery. No renal replacement therapy was required. Due to the severe renal failure, which is more common in the setting of TMA, we evaluated the regulatory factors of alternative complement pathway. We found a high titre of complement factor H (CFH) antibody (1000 UA) associated with the homozygous deletion of complement factor H-related genes CFHR1 and CFHR3. Five months later, her laboratory parameters completely normalized including serum creatinine (78 μmol/l) and the CFH antibody titre decreased to 420 UA.
Conclusion: Increasing data suggest that an abnormal control of the complement alternative pathway is a risk factor for the occurrence of preeclampsia. In our patient CFH antibodies associated with deletion of CFHR 1 & 3 genes, known as one of the aetiologies of atypical haemolytic uremic syndrome, were detected. Both HELLP syndrome and pregnancy associated TMA can potentially be associated with serious maternal morbidities, although our patient showed a favourable outcome. The evaluation of complement regulatory proteins in patients with severe preeclampsia/HELLP syndrome is recommended to adapt patient management.

P 36

Are hospitalised patients aged 90 years and over treated well for hypertension? Lessons from a prospective survey in a primary care hospital

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Background: Hypertension increases dramatically with age. In stable nonagenarians, ESH guidelines would recommend lowering blood pressure (BP) to 140–150 mm Hg systolic (SBP) or <90 mm Hg diastolic (DBP) if higher, but it is not clear if all of the oldest old comply with or need these goals. We prospectively analysed the situation in a rural primary care hospital.
Methods: All patients >89 years admitted to the medical ward were prospectively included over 12 months. BP treatment followed ESH guidelines. Sitting BPs were obtained on admission and then in the morning before drug intake. BP treatment was adaptated to minimize side-effects. Excluded were sepsis, circulatory shock, stroke or ST-elevation myocardial infarction, and re-admissions
Results: Fifty-eight patients aged 92 ± 3 years (mean ± SD; 90–101) with 11 hospital days (median) were included (77.6% female, 34.5% diabetics, 24.1% atrial fibrillation, 41.4% coronary heart disease). Main diagnoses were diabetes, non-septic infections, heart insufficiency, rhythm problems, orthopedic pain and neuro-cognitive impairment. Admission SBP was 149 ± 29 mm Hg (<140 mm Hg, 36%; >159 mm Hg, 27.6%), DBP 88 ± 31 mm Hg (>89 mm Hg, 18.4%), heart rate (HR) 87 ± 15/min, weight 62 ± 12 kg, serum creatinine 112 ± 48 μmol/l, cholesterol 4.9 ± 1.2 mmol/l, blood hemoglobin 7.8 ± 1.2 mmol/l. Mid-term SBP was 128 ± 22 and DBP 72 ± 9 mm Hg (HR 76 ± 9/min). Discharge SBP was 128 ± 17 (<140 mm Hg, 62%; >159 mm Hg, 0%), DBP 72 ± 9 mm Hg (>89 mm Hg, 3.6%) and HR 73 ± 6/min (p <0.01 vs admission). BP drugs/patient (n, admission vs. discharge) without diuretics was 1.0 ± 0.9/1.1 ± 0.9 (p = NS), and including diuretics 1.5 ± 1.2/1.7 ± 1,1 (p <0.05): blockers of beta-adrenoceptors 22.4/25.9%, Ca-channels 8.6/12.1%, the renin-angiotensin system 63.8/63.8%; spironolactone 5.2%/5.2%; others 1.7/3.4% (p = NS); diuretics 48.3/67.2% (p <0.05); percent treated 75.9/86.2, excluding diuretics 67.2/70.7 (changing 43.1%); no sex differences (p = NS).
Conclusion: A substantial proportion of very old hypertensive patients reached well tolerated BP values below recommended goals after significantly increased use of diuretics. Co-morbidity dominated in-hospital treatment decisions, not guideline BP targets.

P 37

Stone composition of patients: data from laboratory

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Background: Nephrolithiasis is a common disease affecting more than 10% of the population in the industrialized countries. Determination of kidney stone composition is an important part in the evaluation of patients with stone disease. More than 100 chemical components have been identified.
Methods: From 2009 to 2014, 3832 urinary calculi were analyzed in our laboratory. Stones provided from patients living in Geneva and Lausanne area. Analysis of stone composition was done by infrared spectroscopy. A retrospective analysis (2009 to 2014) allows us to determine epidemiological parameters (sex-ratio, age) and the frequency of main chemical composition in our population.
Results: Patients with stone were mostly men (sex ratio 2.4). Age average of patients with stone was 49.6 ± 16.1 years and more specifically 50.6 ± 15.8 years for men and 47.3 ± 14.6 years for women. Calculi had one compound in 48%, two in 37%, three in 13% and more than three compounds in 3% of cases. Stone composition and compound frequency is described in table1. The most frequent compounds observed in stone were calcium oxalate, calcium phosphate and lastly uric acid. Concerning the gender, calcium oxalate and uric acid were predominantly found in men. In contrast, calcium phosphate and struvite were more frequent in women (table 2). Patients with stone containing acid uric (average 61 years) were older than patients with calcium oxalate or phosphate (45 and 44 respectively).
During 2009 to 2014, age average had a tendency to decrease from 51.0 to 47.8 years. The frequencies of stone compound were relatively stable during the analyzed period, while the occurrence of uric acid calculi was increasing.
Conclusions: In this study, population and stone composition were comparable with the results of other studies in industrialized areas. The stone analysis gives relevant informations that will help to determine lithogenic cause.

Table 1: Frequencies (%) of main components between 2009 to 2014.

	2009			2010			2011			2012			2013			2014		
%	total	M	W	total	M	W	total	M	W	total	M	W	total	M	W	total	M	W
CALCIUM OXALATE																		
Monohydrate	**49.4**	49.5	49.1	**51.3**	51.8	50.0	**47.8**	54.9	45.3	**48.9**	47.5	52.2	**46.9**	46.7	47.3	**48.5**	48.7	48.0
Dihydrate	**17.6**	19.3	13.6	**14.8**	16.2	11.7	**16.2**	17.5	12.3	**14.3**	15.1	12.2	**16.5**	17.5	13.8	**16.3**	16.6	15.4
CALCIUM PHOSPHATE																		
Carbonate	**21.7**	19.1	28.2	**21.5**	18.2	29.3	**22.2**	23.4	30.1	**22.0**	20.2	26.3	**20.2**	17.1	27.8	**20.4**	17.2	28.1
Brushite	**0.3**	0.4	0	**0.5**	0.7	0	**0.3**	0.5	0.3	**0.3**	0.4	0	**0.5**	0.6	0.2	**0.4**	0.5	0
STRUVITE	**1.9**	1.3	3.2	**0.8**	0.7	1.2	**2.0**	2.4	2.3	**2.0**	2.1	1.8	**0.4**	0.5	0.4	**1.8**	1.8	1.8
URIC ACID																		
Anhydrous	**6.2**	6.9	4.5	**8.4**	9.4	5.9	**7.9**	12.0	6.1	**8.8**	10.4	4.7	**9.8**	11.9	4.7	**8.3**	10.0	4.2
Dihydrate	**2.8**	3.4	1.4	**2.4**	2.8	1.6	**2.8**	4.2	2.6	**3.4**	3.7	2.9	**3.9**	4.6	2.0	**4.0**	4.8	2.2
CYSTINE	**0.1**	0.2	0	**0.3**	0.3	0.4	**0.7**	0.7	1.0	**0.4**	0.6	0.0	**0.4**	0.5	0.4	**0.3**	0.4	0.2

M = men and W = women

POSTER PRESENTATIONS – BASIC SCIENCE / GENETICS / EXPERIMENTAL NEPHROLOGY

P 38

Urinary metabolomic to identify new biomarkers of chronic kidney disease

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Background: Chronic kidney disease (CKD) is associated with increased oxidative stress. Some metabolites reflecting this stress can be found in urine and used as biomarkers. The aim of this pilot study was first to set a method for measuring urinary 8-isoprostane in patients with CKD compared to healthy ones; secondly to evidence new markers of oxidative stress using a non-targeted approach.
Methods: For the targeted analysis, 19 CKD patients and 20 healthy subjects with normal renal function were selected from ongoing cohorts (Implicate and SKIPOGH). LC-MS/MS was used to measure 8-isoprostane levels in urine, correcting for urinary creatinine. For the non-targeted approach, a larger sample of CKD patients was used to compare progressors (n = 29) and non-progressors (n = 17) to controls (n = 40). For the phase II, s teroid metabolites were used as an exploratory discrimination subset thanks to advanced mass spectrometry selection.
Results: CKD patients had a mean age of 69 years and eGFR of 37 ml/min/1.73 m^2. Healthy subjects had a mean age of 62 years and eGFR >60 ml/min/1.73 m^2 without proteinuria. In CKD patients, median 8-isoprostane levels were surprisingly lower than in controls: 0.05 vs 0.02 ng/mg, p = 0.001. In the non-targeted approach, we could clearly discriminate between controls and CKD patients. With 93.5% sensitivity and 90% specificity as classification performance, steroid glucuronides performed better than steroid sulfate or isoprostane-related metabolites. However, we could not find differences in metabolites levels between progressors and non-progressors.
Conclusions: We identified a decrease in urinary 8-isoprostane levels in CKD patients compared to controls that could reflect an alteration of the oxidative response pathway. The significance of this decrease still needs to be studied. Although, we could not find differences in urinary metabolites between progressors and non-progressors, other pathways seem to be altered compared to healthy patients, indicating that steroid metabolism may serve as a biomarker signature in CKD.

P 39

Integrated transcriptomic and proteomic analyses reveal the regulatory roles of nrf2 in the kidney (NCCR project)

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Background: The transcription factor Nrf2 exerts protective effects in numerous experimental models of acute kidney injury, and is a promising therapeutic target in chronic kidney disease.

Methods: To provide a detailed insight into the regulatory roles of Nrf2 in the kidney, we performed integrated transcriptomic and proteomic analyses of kidney tissue from wild-type and Nrf2 knockout mice treated with the Nrf2 inducer methyl-2-cyano-3,12-dioxooleano-1,9-dien-28-oate (CDDO-Me, also known as bardoxolone methyl) for 24 h.
Results: These analyses identified 2561 transcripts and 240 proteins that were differentially expressed in the kidneys of Nrf2 knockout mice, compared to wild-type counterparts, and 3122 transcripts and 68 proteins that were differentially expressed in wild-type mice treated with CDDOMe, compared to vehicle control. In light of their sensitivity to genetic and pharmacological modulation of renal Nrf2 activity, genes/proteins that regulate xenobiotic disposition, redox balance, the intra/extracellular transport of small molecules, and the supply of NADPH and other cellular fuels were found to be positively regulated by Nrf2 in the kidney. These data were verified by qPCR, immunoblotting, pathway analysis and immunohistochemistry. In addition, the levels of NADPH and glutathione were found to be significantly decreased in the kidneys of Nrf2 knockout mice.
Conclusions: Together, these data demonstrate the role of Nrf2 as a regulator of genes that coordinate homeostatic processes in the kidney, highlighting its potential as a novel therapeutic target.

P 40

Evaluation of rna extraction kits to enable RNA sequencing of archival renal tissue

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Background: Next generation RNA sequencing (NGS) is a powerful tool to acquire insights into molecular disease mechanisms. Therefore, it is of interest to optimize methods for RNA extraction from archival, formalin fixed and paraffin embedded (FFPE) tissues. Our aim was to find the most appropriate kits to extract RNA from FFPE human kidney tissues to enable NGS.
Methods: We evaluated seven RNA extraction kits: High Pure FFPE-Tissue RNA (Roche), ExpressArt Clear FFPE RNAready (Amsbio), miRNeasy FFPE, RNeasy FFPE (Qiagen), PureLink FFPE Total RNA (Invitrogen), RecoverAll Total Nucleic Acid Isolation Kit (Ambion) and Absolutely RNA FFPE Kit (Agilent). RNA was obtained from approximately 3.5y old FFPE tissue blocks of two healthy, male Wistar rats. The four kits with highest RNA yield were tested on human renal biopsies, including whole sections and laser capture microdissected (LCM) glomerular cross-sections. Quantitative analyses were performed using Nanodrop. RNA quality is reflected by DV200 values (% of RNA fragments >200 nucleotides) utilizing an Agilent 2100 BioAnalyzer. Depending upon RNA quality (DV200 value of ≥30%), 20 to 100 ng total RNA is required for NGS.
Results: The High Pure kit yielded 137ng (± 31 ng) and the ExpressArt kit 84ng (±19 ng) RNA per human renal biopsy section (fig. 1). For the LCM samples, the ExpressArt kit yielded 138ng (± 43 ng) and the RNeasy FFPE kit 114ng (± 6ng) RNA per 100 glomerular cross-sections. Qualitative analysis showed high quality (DV200 >70%) of the RNA extracted from renal biopsy sections and from LCM glomerular cross-sections using both the High Pure and the ExpressArt kits (fig. 2).
Conclusion: Total RNA can be extracted from archival renal biopsies in sufficient quality and quantity from one human renal biopsy section or from around 100 microdissected glomerular cross-sections to enable NGS using both the High Pure and the ExpressArt kits.

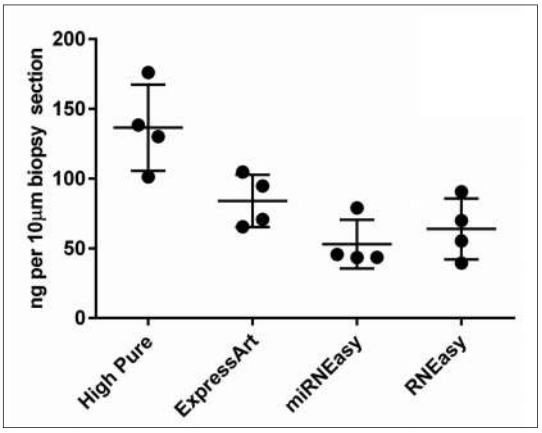

Figure 1

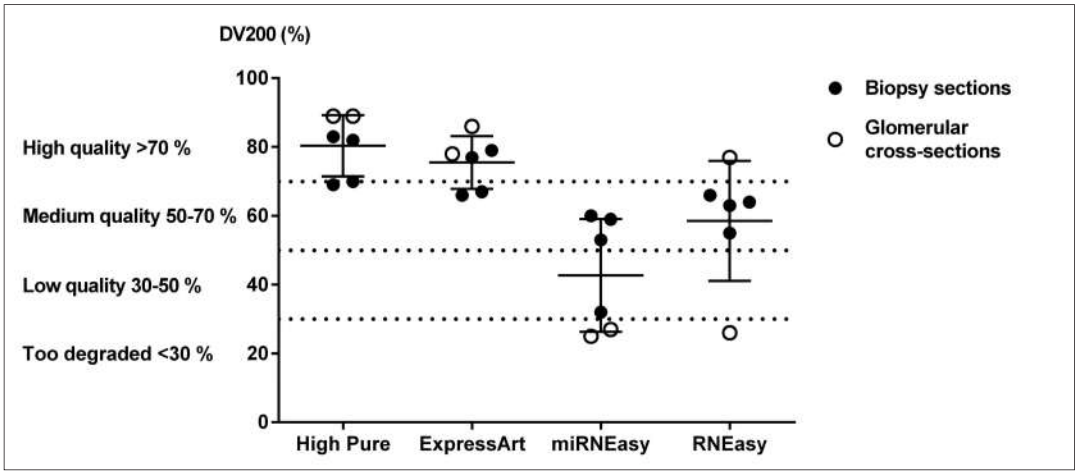

Figure 2

P 41

Siblings with two different rare genetic kidney diseases

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Background: Genetic disorders with kidney involvement are not uncommon. Nevertheless finding two different monogenic kidney diseases in one family is exceptional. We present siblings with distal renal tubular acidosis (dRTA) and Alport syndrome.
Methods: Laboratory investigations were performed in Yerevan and Zurich, renal biopsy was evaluated in Zurich and molecular genetics were studied at the Hôpital G. Pompidou in Paris (R. Vargas-Poussou) and the Guy's Hospital in London (F. Flinter).
Results: A 3.5 y/o boy referred for metabolic osteopathy and developmental delay showed growth retardation (–5.3 SDS), polyuria, rickets, hypokalemia, elevated urinary pH 6.8–7.4 despite severe non-anion gap metabolic acidosis, and medullary nephrocalcinosis. Diagnosis of dRTA with bilateral sensorineural deafness was made. Genetic analysis showed homozygous mutation on exon 4 of the ATP6V1B1 gene coding for the B1 subunit of the H+-ATPase. Hearing aids improved his mental development, and potassium citrate and (initially) vitamin D his growth (–0.7 SDS when 7 y/o) and chemistry. Nephrocalcinosis was no more detectable.
His 11 y/o sister showed proteinuria and microhematuria. Parents had no hematuria. Alport syndrome was found at renal biopsy and treated with ACE inhibitors. At the age of 13 years proteinuria was 9.9 g/l with hematuria; renal function was preserved. Genetic analysis revealed heterozygous sequence variant in COL4A4 predicted to interrupt an important domain of the α4 chain. Since the father died due to an accident, no further material is available for genetic analysis.
Conclusion: This is a unique example of two rare hereditary nephropathies in one family. Both diseases required special examinations that would not have been possible without cooperation of different laboratories and centres in Europe. In case of dRTA catch-up growth and steady improvement could be obtained by simple means.

