Abstracts
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28 S
Reduced cortical oxygenation predicts progressive renal function decline in humans: results of a prospective study

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Background: Renal tissue hypoxia is generally considered as the final pathway in the development and progression of chronic kidney disease (CKD), but whether renal oxygenation predicts renal function decline in humans has not been proven.

Methods: We performed a prospective study and measured renal tissue oxygenation with Blood oxygen level-dependent MR imaging (BOLD-MRI) in 112 CKD patients, 47 hypertensives and 24 controls. Images were analyzed with the twelve-layer concentric object method that divides renal parenchyma in 12 layers of equal thickness, and reports the mean R2* value of each layer (high R2* corresponding to low oxygenation), along with the change in R2* between layers called the R2* slope. Creatinine values were collected to calculate the yearly change in estimated glomerular function rate (eGFR)meas.

Results: Follow up was 3.0 ± 1.1 years. The change in eGFR in CKD, hypertensive and controls was −2.0 ± 1.0, 0.5 ± 4.9 and −0.2 ± 5.3 ml/min/1.73 m²/year, respectively. A multivariable regression analysis adjusted for age, gender, diabetes, RASblockers, eGFR and proteinuria, the yearly eGFR change correlated negatively with baseline 24h proteinuria and mean R2* value of the cortical layers, and positively with the R2* slope, but not with the above mentioned controls. CKD patients with high outer R2* or a flat R2* slope were three times more likely to develop an adverse renal outcome (renal replacement therapy or >30% increase in creatinine).

Conclusions: We demonstrate that low cortical oxygenation is an independent predictor of renal function decline. These data stimulate studies exploring the impact of treatments improving renal oxygenation on renal disease progression.

Prevalences of distal renal tubular acidosis and other metabolic abnormalities among 534 non-selected kidney stone formers – a single center study

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Background: Impaired renal H+ ion secretion (distal RTA) can be associated with elevated urine pH, hypercalciuria and hypocitraturia.

Methods: From January 1, 2006, until December 31, 2016, 534 SF (381 men, 153 women) were evaluated (544 calcium, 63 uric acid, 9 struvite and 8 cystine SF), with a mean of 8 stones. Fasting venous blood, fasting urine as well as 24-h-urines on free-choice diet were analysed. Fasting urine pH (U-pH) in 2nd morning urines was measured by test strips and pH-meter. If U-pH remained >5.80, SF underwent 1-day acid loading by ammonium chloride (NH4Cl, 50 mg/kg BW, 3 oral doses, Urolithiasis 45, 263-, 2017), and U-pH and venous blood were remeasured the next morning. Values are mean ± SD.

Results: The most frequent abnormalities were protein consumption >10.0 g/kg normal BW (68.7%), urine volume <2.5 L/day (49.3%) and hypocitraturia (25.1%). 80 SF (15.0%) had distal tubular acidosis (dRTA). 11.3% males, 24.2% females. Only 1 SF had overt distal RTA. Compared with idiopathic calcium SF (ICSF), fasting S-K+ was lower in dRTA-SF (3.38 ± 0.31 vs. 4.00 ± 0.29 mEq/L, p = 0.002). Urease pH was higher in dRTA-SF in fasting (6.48 ± 0.2 vs. 6.17 ± 0.48, p = 0.001) as well as 24h urine (6.36 ± 0.35 vs. 5.76 ± 0.61, p = 0.001). 24h urine calcium was 6.80 ± 5.0 mg/d in dRTA-SF vs. 5.87 ± 4.6 mg/d in ICSF (p = 0.009). Ca/Cit ratio was higher in dRTA-SF (3.10 ± 2.75 vs. 2.46 ± 2.19, p = 0.033).

Conclusions: 1 Most frequent abnormalities in SF are protein oversaturation and acidosis, followed by volume, 2 Type 1 dRTA occurs in 15%, more frequently in females than males. 3 Key features of dRTA are female gender, lower S-K+ and elevations in U-pH, U-calcium and U-Ca/Cit (relative hypocitraturia).

Dietary sodium intake modulates urinary potassium excretion in humans

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Background: Dietary sodium intake modulates urinary potassium excretion via activation of the renin-angiotensin-aldosterone system while effect of the sodium intake on urinary potassium excretion remains to be determined. Moreover, the inverse relationship between the activity of the thiazide-sensitive cotransporter and urinary potassium excretion described in mice remains to be demonstrated in humans.

Methods: Sixteen male volunteers aged 18–30 were allocated to receive 3 sequences of 1 week of a diet with a fixed amount of salt in two groups with different order of sequences. Eight volunteers were assigned to group 1: low (3 g/day), high (12 g/day) and normal (6 g/day) salt diet, and eight to group 2; high, low and normal salt diets. Dietary intake and urinary excretion of sodium and potassium were recorded daily. Activity of the distal tubule NaCl cotransporter was assessed at steady-state by the natriuretic response to 100 mg of hydrochlorothiazide.

Results: Results showed that steady state sodium balance was reached after 3 to 4 days for each salt intakes. In group 1, urinary potassium excretion was lower under high salt and unchanged under low salt diet as compared to normal salt diet while in group 2, urinary potassium excretion increased to the same extent under high and low salt diets. The natriuretic response to thiazides was the highest under high salt diet and the lowest under low salt diet.

Conclusions: This study shows that in sodium-repleted subjects, kaliuresis increases in response to high and low