P42

The sodium/proton exchanger NHA2 is a novel regulator of sodium and calcium homeostasis in the distal convoluted tubule

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Background: NHA2 is a recently cloned sodium/hydrogen exchanger present in all metazoan genomes with unknown biological function. We recently demonstrated that NHA2 is critical for insulin secretion in β–cells (Deisl et al., PNAS 2013).
Methods: To test the physiological role of NHA2 in the kidney, we performed telemetric blood pressure measurements and metabolic balance studies in NHA2 wild-type and knock-out mice. Kidneys of NHA2 WT and KO mice were further analyzed by immunoblotting. For in vitro studies, we used the distal tubular cell line mpkDCT4 and HEK293 cells.
Results: NHA2 was expressed in distal convoluted tubules of both mice and humans. Blood pressure was lower in NHA2 KO mice compared to WT mice on low, normal and high sodium diet. In addition, NHA2 KO mice exhibited normocalcemic hypocalciuria. Interestingly, immunoblotting of kidney tissue lysates revealed reduced phosphorylation of the sodium/chloride co-transporter (NCC) in NHA2 KO mice. Similarly, phosphorylation of SPAK and abundance of WNK4, kinases regulating NCC phosphorylation, were lower in kidney lysates of KO mice, compared to WT kidney lysates. In line with these findings, NHA2 KO mice exhibit a reduced natriuretic response to hydrochlorothiazide compared to WT mice. In the DCT cell line mpkDCT4, stimulation of NCC phosphorylation is reduced upon siRNA mediated knockdown of NHA2, compared with control siRNA treated cells. In HEK293 cells, knockdown of NHA2 increased ubiquitylation and consequently reduced abundance of WNK4. To affirm that the phenotype observed is mediated solely by reduced activation of the WNK-SPAK-NCC phosphorylation cascade, we generated NCC-NHA2 double KO mice (DKO). We observed that both calciuria and blood pressure were similar between NCC KO/NHA2 WT and NCC KO/NHA2 KO (= DKO) mice.
Conclusion: Our data reveal the sodium/hydrogen exchanger NHA2 as a novel regulator of calcium, sodium and blood pressure homeostasis in the distal convoluted tubule of the kidney.

P 43

Implementation of a "next generation sequencing-first" strategy for the diagnosis of genetic kidney disease in Switzerland: the Geneva experience (Ge-RenOME)

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Background: Except monogenic diseases, such as ADPKD, kidney diseases are complex genetic traits, often with several mutations involved and overlapping phenotypes. Therefore, "candidate gene" approach may be inefficient in some selected cases. Since January 1st, 2015, in Switzerland, the next generation sequencing (NGS) has been added to the list of laboratory analysis with health insurance reimbursement. We retrospectively analyzed the results of NGS in our patients at a genetic consultation.
Methods: We evaluated the patients from the Nephrogenetic consultation in Geneva University Hospitals from January 1st to June 30th 2015. NGS was performed when deemed appropriate in agreement with NGS-Swiss good practice guidelines (December 2014). Any found mutation was then verified by Sanger sequencing.
Results: In the first semester of 2015, 22 patients were evaluated by our nephrogenetic consultation. 8 patients were offered targeted analyses (atypical hemolytic and uremic syndrome, autosomic dominant polycystic kidney disease). NGS was performed in 10 Patients (age: 1 to 57 years old; 6 patients <18 years old); results were delivered within 5 months (including Sanger confirmation). 3 patients had an a priori diagnosis matching the initial clinical suspicion, 4 were reclassified to another diagnosis. Results for 3 patients are pending. We currently target our NGS (Ge-RenOME) by regularly updating the pipeline with new databases and variant annotation software.
Conclusions: The Ge-RenOME, available to all centers, is based on targeted NGS technology. It requires expertise with a high potential for cutting the cost, avoiding fruitless testing and unnecessary kidney biopsies in selected cases. It may also permit to reclassify diseases.

P 44

Cross-talk between oxygen sensing and sodium handling in the collecting duct "NCCR project"

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Background: Regulation of sodium reabsorption by the collecting duct is crucial to maintain body sodium balance. Tubular handling of sodium is the major factor influencing renal oxygen consumption. We hypothesized that mismatching between oxygen supply and oxygen consumption in response to increased sodium transport may lead to activation of oxygen sensing mechanisms.
Methods and results: Using mpkCCDcl4 cells, a model of collecting duct principal cells, we showed that stimulation of sodium transport by aldosterone induces HIF signaling pathway activation revealed by HIF1α protein stabilization and increased HIF target genes expression such as Pdk1 and Pgk1. Using rats subjected to normal or high salt diet and infused with aldosterone, we observed a correlation between HIF target genes expression and aldosterone signaling pathway activation. Besides, activation of HIF signaling pathway by hypoxia, DMOG or CoCl2 inhibited the transepithelial sodium transport by 70% and decreased expression of ENaC subunits in mpkCCDcl4 cells. Involvement of HIF1α and HIF2α in regulation of sodium transport was clearly confirmed by HIF1α or HIF2α silencing using lentivirus encoding HIF1α or 2α specific shRNAs. Knock-down of HIF1α or HIF2α induced a strong increase of sodium transport associated with up-regulation ENaC subunits in mpkCCDcl4 cells. In contrast, overexpression of constitutively active HIF1α or 2α mutants down-regulated ENaC subunits. Kinetics of aldosterone treatment on mpkCCDcl4 cells revealed that up-regulation of sodium transport peaked at 24h and then progressively decreased in parallel with down-regulation of β and γ ENaC subunits. In HIF1α depleted cells, sodium transport activation by aldosterone remained constant for 72 h

while the down-regulation of β and γ ENaC subunits was abolished.
Conclusion: Stimulation of sodium transport by aldosterone induces HIF pathway that may decrease oxygen and energy utilization through a negative feedback on sodium transport in order to equilibrate oxygen supply and demand.

P 45

RNA Sequencing reveals Tumor Necrosis Factor α Inducible Protein 6 (TNFAIP6) as a potential Single Gene Classifier of Renal Cell Carcinoma

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Background: The recent release of a new library preparation kit improved the cDNA library quality from archival formalin-fixed, paraffin-embedded (FFPE) tissues. In this study we present a novel single gene classifier in clear cell renal cell carcinoma (ccRCC), thus demonstrating the strength of this technique.
Methods: Paired biopsies from 16 patients with ccRCC and adjacent non-tumorous tissue were either FFPE or stored in RNAlater® (Qiagen) for up to one year. Total RNA was extracted utilizing the miRNeasy FFPE kit or the miRNeasy micro kit (Qiagen), respectively. Sequencing libraries were prepared using the TruSeq RNA Access Library Prep Kit® (Illumina). Sequencing was performed at Illumina HiSeq 2500. Alignment of reads to the GRCh38 reference genome was guided by Tophat and Bowtie. Comparative analysis was done using voom/Limma R-package.
Results: The analysis of FFPE and RNAlater® datasets yielded similar numbers of detected genes, differentially expressed transcripts and affected pathways. The FFPE and RNAlater datasets shared 80% (n = 1106) differentially expressed genes. The average expression of these transcripts in both datasets correlated with R2 = 0.97, and the log2 fold changes of these transcripts, which are significantly altered in both datasets, correlated with R2 = 0.96. A classifier model with TNFAIP6 was developed for the FFPE dataset with a specificity of 100% and sensitivity of 94%; ROC AUC = 0.99; only one normal sample was misclassified due to small admixture of cancer tissue. TNFAIP6 up-regulation in cancer was confirmed by immunohistochemistry. Subsequently, this classifier was also applied to the RNAlater® dataset with similar results. Classifier validation in an Affymetrix microarray dataset obtained from GEO (GSE53757) showed TNFAIP6 up-regulation in all tumor stages with both sensitivity and specificity of 94%; ROC AUC = 0.98.
Conclusions: We describe a potential nover single gene classifier for ccRCC. Furthermore, this study confirms that NGS in FFPE tissues is feasible and correlates well with RNAlater® stored tissue.

P 46

Development and characterisation of a mass-spectrometric method for the quantification of uromodulin in human urine (NCCR)

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Uromodulin is a 68 kDa protein synthesised almost exclusively in the thick ascending limb (TAL) of the loop of Henle. The biological role of the protein has not yet been completely ascertained, and recently suggestions have been made towards its potential utility as a biomarker of chronic kidney disease. Uromodulin is currently measured by ELISA assay. However, factors including the protein's glycosylation and aggregation may in some situations inhibit its accurate quantification. Here we present the development of a mass-spectrometric (MS/MS) method for the quantification of uromodulin, and compare data achieved with an established ELISA assay.
MS/MS analysis of 2 ug of purified human uromodulin using a data-dependent scan allowed peptide identification of 34% of the protein's sequence. From these peptides STEYGEGYACDTDLR and DWVSVVTPAR were selected as surrogate peptides for the protein's quantification. Heavy versions of these peptides were purchased, and a pseudo multiple reaction monitoring (pMRM) method for heavy and light versions of these peptides was developed. This method was used to quantify urinary uromodulin in patients homozygous for a cytosine to threonine substitution in the genetic variant rs4293393, which has previously been shown to result in increased urinary uromodulin. This finding was repeated when samples were measured by ELISA and pMRM assays; however greater significance was detected when the pMRM method was used. This is because the pMRM was able to more accurately quantify uromoduln in concentrated urine samples. The pMRM assay also showed greater reproducibility than the ELISA (r2 = 0.9903 n = 13 compared to 0.3407 n = 23) when the same samples were re-analysed. From this data, improved performance of the pMRM assay over ELISA in the absolute quantification of uromodulin in samples was observed. However, the long run-times of the pMRM method mean that it is not suitable for large cohort studies, where the ELISA remains the analytical tool of choice.

P 47

Reduced β-catenin levels promote cyst formation during fetal development (NCCR project)

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Background: Many studies have found a critical association between cystic transformation of the kidney in ADPKD and canonical Wnt/β-catenin signaling. However, whether an increase or decrease in canonical Wnt/β-catenin signaling activity is responsible for the development of cysts is still a matter of intense debate. Recently, it was shown that GSK3β, an inhibitor of canonical Wnt/β-catenin signaling, is upregulated in cyst-lining epithelia and that its inactivation slowed down the progression of cyst expansion. Here, we genetically reduced the level of β-catenin in the developing kidney and evaluated its effect on cystogenesis.
Methods: The level of β-catenin expression was reduced to 25% compared to wild type mice by switching the expression from the endogenous to the ROSA26 locus. Fetal kidneys were isolated at E17.5 and analyzed histologically and by qRT-PCR.
Results: Embryos with reduced β-catenin expression levels had smaller kidneys at E14.5 without apparent cysts. However, at E17.5 the kidneys presented multiple cysts of different size. Using marker proteins of different tubular segments, we confirmed the cysts to be of collecting duct origin. Interestingly, superimposed hypoxia appears to have ameliorating effects on the degree of cyst formation, suggesting that low oxygen levels might enhance canonical Wnt/β-catenin signaling.
Conclusions: The correct dosage of β-catenin is crucial for proper kidney development and patterning of the nephron. The lowered β-catenin level applied here progressively promotes the formation of cysts in the collecting duct during the late stages of pregnancy. Further studies are planned to decipher the connection between β-catenin expression level, the segmental origin of the cysts along the nephron and time point of cyst formation.

P48

Chronic hypoxia during fetal development induces renal cellular senescence (NCCR project)

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Background: Cellular senescence is a state of permanent cell cycle arrest, which can be induced by a multitude of exogenous or endogenous stress factors. The higher the degree of cellular senescence and the earlier it is activated in a tissue, the more limited becomes it regenerative capacity. Chronic intra-uterine growth restriction (IUGR) is known to be associated with an increased risk to develop chronic kidney diseases (CKD) later in life. In this study, we explored the potential link between chronic fetal hypoxia and renal cellular senescence in a mouse model.
Methods: Pregnant dams were exposed to either normoxic or hypoxic conditions (9.5% O_2) from E14.5 until E18.5 and sacrificed. Fetal kidneys were assessed for the expression of cellular senescence-associated markers: β-galactosidase, cyclin dependent kinase inhibitors p16 and p21, and heterochromatic foci. Furthermore, the proliferative and apoptotic status were analyzed.
Results: Hypoxic kidneys were smaller in size and showed a strong upregulation of senescence-associated β-galactosidase staining in the proximal tubuli, as well as an increased expression of p16 and p21.

Upregulation of p16 and p21 promotes the withdrawal from the cell cycle independent from telomere shortening. Apoptotis in the affected tubuli was not increased, however, the overall proliferative activity was diminished. Lastly, adult mice that had experienced fetal hypoxia showed signs of premature ageing, including reduced body weight, hair greying, and impaired kidney function.

Conclusions: Using our newly validated murine model of hypoxia induced IUGR, we demonstrated that chronic fetal hypoxia results in the activation of senescence in cells of the proximal tubulus. These cells consequently cannot further participate in damage repair responses, leading to preterm deterioration of kidney function.

POSTER PRESENTATIONS – HEMODIALYSIS / PERITONEAL DIALYSIS

P 49

A rare but shocking complication of haemodialysis

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History: (**Background**)**:** A 56-year-old woman with a history of empyema and lung abscess after a pneumococcal superimposed influenza pneumonia underwent multiple thoracic interventions. She developed a pleura cutaneous fistula with ochrobactrum species in the microbiologic cultures.
The patient became septic and was transferred to the intensive care unit. She developed kidney failure with necessitation of hemofiltration and haemodialysis.
Clinical and Laboratory Evaluation: (Methods): CRP levels remained high at 290 mg/l; Patient developed leucocytosis of 50.9 G/l and eosinophilia of 42 G/l. During haemodialysis blood pressure dropped from a mean of 78 mm Hg to 40 mm Hg after 5 to 10 minutes after initiating haemodialysis session and oxygen saturation dropped 98% to 92%. In each following haemodialysis session the fall in blood pressure and the gas exchange problems were more impressive. Volume substitution and noradrenaline could not prevent these symptoms. After stopping the blood pump, hypotension and ventilation problems resolved within minutes. Echocardiography showed a normal cardiac function.
Course: (Results): We assumed that the hypotension and gas exchange problems were caused by the eosinophilia, which resulted in a release of cytokines and toxic granules (eosinophilic peroxidase and eosinophil protein X) in contact with the dialyzer membrane as described in the paper of Gwinner et al. (2005).
Prednisolone treatment lead to a significant reduction of eosinophilia and following haemodialysis sessions were performed without any complication until renal function recovered.
Renal biopsy revealed a heavy acute eosinophilic interstitial nephritis.
Conclusion: Hypotension and bronchospasm caused by degranulation of eosinophils after contact with the dialyzer membrane is a very rare, but life-threatening complication in patients with eosinophilia undergoing haemodialysis.

P 50

Automated peritoneal dialysis (apd) in systemic amyloidosis with amyloid infiltration of the peritoneum

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Background: Amyloidosis is a disease characterized by extracellular deposition of proteinic fibrillar material. In light-chain amyloidosis the deposited amyloid protein is derived from immunoglobulin light chains in patients with multiple myeloma. Kidneys are often affected by amyloid deposits and the clinical manifestations include proteinuria/ nephrotic syndrome and progressive renal failure, leading to end-stage renal disease (ESRD).
Case report: A 73-year-old man, affected by IgG-lambda monoclonal gammopathy with a 13% plasma cell infiltration at the bone marrow biopsy complicated by amyloid infiltrative cardiomyopathy, was referred to our nephrology department for acute worsening of renal function and chronic fluid overload. Blood urea was 33.9 mmol/l, creatinine 285 µmol/l, NT-proBNP 2335 ng/l, Troponin I 0.64 µmol/l, albumin 28 g/l and proteinuria 740 mg/24 hours. Renal biopsy showed amyloid deposits and colorectal biopsy demonstrated colonic amyloidosis. The patient was treated with hemodialysis for a short period, subsequently, peritoneal dialysis (PD) on APD modality has been started. During PD catheter insertion, we performed a peritoneal biopsy that showed amyloid deposition in the walls of blood vessels (figures).
The patient continued APD treatment for 11 months with an adequate urea and creatinine clearance and a satisfactory ultrafiltration, until he died due to end-stage heart failure. We never observed episodes of peritonitis or presence of catheter exit site/tunnel infection.
Conclusions: Some authors described that PD has several advantages over HD for the treatment of ESRD in the presence of amyloid cardiomyopathy because it is not associated with the hemodynamic stress of intermittent haemodialysis.
Other authors reported that amyloid infiltration of the peritoneum makes PD ineffective and that in patients with systemic amyloidosis the frequency of peritonitis is higher.
In our experience, amyloid infiltration of the peritoneum did not render PD ineffective in terms of control of uraemia, incidence of peritonitis and quality of life.

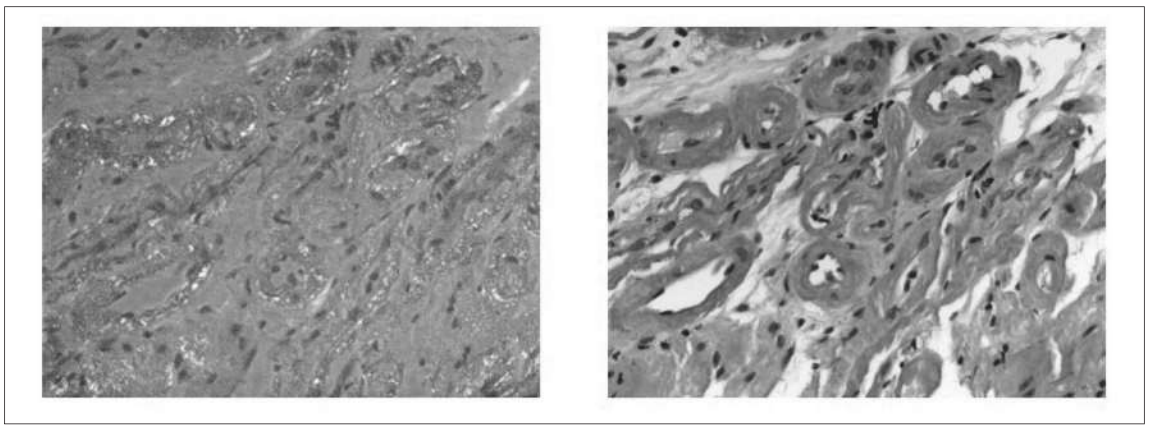

Figure: Histological sections of peritoneum biopsy: In the left panel a Polarized light microscopy sect depicting amorphous material in the thickened walls of the small vessels (in green). In the right panel, same section Congo red stain-positive.

P 51

Calciphylaxis and haemodialysis: comorbidity or iatrogenicity?

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Background: Calciphylaxis, calcific uremic arteriolopathy (CUA), is a rare and serious disorder characterized by systemic medial calcification of the arterioles that leads to ischemia and subcutaneous necrosis that may occur in patients with end-stage renal disease (ESRD). Characteristic lesions include violaceous, painful, plaque-like subcutaneous nodules that progress to ischemic/necrotic ulcers, with eschars that often become superinfected.
An early diagnosis is fundamental for a better prognosis, even if the optimal treatment for CUA is not known. A multi-interventional strategy is likely to be more effective than any single therapy.
Here a case report with efficient therapeutical strategy.
Methods: 71-year-old woman with metabolic syndrome and end stage renal disease in haemodialysis treatment since 2010 presents with a painful left perimalleolar ulcerative lesion. A vascular, diabetic or infectious origin is excluded. Two other smaller eschars are present distally on the right leg.
A surgical debridement with biopsy of marginal tissues confirm the clinical suspicious of a calciphylaxis. An aggressive program of wound care follows. In order to decrease the calcium-phosphate product all calcic medications are stopped, in addiction to administration of intravenous sodium thiosulfate, increased doses of calcimimethic therapy and more frequent hemodialysis. Moreover, in patient with oral anticoagulation therapy for an atrial fibrillation, Acenocoumarol is substituted by low molecular weight heparine.
Results: At one-month follow up we obtained an interruption in the lesions progression with progressive resolution by tissues regrowth with granulation. Therefore a better pain control was possible.
Conclusions: Although previously rare, the incidence of calciphylaxis appears to be increasing, due in part to the awareness and the recognition of clinical signs and associated risk factors. An optimal therapy is still not known, but a multifactorial approach acting also on possible iatrogenic effects of haemodialysis related treatments appears to be the best, as demonstrated in our case report.

P 52

Challenge and limitations in the use of Slow Continuous Ultrafiltration (SCUF) with regional citrate anticoagulation (RCA) for refractory fluid overload.

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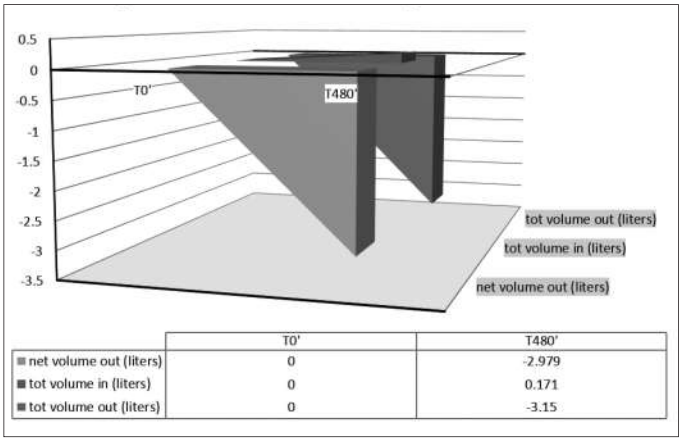
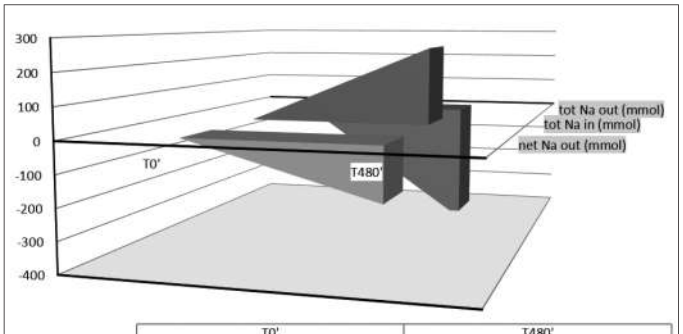
Background: Slow continuous ultrafiltration (SCUF) is indicated for congestive heart failure with refractory fluid overload. Only a few descriptions of regional citrate anticoagulation (RCA) have been reported during SCUF. We report one didactic case with the aim to demonstrate the extreme narrowness of the therapeutic window for this metabolically challenging extracorporeal treatment.
Methods: We treated a 70 yo patient with SCUF for refractory congestion during cardiorenal syndrome. SCUF was initiated using Multifiltrate with Ultraflux AV-Set paed (polysulfone, surface 0.2 m^2, Fresenius). RCA was chosen because of ongoing digestive and muscular bleeding. Citrate (trisodium 500 mmol/L) was infused prefilter according to a local protocol. Calcium was infused postfilter as necessary. Parameters were as following: Blood flow rate 45–50 mL/min; ultrafiltration rate 400 mL/h (Hematocrit 35–38%; filtration fraction on plasma 25%). Four 8 hours treatments were performed over 5 days. Close monitoring of plasma water sodium (Na) and acid-base balance was carried out in blood lines at baseline, 30 minutes, 2, 4, 6, and 8 hours.

Figure 1a: Volume balance during SCUF with RCA.



	T0'	T480'
net volume out (liters)	0	-2.979
tot volume in (liters)	0	0.171
tot volume out (liters)	0	-3.15

Figure 1b: Sodium balance during SCUF with RCA.



	T0'	T480'
net Na out (mmol)	0	-168.75
tot Na in (mmol)	0	256.5
tot Na out (mmol)	0	-425.25

Figure 2: Treatment plasma Na, days 1–4.

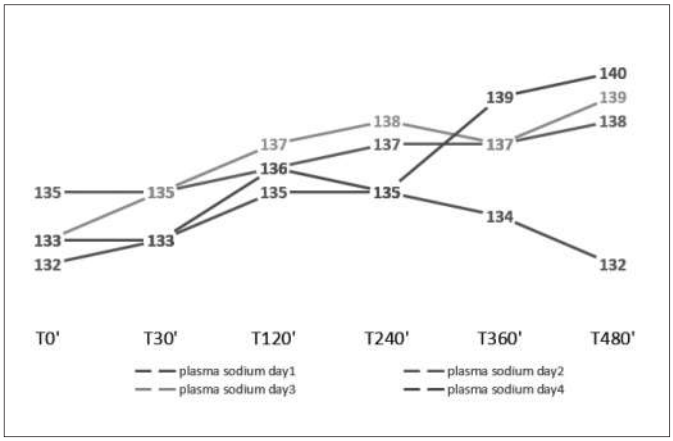
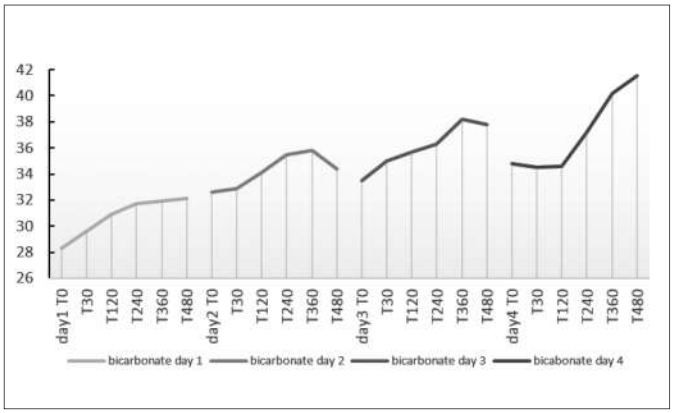


Figure 3: Plasma bicarbonate (mmol/L) days 1–4.



Results: Mean net volume withdrawal was 3000 mL (fig. 1a) per treatment. Net Na withdrawal was defined by the gap between total Na input and output (fig. 1b). The Na-rich citrate solution caused the volume and Na balances to dissociate (fig. 1 a,b), leading to a plasma Na increase (fig. 2). After a theoretical correction, total negative balance related to SCUF was 1.3 kg per treatment and allowed the patient to lose weight thanks to some diuresis under maximal diuretic treatment. The patient underwent SCUF without any complications. Plasma ionized calcium remained stable. Plasma bicarbonate increased progressively despite intensive acetazolamide treatment (fig. 3).
Conclusions: SCUF with RCA can be proposed in only restrictive conditions mostly because of insufficient negative Na balance. Optimization of the prescription is mandatory, as is solid knowledge in citrate pharmacodynamics and handling.

P 53

Chronic dialysis, medication adherence and beliefs about medicines: a comparison between patients born in Switzerland and migrant patients (diana study)

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Background: In the chronic dialysis unit of the Lausanne University Hospital, 52% of the patients are migrants. It is actually unknown whether native patients (born in Switzerland) and migrant patients (born abroad) differ according to medication adherence and beliefs.
Methods: Medication adherence was measured with the self-reported 8-item Morisky questionnaire (MMAS). The 'Beliefs about Medicines Questionnaire' (BMQ) was used to assess general and specific beliefs toward medicines. Results were completed through qualitative interviews, analysed according to the Grounded Theory.
Results: Forty-five out of 94 dialysis patients (48 %) accepted to participate; of these, 24 (53%) were migrant patients. Baseline characteristics are shown in table 1. 33% (n = 15) were classified as highly adherent by MMAS, 40% (n = 18) as moderately adherent and 27% (n = 12) as low adherent. Medication adherence, as measured by MMAS, did not differ between native and migrant patients (Fisher-exact test, p = 0.326). The BMQ showed that all dialysis patients are unanimous in asserting that their treatment is necessary. Opinions differed more in the specific-concerns, the general-harm and the general-overuse subscales. No differences were identified between native and migrant patients (Mann-Whitney test, p >0.05). Qualitative analyses are on-going (n = 18). Themes identified at present are (1) a lack of knowledge and doubts regarding the medication's long-term effects (especially native patients): analogies were identified with the BMQ specific-concerns and general-harm results; (2) relation with caregivers and quality of care: confidence and gratefulness (especially migrant patients) but, for some patients (especially native patients) a need for improved communication.
Conclusion: Medication adherence did not differ between native and migrant patients, yet differences were identified in medication beliefs and knowledge. Understanding patients' cultural background, recognizing individual vulnerabilities and providing tailored answers could improve native and migrant patients' care.

	Migrant patients	Native patients	P-value
Socio-demographic characteristics			
Patients	n_1=24	n_2=21	
Sex			
Female sex	46%	29%	p= 0.233
Age (mean, SD)	49 ± 11	65 ± 16	p=0.0008[2] Δ = -15.3 IC95% [-23.3; -7.24]
Employment (%) (n_1 =15 n_2= 19)			
Employed	13%	32%	p=0.257[3]
Clinical characteristics			
Dialysis			
Hemodialysis	92%	76%	p = 0.225[3]
Peritoneal dialysis	8%	24%	
Transplant list			
Yes	54%	38%	p=0.281
Dialysis vintage, months (median, IQR)	47 (25,89)	22 (9, 40)	p =0.034[4]
Medication characteristics			
Number of pills taken daily (mean, SD)	8 ± 3	9 ± 3	p=0.308[2] Δ = -1.1 IC95% [-3.1 ; -1.0]
Medication (solid form)			p>0.05[1] (for all categories)
Antihypertensive	67%	76%	
$n_{antihypertensive}$=1	54%	57%	
$n_{antihypertensive}$ =2	13%	14%	
$n_{antihypertensive}$ =3	0%	5%	
Phosphate binders	75%	53%	
$n_{phosphate\ binders}$ =1	54%	48%	
$n_{phosphate\ binders}$ =2	21%	5%	
Analgesics	58%	43%	
$n_{analgesics}$=1	50%	38%	
$n_{analgesics}$ =2	8%	5%	
Proton-pump inhibitor	54%	43%	
Potassium binder	25%	33%	
Adherence tool (n_1=20 n_1=14)			p=0.341[3]
No	25%	36%	
Pill organizer (prepared by patient)	10%	29%	
Pill organizer (prepared by pharmacist)	50%	21%	
Pill organizer (prepared by the family)	10%	14%	
MEMS (Medication electronic monitoring system)	5%	0%	

[1] Chi-squared test
[2] Student test
[3] Fisher exact test
[4] Mann-Whitney test

P 54

Preliminary results of dialysis study: single pool variable-volume calcium kinetic model

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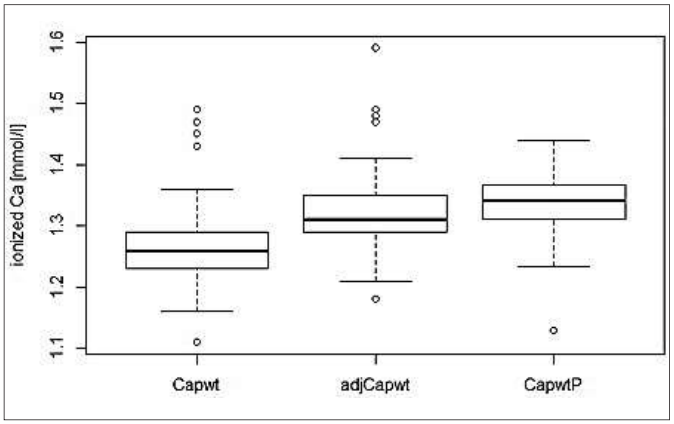
Background: The primary aim of the international study DialysIS (Dialysis therapy between Italy and Switzerland) is the increased personalization of hemodialytic treatments through a modellistic approach. Within the DialysIS study, we investigated the use of a single-pool variable-volume Ca kinetic model to assess the intradialytic calcium mass balance (Ca2 + MB) in chronic and stable dialysis patients.
Methods: 34 patients on thrice-weekly bicarbonate high-flux hemodialysis were studied during 240 dialysis sessions (mean 6.5 ± 1.9 for each patient; range 3–9). All patients were dialyzed with a nominal d[Ca] of 1.50 mmol/l. Ionized calcium concentrations of plasma water (Ca2 + pw) and dialysate (Ca2 + di) were determined at the beginning and end of each session; calcium dialysance (DCa) was estimated from conductivity dialysance. The most useful variable for validating this methodology was considered being the difference between end-dialysis ionized plasma water calcium concentration measured value, normalized to pH 7.40 (adjCa2 + pwtM), and predicted by the model (Ca2 + pwtP) applying:
Ca2 + pwtP = 1/α·(Ca2 + di-(Ca2 + di–α·Ca2 + pw0)·(VtCa/V0Ca) (DCa·α·(1/Qfecv-1/Qpwi)))
With α (Donnan's factor) equal to 0.938. Results shown as mean ± standard deviation when normal, median (range) when non-normal.
Results: A mean negative Ca2 + MB (–0.83 ± 1.33 mmol) and a statistically significant temporary parathyroid hormone (PTH) reduction was found (PTHt-PTH0: –128 (–488 ÷ 432) pg/ml p <0.01). Figure 1 shows the difference between the distribution of the predicted values, the adjusted values (Ca2+pwtP – adjCa2+pwtM: 0.016 (–0.08 ÷ 0.16) mmol/l)and the non-corrected values (Ca2+pwtP – Ca2+pwtM: 0.073 (–0.03 ÷ 0.20) mmol/l).
Conclusions: The very low differences between predicted and adjusted Capwt suggest that it is possible to model and predict Ca2+MB during dialysis with a nominal dialysate calcium concentration of 1.5 mmol/l and a final calcium level in physiological range.
Acknowledgments: Portions of this work were presented in abstract form at the Annual Meeting of the American Society of Nephrology in Philadelphia in November 2014 and the 52nd Congress of the ERA-EDTA.



P 55

"sometimes peritoneal dialysis can last and last and last…" Two cases with a favorable long-term outcome

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Background: Long-term peritoneal dialysis (PD) is often complicated by peritoneal infection, membrane failure and other complications associated with this treatment modality.
Methods: Here we report two cases of elderly women (73 and 83 years) performing uninterrupted PD for more than 8 and 10 years, respectively.
Results: Both patients reached ESRD because of a slowly progressive nephropathy (analgetic nephropathy and chronic glomerulonephritis, respectively).
In both, PD during the whole observation period was performed through the originally implanted catheter with a 4×/day exchange of biocompatible PD fluids. Although in patient one, a single episode of a staphylococcus epidermidis peritonitis occurred 1 year after dialysis start and a surgical mesh reinforced correction of a periumbilical hernia had to be performed, PD was never interrupted. In patient two, neither peritonitis, exit-site infection nor another PD-associated complication were observed during the uninterrupted treatment period reported here.
Although changes of peritoneal membrane function and changes of the residual renal function were observed over time, in both patients dialysis treatment remained reasonably good according to the actual recommended targets by guidelines concerning clearance, mineral and bone metabolism, anemia and hypertension. Furthermore, both patients displayed an excellent and preserved health status over the whole observation period. Unfortunately, patient one died from a sudden, non-PD related complication (stroke) after 8 years and 2 months of performing this modality, whereas patient two is still performing well (10 years and 3 months on PD).
Conclusion: In most PD patients a modality failure due to various PD-associated complications is observed after a few years. However, selected patients may preserve their residual renal function and present with favourable courses. As shown here, these patients can be safely managed for even very long time periods by this technique.

P 56

Is alveolar-arterial pO_2 gradient using arterio-venous fistula sampling useful in estimating dryweight in dialysis patients?

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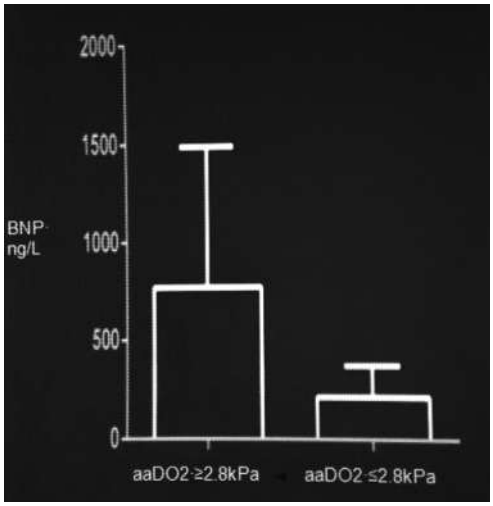
Background: Determination of dryweight remains one of the biggest challenges in hemodialysis (HD) treatment not having a gold standard method to assess it. Alveolar-arterial pO_2 gradient ($aaDO_2$) is a well known parameter for lung water determination that could be useful in estimating overhydration in dialysis. In this study, we compare $aaDO_2$, using well functioning arterio-venous-fistula (AVF) sampling, to other non gold standard methods.
Methods: In a retrospective observational study, we compared $aaDO_2$ and the difference between measured aaDO2 and age-expected $aaDO_2$ ($DaaDO_2$) to brain natriuretic peptide (BNP) and to the OverHydration measured by the Body Composition Monitor from Fresenius Medical Care (OH-BCM).
Results: 31 HD-patients (19 men, 14 women; mean age 70.45 ± 13.85) over a period of 3 years were evaluated. We found a significant positive correlation between $aaDO_2$ and BNP (r = 0.56; p = 0.001), $DaaDO_2$ and BNP (r = 0.46.; p = 0.009), $aaDO_2$ in HD-patients with FE



>55% and BNP (r = 0.64, p = 0.0004), $DaaDO_2$ in HD-patients with FE >55% and BNP(r = 0.52, p = 0.0059) and between $aaDO_2$ and BNP in male HD-patients (p = 0.0258); the correlation between $aaDO_2$ and BNP did not reach strong significancy in female HD-patients (p = 0.05). Patients with $aaDO_2$ >2.8 kPa had a mean BNP of 769 ± 174 ng/L while patients with $aaDO_2$ <2.8 kPa had a mean BNP of 210 ± 41 ng/L (p = 0.0079) [fig.1].
We did not find a significant correlation between overhydration (OH-BCM) and $aaDO_2$ (p = 0.68) or $DaaDO_2$ (p = 0.13). We did not find significant correlations between these parameters and overhydration of >3L or <3L or EF (ecocardiography) of >60% or <60% or positive or negative history of chronic lung disease.
Conclusions: We found a statistically significant correlation between BNP and $aaDO_2$ and $DaaDO_2$ in this group of patients. There was no significant correlation between $aaDO_2$ and BCM-results. Further studies, conducted in a larger sample, are needed to understand if this parameter could be useful in dryweight assessment.

P 57

Pseudomonas exit site infection: treatment outcomes with topical gentamicin in addition to systemic antibiotics

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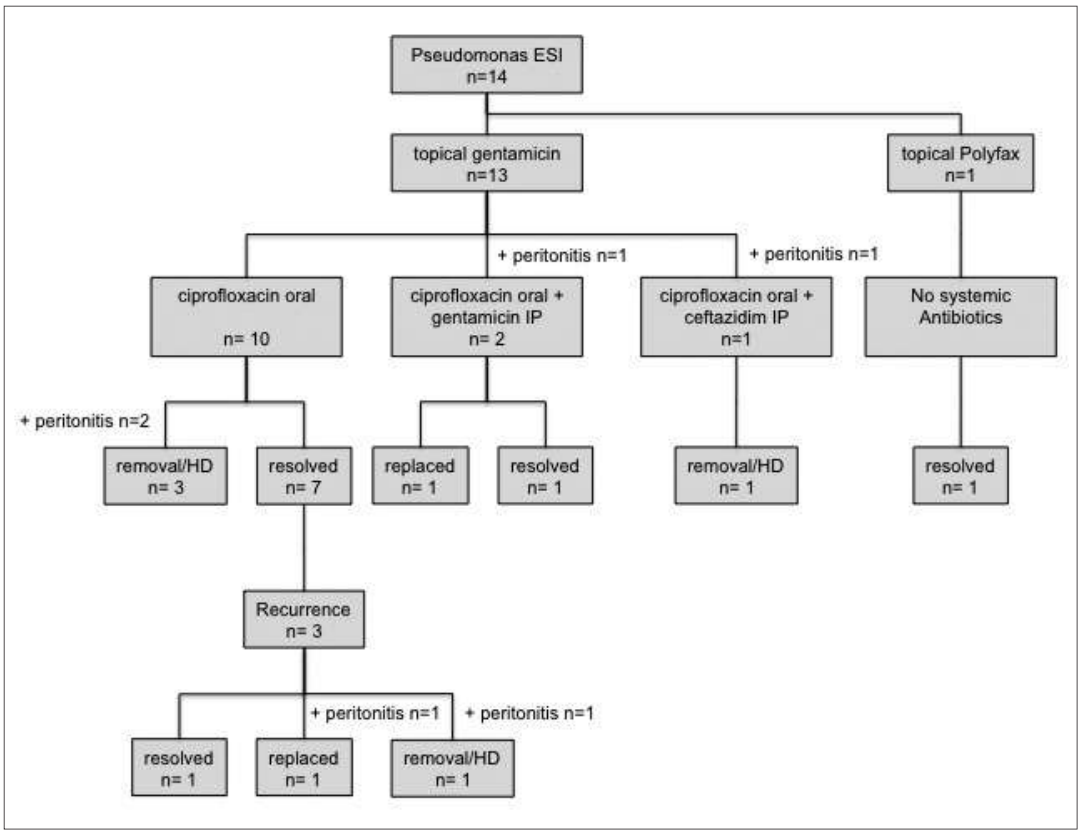
Background: Although, Pseudomonas exit site infection (ESI) is recognised as a major complication of peritonealdialysis (PD) with high risk of catheter loss due to refractory/recurrent infection or Peritonitis, there is remarkably little literature about treatment outcomes. Guidelines advise use of 1–2 antibiotics; in addition we change standard exit site care by stopping prophylactic mupirocin and starting regular use of gentamicin 1% cream.
Methods: This is a single centre retrospective review of the outcomes of Pseudomonas ESI in PD patients from January 2012 until March 2015 at the Imperial College Renal and Transplant Centre, Hammersmith Hospital, London. Patient with Pseudomonas ESI received systemic antibiotic treatment for at least 14 days and the prophylactic topical mupirocin was changed to regular topical gentamicin 1% cream.
Results: During the study period a total of 135 patients were on PD with an overall incidence of any ESI of 0.36 per patient year. There were 14 patients with ESI episodes with Pseudomonas with a rate of 0.12 per patient year. In total 13/14 patients with ESI episodes were treated with oral ciprofloxacin and/or (IP) gentamicin or ceftazidime, plus topical gentamicin with a success rate of 38% (5/13). One patient had gentamicin resistent pseudomonas species and was treated successfully with topical polymyxin/bacitracin. Median follow-up time in cured patients was 385 days (74–1107). Six patients had associated Pseudomonas peritonitis, four during follow-up and two at initial presentation. Three patients had recurrent ESI with Pseudomonas with one successfully retreated with topical and IP gentamicin. In total in only 50% of the patients Pseudomonas ESI was successfully treated. Five of the patients (36%) changed modality to permanent haemodialysis following catheter removal.
Conclusion: Eradication of Pseudomonas ESI remains difficult even with the addition of topical gentamicin to the exit site. There should be a low threshold for catheter replacement.



P 58

Characteristics and outcome of migrant patients without a stable resident status starting hemodialysis in a Swiss university hospital center

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Background: Migrants without permanent resident status is a vulnerable population in regards of medical care access. They frequently present with chronic medical conditions, including CKD. In this work, we analyzed the characteristics and the outcome of migrant patients starting chronic hemodialysis in our center.
Methods: Migrant patients without a stable resident status in Switzerland were retrospectively identified among patients who started hemodialysis between 2010 and 2014 in the hemodialysis center of the University Hospital of Geneva. Demographic and medical data were recorded by reviewing their medical records.
Results: Among 197 patients starting hemodialysis, we identified 13 migrant patients (6.6%, 2.6 patients per year). Seven were asylum seekers, 3 had a tourist visa, and 3 were undocumented. Their demographic and medical characteristics are summarized in table 1 and 2, respectively. Median duration stay in Switzerland before starting hemodialysis was 1288 days, but hemodialysis was started in 4 patients within 30 days. Three of them were already hemodialyzed before arriving in Switzerland. Nine migrant patients (69%) obtained a permanent resident status, 3 went back to their home country and 1 was lost of follow-up. To date, among these 9 patients, 1 died while in hemodialysis, 2 were transplanted and 6 are still receiving hemodialysis. Compared to Swiss resident patients, migrant patients were significantly younger (mean age was 48 vs. 62 years old, p = 0.003) and there were a higher proportion of women (54% vs 32%, p = 0.09).
Conclusions: In our center, nearly 3 migrant patients per year start hemodialysis without a permanent resident status in Switzerland. They are significantly younger and more often female, but otherwise exhibit similar medical characteristics to our resident patients. They are very likely to obtain a permanent resident status. Further analysis will be performed to assess whether they receive similar health care quality once permanent resident.

Table 1: Demographic characteristics of migrant patients.

Age (years old, mean+/-SD)	48 +/- 17
Gender male/female (%)	6/7 (46%/54%)
Country of origin	
West Africa	4
North Africa	2
Horn of Africa	2
Sub-Saharan Africa	2
Afghanistan	1
Kosovo	1
Brazil	1

Table 2: Medical characteristics of migrant patients.

Cause of ESRD	
HTN and DM	4
HTN	1
DM	1
Glomerulopathy	2
Unknown or other	4
Comorbidities	
DM	5
Smoke	4
Heart failure	1
Vascular disease	4
Alcohol abuse	1

P 59

Association between mortality and glycemic control in a large Swiss hemodialysis cohort

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Background: Diabetes is one of the leading causes of end stage renal disease (ESRD) and initiation of renal replacement therapy (RRT) of which haemodialysis (HD) is most prevalent. The Dialysis Outcomes and Practice Patterns Study (DOPPS) as well as others have shown a clear link between poor glycaemic control and early mortality. There is scant information regarding prevalence and outcomes for diabetic patients receiving hemodialysis in Switzerland.
Methods: A prospective, dynamic, 3 year follow-up cohort study of hemodialysis patients from 6 centers in Switzerland (monitor! cohort). Glycaemic control was assessed from HbA1c results that were then further adjusted for albumin (Alb) and hemoglobin (Hb). Biochemical data was collected from routine annual reviews.
Results: Out of 565 patients assessed 37% (n = 207) had diabetes. Cox regression suggested a trend for presence of diabetes and mortality of HR 1.35 that was not significant (p = 0.128; CI 95% 0.917 to 1.978). There was a trend in mortality by gender and diabetes with female HR of 1.63 (CI 0.89 to 2.98) and male HR 1.20 (CI 0.72 to 2.01) which was not significant at p = 0.11 and p = 0.48, respectively. Within the diabetic cohort there was a trend for patients in the "at risk" HbA1c categories (<5.6% = >7.9%) of HR 1.2 and 0.67 for original HbA1c results and HbA1c results adjusted for Hb/Alb, respectively, which were not significant (p = 0.576; CI 95% 0.659 to 2.120 and p = 0.39; CI 95% 0.263 to 1.686).
Conclusions: Unlike many other countries who have found diabetes to be a clear mortality risk factor in hemodialysis patients, there was no significant association noted in this Swiss cohort. The causational factors warrant further investigation.

P 60

Are our patients on hemodialysis at risk for scurvy?

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Background: Vitamin C is considerably removed by hemodialysis, up to several hundred mg per dialysis session. Symptoms of scurvy generally occur with plasma levels ≤ 10µmol/l.
Deficiency of vitamin C is common in dialysis population. A random sampling in our patients without vitamin C supplements confirmed this finding. However, no standardized strategy of supplementation exists so far. The aim of our study was to asses symptoms of scurvy with and without supplementation of Vitamin C.
Methods: Substitution of water soluble vitamins (Dialvit ®) was discontinued in our dialysis population due to a supply shortage by the manufacturer. After six month a questionnaire was handed out to detect symptoms of scurvy (see results). Six weeks after restart of vitamin supplementation (1 capsule Dialvit after each dialysis session = 600 mg/week of vitamin C) the questionnaire was handed out again. Changes in symptoms were analysed in patients with two complete questionnaires.
Results: 69 Patients were included in our analysis. Mean age was 66 years (±15), 62% were male and median time on dialysis was 2.3 [1.3–4.8]. Symptoms of scurvy were common in patients without vitamin C supplementation. Hematoma, sicca symptoms and gum bleedings were reported in 18% (13/69), 17% (12/69) and 4% (11/69), respectively. Subjective symptoms, expressed with a visual analogue scale from 1 to 5 (from 1 = not at all to 5 = absolutely) showed median values for malaise, weakness, muscle or joint pain and depressive mood of 2 [1–3], 2 [1–3], 3 [1–3], 1 [1–3], respectively. Of all symptoms only malaise was significantly decreased after supplementation of vitamin C (p = 0.006, n = 55).
Conclusion: Symptoms of scurvy are frequent on hemodialysis. With our supplementation strategy malaise significantly improved during our observation period. The optimal dosage for supplementation remains unclear. Further studies are needed to clarify the role of vitamin C supplementation in patients on hemodialysis.

P 61

Treatment satisfaction with renal replacement therapy in the frail elderly depends on recovery time after dialysis: Data from Frail Elderly Patients Outcomes on Dialysis (FEPOD) Study

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Introduction: Treatment goals in older patients on dialysis should focus on quality of life (QoL) and satisfaction with treatment. Longer recovery time (RT) after haemodialysis (HD) is known to be associated with poorer QoL, but its effect on treatment satisfaction is unknown. There are no data about RT after automated peritoneal dialysis (APD) especially in old frail patients.
Methods: In this cross-sectional multicentre case control study in frail elderly patients on HD or assisted APD (aPD), influence of RT on QoL and treatment satisfaction was analyzed. Frailty was assessed using the Canadian Study of Health and Aging Frailty scale, QoL assessments included Hospital Anxiety and Depression Scale, Illness Intrusiveness Rating Scale (IIRS) and Renal Treatment Satisfaction Questionnaire.
Results: RT was available for 203 patients (100 HD, 103 aPD) of 251 patients included in FEPOD. aPD patients had higher frailty score ($p = 0.049$) than HD patients. RT after dialysis was significant longer in HD patients compared to aPD patients ($p < 0.0001$). There were 34 HD patients with a RT of 0–2h, 38 patients with 2–6h, 11 patients with 6–11h and 16 patients with >12h. Only 6 patients on aPD had RT >2h. The longer RT was independently associated with lower satisfaction ($p = 0.0273$) and higher IIRS ($p = 0.0039$) in HD patients. Despite the higher frailty score of aPD patients, they were more satisfied with their treatment than HD patients ($p = 0.0042$).
Conclusion: Prolonged RT after APD is rarely observed in frail elderly patients, whereas in HD patient it is very common. The prolonged RT in HD patient is associated with lower treatment satisfaction. Overall treatment satisfaction was significant better in aPD patients compared to HD patients despite higher frailty score. This observation should be part of the information given to elderly frail patients when making decisions about dialysis modality.

P 62

Safety of Regional Citrate Anticoagulation during extended High Cut-Off hemodialysis for the clearance of serum free light chains: The Lausanne experience.

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Background: Extended High Cut-Off (HCO) hemodialysis is a particular blood purification treatment dedicated to the clearance of serum Free Light Chains (sFLC) during myeloma cast nephropathy. Heparin is the anticoagulant most frequently used during HCO hemodialysis. Heparin can be however contraindicated in this particularly frail population of patients whose condition is typically characterized by an increased risk of bleeding. Indeed, Regional Citrate Anticoagulation (RCA) is a very attractive method at some point during these patients medical history. During the last 3 years at the CHUV, we implemented a protocol of RCA for hemodialysis for which a motivated team was trained. We prospectively assessed the safety of our local protocol for RCA during HCO hemodialysis.
Methods: Confirmation of cast nephropathy by biopsy was mandatory. Bleeding risk was considered to be increased in relation with active bleeding, severe thrombopenia or in the week after a renal biopsy. HD was performed with the high cut-off hemodialyser Theralite 2100 (Gambro, Baxter). Regional anticoagulation was provided by a citrate solution and a calcium free dialysate (AC-F 219, calcium 0 mmol/L, Fresenius). Trisodium citrate (500 mmol/L) was infused prefilter and a calcium solution was infused post filter according the local protocol. Parameters were as following: Blood flow rate 300–350 mL/min; Dialysate flow rate 500 mL/min. Albumin was substituted as requested. Close monitoring of plasma electrolytes and acid-base balance was carried out in blood lines at baseline, time 15, 60, 120, 180, 240, 300, 360, 420 and 480 minutes.
Results: we reported 70 HCO hemodialysis in 10 patients. Treatment was well tolerated without any metabolic and electrolytic complication. Ionized calcium showed to be stable throughout the duration of treatment (fig. 1).
Conclusions: RCA during HCO hemodialysis can be safely implemented in a tertiary hospital providing that a secure protocol is mastered by a well trained team.

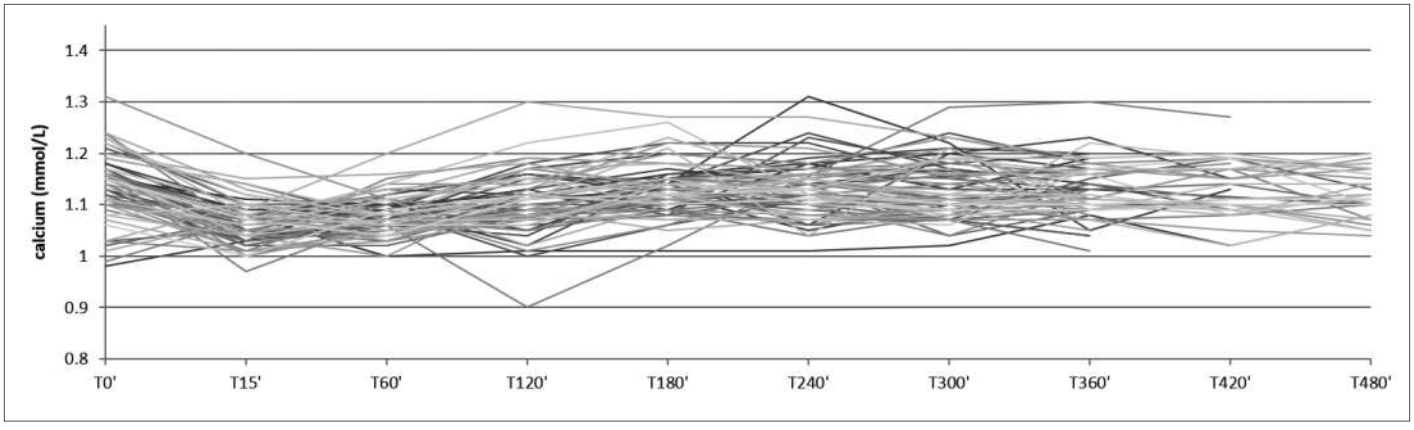

Figure 1: Plasma ionized calcium during HD with RCA (6–8 hours treatment).

P 63

Statistical analysis of large amount of data aimed at the development of a index to predict intra-dialysis hypotensive events

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Background: The increase of aged patients with concurrent comorbities imply also a growth in end stage renal diseases incidence. HaemoDialysis (HD) has than a large medical, social and economical impact for health care systems. The personalization of the therapy is strategic to reduce costs and it can be performed basing on the information acquired by the collection the clinical data related to the treatment.
The current work attempts to the extraction of an intradialytic hypotensive (IDH) events prediction index through the statistical mining of HD data coming from a multicentric study involving four different Italian and Swiss clinical centers. This work is part of the Project DialysIS, founded by a Cross-border Cooperation Programme (INTERREG IT/CH 2007–2013).
Methods: Data referred to a total of 516 sessions performed on 70 adult patients undergoing dialysis treatment were collected. Clinical prescriptions, hydration status, dialysis machine data and

hematochemical data were recorded in a flexible structured database. A statistical analysis was performed to find risk factors for IDH onset. The enrolled patients were classified in IDH prone and resistant, defining Hypotension Prone (HP), a patient who suffered of IDH in 2 or more session and Hypotension Resistant (HR) a patient who suffered at most 1 IDH episode. F and T test was performed on data to determine the significantly different parameters among the two groups. The new index J was defined as a weighted patient-specific combination these parameters, and was calculated for each session of each patient.
Results: Using these patient specific coefficients, J results able to predict the 100% of treatments characterized by IDH events, with 38% of false positives (session at risk of IDH, without IDH onset).
Conclusions: The J index can point out the risk to develop cardiovascular instabilities during each single treatment based on longitudinal observations of the patient specific parameters.

P 64

Evaluation of the reliability of different methods for the determination of the hydration status in haemodialysis patients

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Background: Determination of hydration status in Haemodialysis patients is crucial to correctly assess the dry weight and calculate the amount of excess fluid to be removed by ultrafiltration (UF). The Total Body Water (TBW) can be estimated by different techniques, from mathematical equations to bioimpedance analysis. Several formulas were used to estimate initial Total Body Water (TBW0) based on demographic or anthropometric data. The aim of this study was to compare the different available methods to identify the most objective and reliable method to be used for a correct identification of the TBW in patients undergoing haemodialysis. This work is part of the project DialysIS, founded by a Cross-border Cooperation Programme (INTERREG IT/CH 2007–2013).
Methods: TBW0 was calculated by using a classical basic anthropometric formula (TBW-A), the Watson formula (TBW-W) and the Watson formula modified with a correctional term (TBW-Wc), accounting for the part of fluids not drained by the kidneys. The last equation was applied using either real end session weight (TBW-WcR) or the clinically prescribed dry weight (TBW-WcP). TBW0 was computed using the listed methods for 450 haemodialysis sessions pertinent to 70 patients dialyzed in two different dialysis centres (A. Manzoni Hospital, Lecco, Italy; EOC Lugano, Switzerland).
Results: The modified Watson formula, thanks to the correctional term, allows obtaining more precise measurements: TBW0 values were comprised between those determined with TBW-A (overestimation) and those achieved by TBW-W (underestimation). The differences among the set of values were statistically significant; exception made for those obtained using TBW-WcR and TBW-WcP.
Conclusions: TBW-WcP enables to reach estimations of the TBW initial value comparable to the ones calculated considering the real end session dry weight (TBW-WcR), with the advantage to be suitably used in a predictive algorithm. The anthropometric formula, as well as Watson equation without correctional term, showed to be less robust methods.

P 65

Peritoneal dialysis: training and peritonitis

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Background: The incidence of peritonitis (P) is an indicator of quality which we collect every three months. Since this index has worsened in the last 3 years, the purpose of this study is to analyse the causes and verify how effective the corrective measures are.
Methods: We analysed all the cases of P, the type of germ and the outcome before and after the introduction of a care therapeutic diagnostic course (Italian acronym PDTA). This PDTA is an easy-to-use instrument composed of coloured squares which take the pt from the “symptoms” to the “diagnosis” to “what to do” step by step.
Results: From 01.01.12 to 31.12.14, we treated a total of 115 patients in PD, 78 had no sign of P, in 17 there was 1 case of P, in 20 2 or more cases of P. The first P occurs 22 months after the beginning of peritoneal dialysis, in 34% of the P the diagnosis is not recognised by the patient and is made when he arrives in the ward. The incidence of P goes from 1P/55m/pt in 2012 to 1P/35m/pt in 2013 and 1P/22m/pt in the first 9 months of 2014 (A2014). In 2012 the P from GRAM- prevailed (56%), in 2013 the cases of peritonitis from GRAM- were 6%, whereas the cases of peritonitis from GRAM+ were 88%, in 2014 the P from GRAM- were 17% and the cases from GRAM+ were 62%. After the PDTA the incidence of P fell to 1P/26m/pt. (B2014) In the first three months of 2015 the incidence of P was 1P/58m/pt.
Conclusions: The PDTA has made patients more aware and they have asked many questions relating to prevention, risks and complications of P. The PDTA has proved to be a simple and effective instrument.

P 66

Bloodstream infections and local access site infection surveillance program in hemodialysis, Vaud, Switzerland

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Background: Patients on chronic hemodialysis (HD) are at risk of developing bloodstream infections (BSI) and local access site infection (LASI) that engender high morbidity and mortality. In 2007, a BSI and LASI infections surveillance program was created in the HD centers of the canton of Vaud. Between 2007–2013, this surveillance program encountered organizational difficulties and failed to obtain representative data. The aim of this intervention was to improve the surveillance program and to produce usable data reflecting the local situation.
Methods: In order to improve infection data collection, a nurse was designated as Surveillance nurse in each center in 2013. A standardized methodological framework was established. Surveillance nurses in the centers were audited on work methodology and trained by the Senior Infection Control Nurse Specialist to recognize and report infections in the questionnaire and they were offered regular contact to discuss problems encountered.
Results: The number of reported infections is increasing, in particular regarding LASI. 54 episodes of BSI and LASI were reported in 2014 compared to 16 in 2013, for an equivalent number of HD sessions. In 2013, among the 16 episodes, 12 were BSI and 4 were LASI (3 catheter infections and 1 fistula infection). In 2014, 30 were BSI and 23 were LASI (21 catheter infections and 2 fistula infections).
Conclusion: The adapted surveillance strategy lead to a 3.5 fold increase in the number of reported infections, especially LASI. These results strongly suggest that auditing and training nurses in HD centers helped us to increase the quality of BSI and LASI reporting. Whether the increased number of reported infections is solely due to improved surveillance or also represents an increase incidence of infections among dialysis patients in the canton of Vaud will- thanks to this program -become clear in the coming years.

P 67

Not everybody is created equal: Do we have a gender issue in the Swiss dialysis population?

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Background: For many medical specialties, a gender gap regarding diagnosis, research and treatment has been postulated. Specifically, enrollment of women into clinical trials is lower and cardiovascular disease outcomes are worse compared to men. No systematic analyses on gender distribution and characteristics have been performed so far in patients with endstage renal disease (ESRD) on renal replacement therapy in Switzerland.
Methods: The Swiss Renal Dialysis Registry (srrqap) has been analyzed on prevalent data as per December 31 2014. Demographic and clinical factors were compared stratified by gender.

Results: A total of 4177 patients with valid gender information were available for analysis. Among those, only 36.6% were female. Women and men were of comparable mean age (67.4 vs. 67.1 yr, respectively), but time since start of dialysis in female patients was significantly longer (62.9 vs. 55.5 months). In contrast, Charlson comorbidity score was significantly lower in women (4.13 vs. 4.57). Specifically, the prevalence of type 2 diabetes mellitus (T2DM) was only 28% among female compared to 34% in male dialysis patients (p = 0.000). Also, T2DM with end organ damage was less frequent in women (25% vs. 29%, p = 0.000). Accordingly, myocardial infarction (12 vs. 8%), heart failure (22 vs. 20%) and peripheral vascular disease (22 vs. 29%) were all significantly less prevalent among women vs. men. The percentage of women vs. men dying on dialysis in the year 2014 was 11.6 vs. 10.7%, respectively (p = NS).
Conclusions: Like in many other European countries, less than 40% of the dialysis population in Switzerland is female. This may be explained in part by a potentially lower prevalence of T2DM in women with chronic kidney disease. However, referral bias or poorer survival of females on dialysis cannot be ruled out from these data.

P 68

The first hemodialysis unit in a nursing home in Switzerland: experience of the first 4 years

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Background: The ''Istituti Sociali Comunali di Lugano" has 6 nursing homes (NHs) with a total of 567 residents. On April 1st /2011, to our knowledge, the first hemodialysis unit in Switzerland was opened, under our direction, in the biggest and most centrally located NH.
Methods: We report our experience of the first 4 years as a retrospective observation.
Results: During the observation period 33 patients were treated.
21 patients were admitted to the NH for old age. 2 patients entered for chronic psychiatric disease, 7 for end-of-life care (tumor 6, amyloidosis 1) and 3 for vascular complications of diabetes mellitus; most of these patients were younger.
20 of the old patients started with hemodialysis before entering in NH: age at entry 82.05 ± 5.85 years (min 70, max 93), time on HD prior to NH-entry: 48.7 ± 31.8 months (min.1, max.111).
During the observation period 63.6% of these patients died. Mortality was 38.9% at 6 months, 52.9% at 12 months, 62.5% at 24 months.
1 patient started on HD while he was already resident in the NH, at age of 85 years; despite the short life expectancy, that could be anticipated in his case, he was still alive on March 30/2015, after 41 months on HD.
At the end of the observation period, 9 of the 11 prevalent NH-HD patients had a central venous catheter as vascular access.
Conclusions: The described HD unit allows to treat our most frail and debilitated patients in the comfort of the NH-setting. Our old patients are much older and live longer on HD, compared with the little published data, that come mostly from the US. Central venous catheter is the most frequently used vascular access.

P 69

Demography of the Dialysis Population 2013 in Switzerland – The Swiss Dialysis Registry srrqap

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Background: The national Swiss Renal Registry and Quality Assessment Program (srrqap) has been established in the year 2006. However, participation is significant only since 2013, when data collection became mandatory by law. The primary aim of the "Registry" is to provide quality control and quality improvement in dialysis therapy in Switzerland. In the present analysis, select demographic characteristics of the Swiss dialysis population in 2013 are given.
Methods: All medical establishments in Switzerland (both public and private; N = 85) providing chronic treatment by either hemo- and/or peritoneal dialysis, had to provide relevant data for the year 2013. All individuals being on chronic dialytic therapy in the year 2013 were enrolled. For patients alive on December 31 2013, data were gathered from this date or closest to this date. For patients who died during 2013, data refer to time of death (i.e., age), or to a date closest to death. For all patients, the minimal data set required by the ERA-EDTA registry was applied.
Results: A total of 3712 patients from 81 centers were reported to the Registry, reflecting a coverage of 96% of all patients being treated in Switzerland during 2013. Age, dialysis vintage, number of comorbidities, percentage of hypertensive patients and distribution of sex are given in table 1, stratified by dialysis modality ("in centre" vs. "home" treatment). Diabetic nephropathy was the most frequent cause of ESRD (16.9%), and coronary heart disease the most abundant comorbidity (38.9%). The most common cause of death was termination of dialysis treatment (12%).
Conclusions: After almost two decades, complete dialysis treatment demographics in Switzerland became available again in 2013 and data were being contributed to the ERA-EDTA registry. With a coverage of >95% for both centres and patients, the data gathered by the Registry and reported herein can be considered highly representative.

Table 1

	All (100%)		In Centre (91.5%)		Home (8.5%)	
	Mean	Median	Mean	Median	Mean	Median
Age, yr	67.3	70.2	68.2	71.1	61.6	63.5
Dialysis vintage, months	57.2	37.0	57.3	39.0	56.9	25.0
Comorbidities, N	4.47	4.0	2.23	4.0	1.86	3.0
Hypertensive, %	79.6		79.2		84.9	
Sex (male), %	62.6		62.4		60.4	

P 70

Belatacept-treated patients had superior estimated glomerular filtration rate (GFR) vs cyclosporine-treated patients: results from a mixed effects modeling analysis of BENEFIT

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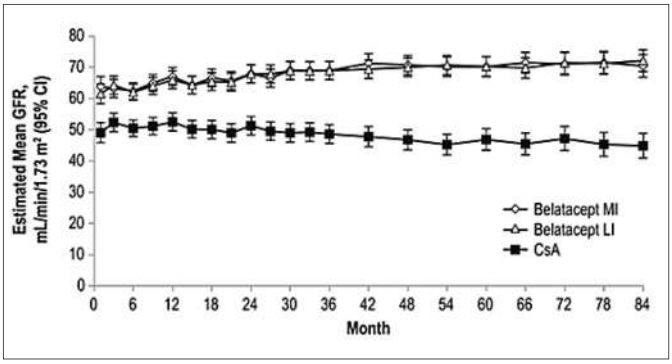
Background: Prior analyses of BENEFIT showed significantly higher mean estimated GFR for belatacept vs cyclosporine. We report GFR estimated from a longitudinal modeling analysis of the BENEFIT ITT population over 7 years. This model accounts for between-subject variability and the intrasubject correlation between GFR across all time points and assumes that missing data are missing at random.
Methods: Recipients of living or standard criteria donor kidneys received belatacept-based more (MI) or less intense (LI) or cyclosporine-based immunosuppression. Estimated mean GFR and 95% CIs without imputation were determined from months 1–84 using a repeated-measures model with an unstructured covariance matrix that included treatment, time (categorical), and a time × treatment interaction. A slope-based model without imputation was used to determine whether there were differences between slopes. Slopes were compared using contrasts; treatment was regarded as a fixed effect and intercept and time (continuous) as random effects. No adjustment was made for other potentially confounding covariates in either model.
Results: Estimated mean GFR increased slightly over 7 years for belatacept but declined for cyclosporine. Estimated mean GFR for belatacept MI at months 12, 36, 60, and 84 was 67, 69, 70, and 70 mL/min/1.73 m^2, respectively. The corresponding values for belatacept LI were 66, 69, 70, and 72, and for cyclosporine were 52, 49, 47, and 45 mL/min/1.73 m^2. Estimated differences in GFR favored each belatacept-based vs cyclosporine-based regimen (P<0.001 for overall treatment effect). Slope estimates from year 1–7 were 1.30 (95% CI: 0.83–1.77) for belatacept MI, 1.39 (95% CI: 0.93–1.84) for belatacept LI, and –1.04 (95% CI: –1.53 to –0.54) for cyclosporine. Slope estimates favored belatacept vs cyclosporine (P <0.001).
Conclusions: The significant improvement in renal function seen with belatacept vs cyclosporine is sustained over 7 years, with increasing divergence between regimens over time.



P 71

Acute humoral rejection after AB0 incompatible transplantation successfully treated with bortezomib

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Background: The proteasome inhibitor bortezomib was developed for the treatment of multiple myeloma. Bortezomib has a broad spectrum of effects on plasma cells and is therefore an intriguing agent for treating antibody-mediated rejection (AMR).
Case report: A 26-year-old female with end stage renal disease due to lupus nephritis was AB0O-incompatible living donor kidney transplanted (AB to A blood group). Pre-transplant, no donor-specific antibodies (DSA) were detectable by single antigen beads. The desensitization regimen consisted of: 375 mg/m^2 rituximab 4 weeks before transplantation, maintenance immunosuppression including tacrolimus, mycophenolate mofetil, and prednisone starting 2 weeks before transplantation, and 8 antigen-specific immunoadsorption treatments with the aim of reducing isoagglutinin titer to <1:8. On day 5, an indication biopsy was performed due to delayed graft function showing minor glomerulitis and moderate peritubular capillaritis. We started treatment with methylprednisolone and thymoglobuline for 4 days and treated an isoagglutinin titer rebound (anti-B-IgG titer 1:32) with additional 10 plasma exchanges.Serum creatinine stabilized to a baseline of 188 umol/l and isoagglutinin titer remained <1:8. No DSA were detectable.One week later, serum creatinine increased to 306 mumo/l. Indication biopsy showed moderate endotheliitis, and glomerulitis, and severe pertubular capillaritis. A therapy with methylprednisolone, intravenous immunoglobulin, bortezomib, and 14 plasma exchanges was started, thereafter serum creatinine stabilized at a baseline of 181 umo/l (eGFR 30/ml/min/1.73 m^2) until day 60 post-transplant.
Conclusion: In this case report, the combined strategy of bortezomib to abrogate antibody production and plasma exchanges to remove circulating antibodies has proven to be successful as a rescue treatment for AMR in AB0-incompatible transplantation. Bortezomib may be a valid adjuvant to the conventional treatments until more effective antirejection agents will be available.

P 72

The Bernese Renal Osteometabolic Registry (RenOS) – A comprehensive approach of chronic kidney disease-mineral bone disorders (CKD-MBD) in renal transplant recipients

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Background: The chronic kidney disease–mineral bone disorder (CKD-MBD) is a constellation of mineral, bone, and vascular disorders, which is virtually omnipresent in renal transplant recipients (RTR) and linked to adverse outcomes.
Methods: In 2012 we initiated the translational project "RenOS: Renal Osteodystrophy and Sarcopenia" aiming at a comprehensive approach of CKD-MBD in renal transplant recipients (RTR). More than 300 RTR have been assessed in our registry for musculoskeletal disorders utilizing dual x-ray absorptiometry (DXA) for both bone mineral density (BMD) and muscle/fat mass and vertebral fracture/calcification analysis, along with laboratory markers of CKD-MBD.
Results: A cross-sectional analysis of our cohort showed that 52/301(17.3%) experienced an osteoporotic-related fracture (ORF) during follow-up. There were no statistically significant differences between patients with ORF vs non-ORF concerning demographics, clinical characteristics, CKD-MBD related drugs (incl. calcium and vitamin-D supplements, phosphate binders and cinacalcet) and laboratory parameters. BMD evaluation by DXA showed that patients with ORF had significantly lower BMD at the lumbar spine (BMD:0.909 ± 0.167 vs. 0.987 ± 0.160, p = 0.075; T-Score:-1.58 ± 1.49 vs 0.78 ± 1.45, p = 0.002) and the femoral neck (BMD:0.684 ± 0.123 vs 0.727 ± 0.130, p = 0.04; T-score:-1.74 ± 0.96 vs -1.37 ± 1.02, p = 0.028) compared to those without ORF.
Conclusion: Osteoporotic related fractures are common among RTR and linked to diminished BMD at lumbar spine and femoral neck. Our registry can serve as an excellent research basis for the exploration of relevant clinical questions and facilitate patient recruitment for future interventional trials.

P 73

Association of a common polymorphism of the ABCB1 gene (rs1045642) with bone mineral density and blood pressure at one year in a single center kidney transplant recipient cohort: intermediate analysis (supported by the Swiss Kidney Foundation)

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Background: The efflux transporter permeability glycoprotein (PGP) modulates the absorption of corticosteroids, commonly prescribed during the first year after kidney transplantation, and which adverse events include among others, bone mineral density (BMD) loss and hypertension (HTN). ABCB1, encoding for PGP, has several known single nucleotide polymorphisms (SNPs) influencing the transporter selectivity and, thereby the exposure to corticosteroids. We investigated the association of a SNP for ABCB1 (rs1045642; C3435T) with the evolution of BMD and systolic/diastolic blood pressure (SBP/DBP) at one year among a cohort of kidney transplant recipients.
Methods: 40 first kidney transplant recipients have been included in Geneva University Hospitals. We excluded patients of African or Asian descent, and those receiving a steroid free protocol. Genotyping was performed by pyrosequencing using specific primers in a lab blinded for clinical data.
Results: Mean patients age was 52 years (±14). Frequency of the rs1045642 genotypes (CC: 37%, CT: 45% and TT: 17.5%) did not deviate from Hardy Weinberg equilibrium (chi-test 0.15; p 0.69). Patients with a non-CC genotype (i.e. CT and TT) had a significantly lower office SBP at one year when compared with CC (130 mm Hg +/–13 vs 145 mm Hg +/– 13; p-value = 0.003; fig. 1). An association was confirmed when adjusting for several confounding factors (age, BMI, kidney function, nephropathy). A clear trend (fig. 2) but no statistically significant association was observed between rs2032588 genotypes and BMD and/or t-score. Strikingly, among the TT patients, none had a clinically significant absolute BMD loss (i.e., < –0.028 g/cm^2) independently of comedications (eg. bisphosphonates).
Conclusion: Intermediate analysis found that rs1045642 is associated with office SBP at one year post transplantation. Although not statistically significant, a trend is observed towards an association of TT genotypes with the absence of clinically significant bone loss at one year. Further recruitment and analyses are warranted.

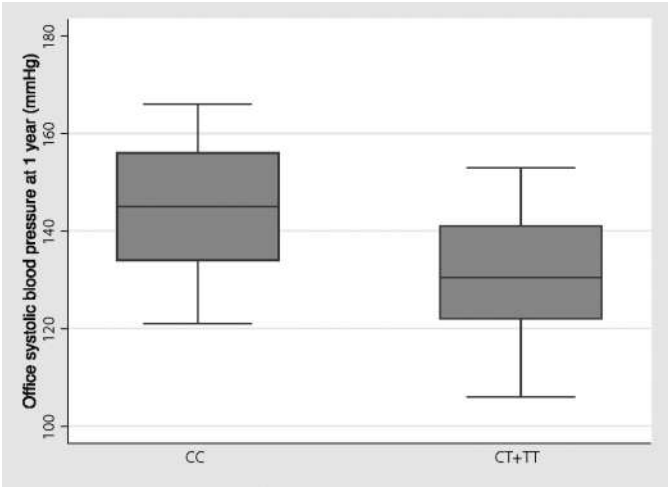

Figure 1

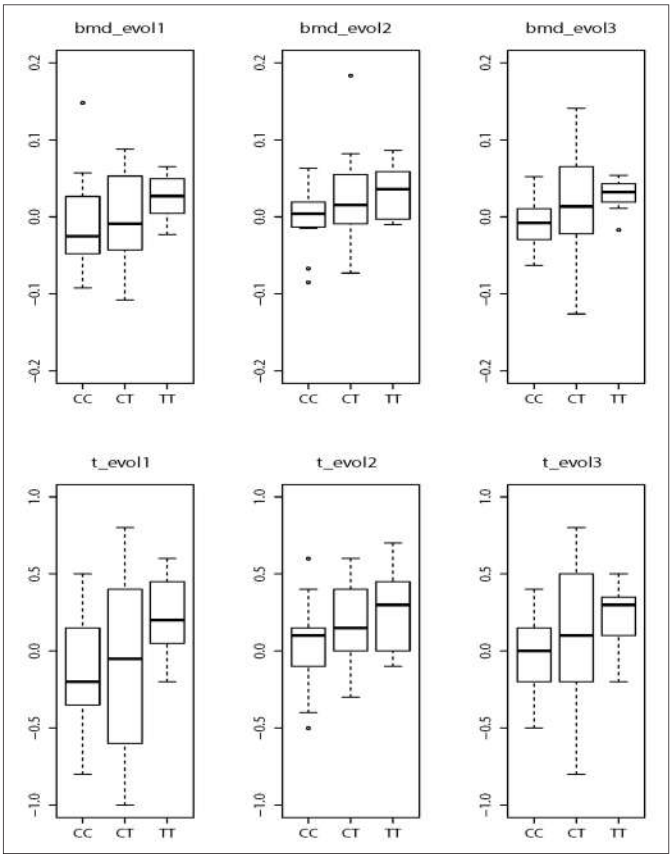

Figure 2: Bone mineral density (bmd) and t-score (t) evolution over one year post transplantation by rs 1045642 genotype (1: lumbar site, 2: proximal right hip, 3: femoral neck)

P 74

Rejection phenotypes in the current era of immunosuppression

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Background: Renal allograft rejection is classified by histology using Banff scores. Beside criteria for the definitive diagnosis of rejection, the Banff classification also includes categories for limited rejection lesions coined as 'suspicious for rejection'. The aim of this study was to assess the frequency of these rejection phenotypes in the current era.
Methods: 316 consecutive ABO-compatible transplants from 2009–2014 were included and grouped by the presence/absence of preformed donor-specific HLA-antibodies (DSA) into DSA+ (n = 65) and normal-risk (n = 251). All adequate indication (n = 122) and surveillance biopsies (n = 557) performed within the first year post-transplant were classified according to the current Banff criteria into antibody-mediated (ABMR) and T-cell-mediated (TCMR) rejection.
Results: Overall, 'suspicious for rejection' phenotypes were slightly more common than definitive rejection phenotypes in DSA+ transplants (28% vs 23%) and three-times more frequent in normal-risk transplants (35% vs 11%). Although 'suspicious for rejection' phenotypes were less frequent than definitive rejection phenotypes in indication biopsies (DSA+ transplant: 25% vs 41%; normal-risk transplants: 21% vs 23%), they were still observed in >20% of the biopsies. The dominant 'suspicious for rejection' phenotypes in DSA+ transplants were of the ABMR type, in normal-risk transplants of the TCMR type. On the patient level, inclusion of 'suspicious for rejection' phenotypes increased the one-year incidence of clinical rejection (DSA+: 24% vs 16%, p = 0.22; normal-risk: 14% vs 8%, p = 0.006) and (sub)clinical rejection (DSA+: 65% vs 34%, p = 0.003; normal-risk: 57% vs 21%, p <0.0001).
Conclusions: In the current era of immunosuppression, 'suspicious for rejection' phenotypes are very common with equal or up to 3-times higher frequency than Banff-defined rejection. Further research is required to investigate the significance of these presumably low-grade rejection lesions.

P75

Clinical significance of isolated v-lesions in kidney transplantation

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Aim: The aim was to investigate the frequency and impact on long-term graft survival of isolated v-lesions appearing <1 year after kidney transplantation with different HLA-risk.
Methods: In this retrospective analysis, 620 recipients with different HLA-risk (AB0-compatible without pre-transplant HLA-DSA: n = 457, with HLA-DSA: n = 111, and AB0-inkompatible: n = 52) were taken protocol and indication biopsies <1year post-transplant and classified into three groups: (i) v+ rejection group, (ii) v- rejection group, and (iii)

no rejection group. Isolated v-lesions were defined as v1-3 but i≤1 and/or t≤1.
Results: Out of 354 patients with rejection episodes, 96 (27%) patients showed v-lesions. Of these, 50 (14%) had isolated v-lesions, 26 (7%) v-lesions with AMR, 16 (5%) with TCR, and 4 (1%) with mixed rejection. At 10 years post-transplant, graft survival was significantly inferior in v+ rejection group: 46% vs 70% for v- rejection and 75% for no rejection group, p <0.007. Isolated v-lesions showed negative impact on long-term graft survival, similar to v+ rejection with AMR, TCR or mixed (p = 0.64). When looking at the different HLA-risk transplantations, isolated v-lesions appeared with similar frequency: 36/68 (53%) and 7/15 (47%) in AB0-compatible without HLA-DSA and with HLA-DSA and 7/13 (54%) in ABO-incompatible transplantations. Also within the different HLA-risk transplantations, isolated v-lesions were as prognostically significant as v+ rejections (p >0.44).
Conclusions: The early appearance of isolated v-lesions is common among patients with v-lesions and negatively affects long-term graft survival in all HLA-risk transplantations. The data suggest that these lesions are more common and clinically significant than previously thought.

P 76

Long-term survival outcomes in belatacept-treated vs cyclosporine-treated patients: final results from BENEFIT-EXT

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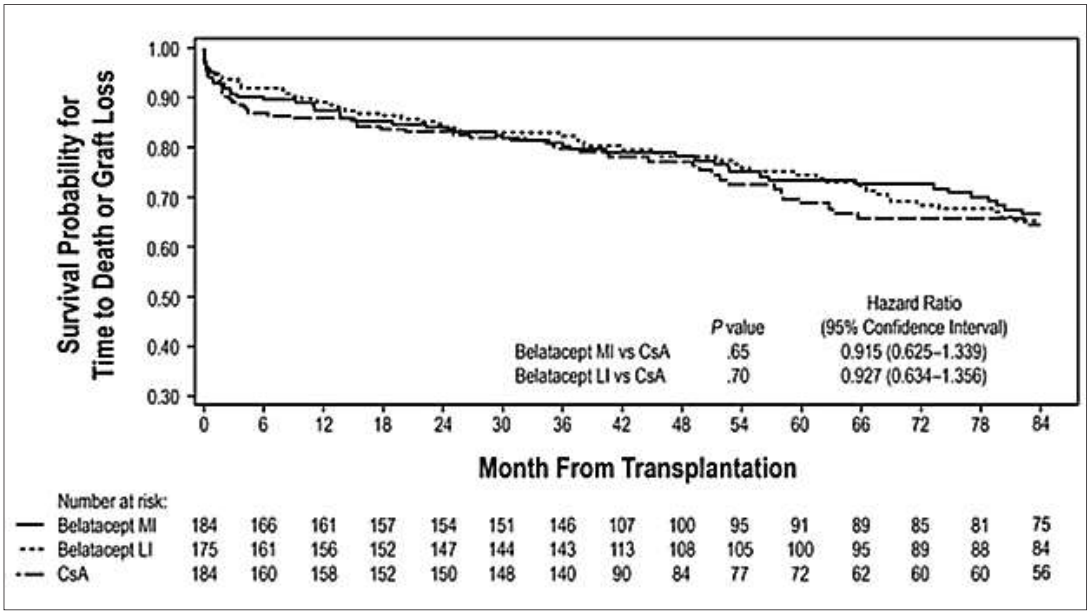
Background: At 3 and 5 years post-transplant in BENEFIT-EXT, renal function benefits and similar patient/graft survival were seen in belatacept-treated vs cyclosporine-treated kidney transplant recipients. We report final 7-year results from BENEFIT-EXT.
Methods: Recipients of extended criteria donor kidneys received more (MI) or less intense (LI) belatacept-based or cyclosporine-based immunosuppression. All randomized, transplanted patients were analyzed through 7 years. In this prospective analysis, time to death or death-censored graft loss was compared between regimens using Cox regression. Presence of donor-specific antibodies (DSAs) was determined centrally. Kaplan-Meier estimates were calculated for the cumulative rate of de novo (DN) DSA development.
Results: In total, 128/184 belatacept MI-treated, 138/175 belatacept LI-treated, and 108/184 cyclosporine-treated patients were evaluable for death/graft loss at year 7. Hazard ratios (HRs) comparing time to death/graft loss were 0.915 for belatacept MI vs cyclosporine (P = .65) and 0.927 for belatacept LI vs cyclosporine (P = .70). Mean MDRD eGFR (ANOVA) at month 84 for belatacept MI, belatacept LI, and cyclosporine was 58, 59, and 45 mL/min/1.73 m^2, respectively. HRs comparing rates of freedom from death, graft loss, or eGFR <20 mL/min/1.73 m^2 were 0.754 for belatacept MI vs. cyclosporine (P = .10) and 0.706 for belatacept LI vs. cyclosporine (P = .05). Cumulative DN DSA rates at years 3, 5, and 7 were 2.32%, 6.21%, and 6.21% for belatacept MI; 1.52%, 2.39%, and 4.48% for belatacept LI; and 11.25%, 17.07%, and 22.87% for cyclosporine, respectively. Rates of serious AEs (87%, belatacept MI; 89%, belatacept LI; 84%, cyclosporine) and exposure-adjusted incidences of serious infections and malignancies were similar across regimens. Nine PTLD cases occurred before month 84 (n = 2, belatacept MI; n = 6, belatacept LI; n = 1, cyclosporine).
Conclusions: At 7-years post-transplant, belatacept was associated with similar death/graft loss, improved renal function, and a reduced incidence of DN DSAs vs. cyclosporine, with a safety profile consistent with prior reports.



P 77

Control of blood pressure at 6, 12 and 24 months after kidney transplantation: data from the STCS

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Background: Prevalence of hypertension (HTN) is high after kidney transplantation and has been associated with graft failure, death-censored graft failure and death. The Swiss Transplant Cohort Study (STCS) is a national prospective of solid organ transplant (SOT) patients since 2008. No data on the prevalence of HTN and uncontrolled HTN (uHTN) has been reported from this cohort so far.
Methods: Patients' characteristics including blood pressure (BP) data were recorded at 6, 12 and 24 months. HTN was defined as BP >140/90 mm Hg or use of antihypertensive drugs. uHTN was defined as BP >140/90 mm Hg despite use of antihypertensive drugs. A stepwise regression analysis was performed to determine which factors were associated uHTN.
Results: A total of 1080 patients received kidney transplant during the study period. We excluded patients who were unable to provide informed consent (n = 64) or aged less than 18 years old (n = 40). A final sample of 976 patients was included for analysis. Mean age was 52 ± 14 years (mean ± SD), and mean body mass index was 25.4 ± 5.5 Kg /m^2. 34.2% of the patients were women.
Prevalence of HTN was different between two groups at 6, 12 and 24 months. Prevalence of uHTN was different between two groups at 6 months but not at 12 and 24 months (table 1). By multivariate analysis, uHTN at 6 months was associated with donor type, kidney function, and number of antihypertensive drugs and uHTN at 12 months was associated with kidney function and number of antihypertensive drugs.
Conclusions: Despite the common use of antihypertensive drugs in most kidney transplant patients, uHTN is frequent after kidney transplantation. Reduced kidney function is associated with uHTN. Reduced kidney function or poor adherence to antihypertensive drugs may explain the high number of antihypertensive drugs used in these patients.

Table 1: Prevalence of hypertension and uncontrolled hypertension according to gender.

	Men	Women	Total	*p*
6 months				
HTN	611 (95.9)	291 (87.9)	902 (93.2)	< 0.001
uHTN	267 (44.6)	103 (36.0)	370 (41.8)	0.02
12 months				
HTN	520 (97.7)	250 (90.9)	770 (95.4)	< 0.001
uHTN	226 (44.2)	91 (38.6)	317 (42.4)	0.15
24 months				
HTN	357 (97.3)	171 (92.4)	528 (95.7)	0.01
uHTN	144 (40.5)	51 (31.7)	195 (37.7)	0.06

HTN: hypertension; uHTN: uncontrolled hypertension. Results are expressed as number of patients (percentage).

P 78

Late onset Avascular Osteonecrosis: A debilitating complication with high prevalence among young renal transplant recipients

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Background: Avascular osteonecrosis after renal transplantation (RT) is a debilitating complication. The aim of this study was to investigate the prevalence, clinical characteristics and outcome regarding development of avascular osteonecrosis in renal transplant recipients (RTR).
Methods: Single-center retrospective study of RTR with a clinical diagnosis of avascular osteonecrosis over the past two decades. Data of patients with radiological/histological confirmed diagnosis (n = 46) were extracted and analyzed.
Results: The prevalence of AO in our center was 5.4% with an average follow-up of 14(± 8) years for RTR. Overall, 41 patients had AO of the femoral head, 23 bilateral AO of the femoral head, 5 of the knee and 5 of other locations. On average, AO was diagnosed 90 (±78) months after RT and the majority of the RTR (71%) developed late onset AO (≥24 months after RT). Furthermore, RTR with late onset were younger at the time of first RT than those with early onset AO (39 ± 15 vs. 53 ± 14 years, p <0.01), had a considerably higher cumulative dose of prednisone (21 ± 11g vs. 4 ± 1g, p <0.001) and received corticosteroids prior to their first RT (48% vs. 15%, p = 0.038) compared to RTR with early onset AO. Overall, 34% of the patients presented with an advanced stage of AO (Ficat III or IV at first diagnosis) and 57% needed total hip arthroplasty.
Conclusions: Late onset avascular osteonecrosis represent a corticosteroid-related complication, with particularly high prevalence among young RTR and is associated with significant morbidity. Most patients have bilateral manifestation and present with advanced structural femur failure resulting in hip replacement.

P 79

Evidence for a two-hit mechanism in mycophenolic acid-related chronic diarrhea in kidney transplant recipients

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Background: Chronic diarrhea after kidney transplantation is often attributed to mycophenolic acid-related toxicity. We hypothesize that drug toxicity alone is not sufficient to induce chronic diarrhea and that intestinal infections trigger chronic mycophenolic acid-related diarrhea.
Methods: In this retrospective study, all patients (n = 726) receiving a kidney transplant between 2000 and 2010 at the University Hospital Zurich were followed until July 2014 for occurrence of chronic diarrhea. Infectious triggers at diarrhea onset were assessed by reviewing medical history, stool microbiology and histology of colon biopsies.
Results: In 46 patients (6.3% of the cohort) a total of 51 episodes of chronic diarrhea under mycophenolic acid treatment were documented. The diarrhea episodes were generally severe, as confirmed by significant weight loss. The cumulative incidence of chronic diarrhea was uniformly distributed throughout the post-transplant period, with 2.0%, 5.1% and 9.6% at 1, 5 and 10 years, respectively. Evidence for intestinal infection at diarrhea onset was found in 38 episodes (74.5%). Occurrence of diarrhea onset showed a seasonal distribution with peaks in April and October/November. Switch of immunosuppression from mycophenolic acid to azathioprine was associated with diarrhea resolution in all episodes. Re-introduction of mycophenolic acid in a subset of patients was not followed by recurrence of diarrhea.
Conclusion: These results suggest a two-hit mechanism of chronic diarrhea. Infections in addition to mycophenolic acid exposure are both necessary to trigger prolonged diarrhea in transplant patients. Hence, clearance of infection and transient switch to a mycophenolic acid-free immunosuppression might be sufficient to stop chronic diarrhea.

P 80

A comparison of ATG-Fresenius® toThymoglobulin® induction therapy in immunological high-risk kidney recipients: a prospective randomized control trial.

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Background: Induction treatment with polyclonal antithymocyte globulins (ATGs) is frequent used in kidney transplant recipients with donorspecific HLA antibodies and shows acceptable outcomes. The two commonly used rabbit polyclonal antithymocyte globulins preparations are ATG-Fresenius® (ATG-F) and Thymoglobulin® (Thymo). These to compounds are slightly different in terms of antigen profile and antibody concentrations. There are so far no studies available where the two compounds have been directly compared in a prospective trial in immunological high-risk recipients. Therefore we performed a prospective randomized controlled trial comparing the two compounds in immunological high-risk kidney recipients in terms of safety and efficacy.
Methods: Immunological high-risk kidney recipients, defined as the presence of HLA DSA but negative CDC-B and T-cell crossmatches were randomized 1:1 to receive ATG-F or Thymo. Maintenance immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil and steroids.
Results: The per-protocol analysis included 35 patients. There was no immediate infusion reaction observed with both compounds. No PTLD or malignancy occurred during the 24 months follow-up in both groups. The incidence of viral and bacterial infections was equal between the groups (p = 0.62). There were in total five clinical rejection episodes, two AMR in the ATG-F-group and two AMR and one TCMR in the Thymo-group (p = 0.66). The prevalence of subclinical AMR and TCMR at 3 and 6 months posttransplant detected by protocol biopsies were not different between the two groups (p = 0.41 and 0.36 respectively). The one-year graft function was similar in both study groups with a median eGFR of 52 ml/min/1.73m2 (29-96) (ATG-F-group) and 57 ml/min/1.73 m^2 (39–125) (Thymo-group) (p = 0.97).
Conclusion: We found no clinically relevant differences between the compared study drugs for induction treatment in immunological high-risk patients regarding safety parameters as well as efficacy during follow-up with good allograft function at 1 year after transplantation.

P 81

Impact of the new Swiss Organ Allocation System (SOAS) using calculated PRA and virtual crossmatching on clinical outcomes: first results from a single center

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Background: Since June 2012 the new SOAS uses calculated PRA and virtual crossmatching based on HLA-antibodies against the HLA-A/B/DRB1 loci with >1000 MFI for deceased donor organ allocation. The aim of this study was to investigate the impact of the new SOAS on clinical outcomes.
Methods: All deceased donor kidney transplantations performed at the University Hospital Basel from June 2007 to June 2015 were included and divided into two groups: (i) old SOAS era (n = 190), (ii) new SOAS era (n = 108). Investigated outcomes were the rate of transplantation across donor-specific HLA-antibodies (DSA), graft survival, as well as the frequency and severity of antibody-mediated rejection (ABMR) in patients with DSA.
Results: The rate of transplantation across DSA (23% vs 25%; p = 0.78), one-year graft survival (94% vs 97%; p = 0.52) and one-year death-censored graft survival (97% vs 99%; p = 0.32) were similar in the two eras. Among transplantations across DSA, one-year graft (89% vs 90%; p = 0.73) and death-censored graft survival (93% vs 96%; p = 0.67) were not different between the old and new SOAS era. However, the one-year incidence of (sub)clinical ABMR was significantly lower in the new SOAS era (16% vs 46%; p = 0.02) with less C4d+ ABMR-phenotypes (36% vs 75%; p = 0.007). In the new SOAS era, DSA directed against HLA-A/B/DRB1 were less frequent (33% vs 58%; p = 0.009), were more often remote (67% vs 35%; p = 0.04), and had significantly lower MFI (median <500 vs 1756; p = 0.008). By contrast, DSA directed against HLA-C/DRB3-5/DQ/DP became more frequent in the new SOAS era.
Conclusions: The new SOAS using a virtual crossmatch approach based on HLA-A/B/DRB1 loci does not reduce transplantation across DSA, but leads to a lower frequency and severity of AMBR in patients with DSA, likely by avoiding more harmful DSA.

P 82

Prevention of Bone Mineral Density Loss in de novo Kidney Transplant Recipients with Twice-Yearly Denosumab: a Randomized Controlled Trial (ClinicalTrials.gov number NCT01377467)

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Background: Kidney transplantation is associated with bone loss and an increased risk of fracture. Since current therapeutic options to prevent bone loss are limited we assessed the efficacy and safety of Receptor Activator of Nuclear Factor κB Ligand (RANKL) inhibition with denosumab to improve bone mineral density (BMD) in the first year after kidney transplantation.
Methods: We randomized 90 patients two weeks after surgery in a 1:1 ratio to receive denosumab (injections of 60 mg denosumab at baseline and after 6 months) or no treatment. The primary endpoint was percentage change in BMD measured by DXA at the lumbar spine at 12 months.
Results: After 12 months, total lumbar spine BMD increased by 4.6% (95% CI 3.3–5.9%) in 46 patients in the denosumab group and decreased by –0.5% (95% CI –1.8–0.9%) in 44 patients in the control group (between-group difference 5.1%, 95% CI 3.1–7.0%, p <0.0001). Denosumab significantly increased BMD at the total hip by 1.9% (95% CI, 0.1 to 3.7%; p = 0.035) over that in the control group. HR-pQCT in a subgroup of 24 patients showed that denosumab significantly increased BMD and cortical thickness at the distal tibia and radius (p <0.05). Biomarkers of bone resorption (β-CTX, urine deoxypyridinoline) and bone formation (P1NP, BSAP) markedly decreased with denosumab (p <0.0001). Subgroup analysis revealed that the effect of denosumab on lumbar spine BMD at 12 months was consistent, with slightly better effects in patients that were younger and of male sex, and in patients having lower T-scores, higher eGFR, and lower PTH levels. Episodes of cystitis and asymptomatic hypocalcemia occurred more often with denosumab, whereas graft function, rate of rejections and incidence of opportunistic infections were similar.
Conclusions: Antagonizing RANKL with denosumab effectively increased BMD in de novo kidney transplant recipients, but was associated with more frequent episodes of urinary tract infection and decreased calcemia.

P 83

The deleterious impact of a previously created AV-fistula on the radial bone in renal transplant recipients

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Background: Distal radius is the typical site for dialysis vascular access and for peripheral DXA measurements in renal transplant recipients (RTR). Vascular access often remains patent after transplantation but there are no data concerning the impact of a previously created arteriovenous fistula (AVF) on peripheral bone characteristics in RTR. We investigated the effect of AVF on bone mineral density (BMD) as mirrored by contralateral differences between forearms in RTR .
Methods: Cross sectional study comparing 40 renal RTR with 40 chronic kidney disease (CKD) patients matched for age, gender and BMI. In addition to relevant demographic, biochemical and clinical aspects we assessed bone characteristics of both forearms, femoral neck and tibia by dual-energy X-ray absorptiometry (DXA).
Results: CKD patients without AVF displayed no differences concerning BMD in both forearms. In RTR BMD was significantly lower in the AVF-forearm in comparison to the contralateral non AVF-

forearm. This was evident at all measured subregions of the AVF radius sides, i.e., at the 1/3 radius (0.710 ± 0.103 vs 0.727 ± 0.104, p = 0.003), ultradistal radius (0.424 ± 0.085 vs 0.444 ± 0.080, p = 0.007) and total radius (0.571 ± 0.090 vs. 0.589 ± 0.090, p = 0.001). the proportional side-to-side difference was 7.5% at the 1/3 radius, 7.2% at the total radius, and 7.0% at the ultradistal radius, respectively. Intersite analysis of BMD between radius and distal tibia showed a strong correlation (r = 0.734–0.875) between corresponding peripheral sites.
Conclusions: A previously placed AVF in RTR exerts a negative impact on the ipsilateral radius resulting in significant side-to-side BMD differences. A strong densitometric association is evident between peripheral sites and thus DXA measurements at the tibia can be considered as a valuable alternative site to radius.

P 84

Unusual reddish-colored plasmapheresate: a case report

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Background: Plasmapheresis (PP) is used in kidney transplant recipients in case of relapsed focal segmental glomerulosclerosis (FSGS) and more and more in certain cases of humoral rejection. There is little literature about PP effect on immunosuppressive drug pharmacokinetics.
Case-report: A 51y.o. woman was performing weekly PP in our Division for FSGS recurrence after kidney transplantation. Her immunosuppressive therapy was tacrolimus (1 mg bid), mycophenolate mofetil (MMF) (750 mg bid) and prednisone (10 mg qd).
PP sessions were repeatedly complicated by a technical problem during the last half-hour: plasmapheresate gradually assumed a reddish color that triggered the machine-alarm for "blood loss", automatically stopping the blood pump. We excluded the presence of hemolysis.
Subsequently, we discovered that the patient had taken MMF during PP. Taking MMF correctly after PP, plasmapheresate was not colored anymore (fig. 1).
Results: Mycophenolic acid (MPA) serum levels, assuming MMF during PP, were 2.0 mg/L before and 5.0 mg/L after PP. Using the same time frame on a non-PP day, MPA serum levels were 2.9 mg/L and 22.7 mg/L, respectively.
The MPA concentration in the plasmapheresate was 2.1 mg/L. Mass spectrometry of the plasmapheresate showed the presence of MPA, but not of other medications (fig. 2).
MMF contains red iron oxide (E172) among its excipients, a dye component of the film coating. E172 could cause the chromatic phenomena if present in high concentration (undemonstrated data; rifampicin, which can produce reddish urine, contains E172).
Conclusions: In contrast with the only report in medical literature, we observed that PP reduces MMF serum concentration, favored by high plasma protein binding (97%) and despite a large distribution volume (3.6–4 L/kg), at least shortly after its intake, during plasma-peak (when MPA is highly concentrated in plasma and not yet distributed to other compartments).
The reddish plasmapheresate coloring is not reported in literature. We can reasonably assume that the reddish color of plasmapheresate is caused by the drug excipient E172.

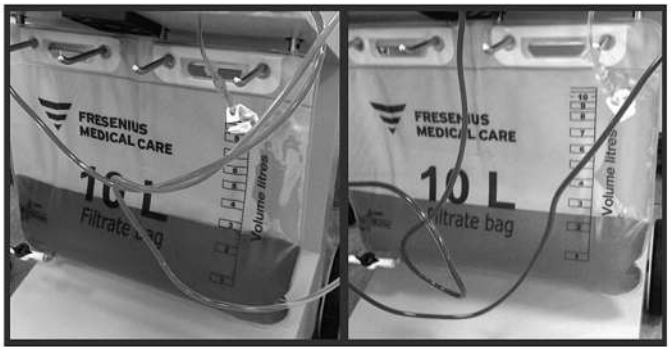

Figure 1: In the left panel the plasmapheresate collected in the bag discharge from a plasmapheresis (PP) session during which the patient took MMF. In the right panel the plasmapheresate collected from a PP session in which the patient has not taken MMF (last MMF dose taken about 10 hours before PP).

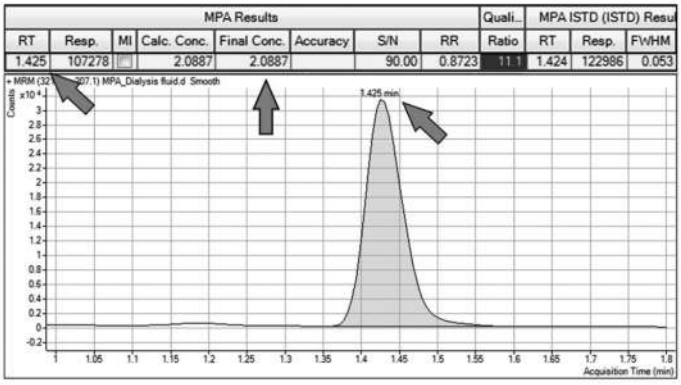

Figure 2: Quantification of mycophenolic acid (MPA) concentration by a Mass Spectrometry System using tandem mass spectrometry (MS/MS) and multiple reaction monitoring (MRM), in a sample of plasmapheresate, with chromatographic separation between MPA and glucuronide MPA. This chromatogram of quantifier MRM transition for MPA shows a peak at 1.425 minutes of the 2-minutes acquisition time, deriving from MPA. MPA and its metabolite glucuronide MPA are the only drugs found in the plasmapheresate.

Table 1: Pharmacokinetic data (MMF serum levels with and without plasmapheresis).

	MMF intake DURING Plasmapheresis (PP)	MMF intake on a NON-PP DA
Blood MPA level at the time of starting PP (mg/L)	2.0	2.9
Blood MPA level at the time of the end of PP (mg/L)	5.0	22.7
MPA level in the plasmapheresate (mg/L)	2.1	----
Collected plasmapheresate (mL)	3000	----

P 85

CEUS guided management of compressive subcapsular hematoma after transplant kidney biopsy

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Background: Subcapsular hematoma complicated by anuric kidney failure is an uncommon complication of transplant kidney biopsy which may particularly occur in transplant biopsies beyond the first year. Its management remains controversial. We present a case of successful conservative management which was guided by Contrast-enhanced ultrasound (CEUS) findings.
Case report: Twenty-six years after cadaveric kidney transplantation for IgA nephritis, a 65-year-old patient underwent allograft biopsy because of decreasing kidney function. Two biopsy cores were obtained from the upper pole. Post-biopsy surveillance was uneventful and the patient was discharged 6h later. On the following day, he presented to the emergency room with nausea, mild discomfort in the transplant region and absolute anuria. Creatinine had increased from 240 to 704 µmol/l.
Grey scale ultrasound revealed a huge subcapsular hematoma around the upper two thirds of the kidney which severely compressed the transplant kidney's parenchyma. Doppler exam of renal arterial vessels revealed a pendular flow pattern with reversed diastolic flow. A CEUS examination clearly delineated the hematoma and – at the same time – demonstrated arterial perfusion of the renal parenchyma.
No attempt to surgically evacuate the hematoma was made, since the CEUS findings suggested maintained tissue perfusion and uncontrollable intraoperative bleeding was feared. Hemodialysis was initiated and the patient was monitored closely for the following days. Early ultrasound follow-up showed stable hematoma size. On Doppler exam the ratio between forward and backward flow increased daily, indicating decreasing pressure within the kidney capsule, despite persistent anuria. From day 9 on, urine production slowly recovered. Dialysis was stopped after 24 days. Two months later, kidney function had recovered to baseline. After 6 months, ultrasound showed complete resolution of the hematoma.
Conclusions: Post-biopsy subcapsular hematoma with anuric kidney failure can be managed conservatively. Renal CEUS is a valuable tool for assessing tissue perfusion in this situation.

The numbers refer to the pages of this supplement.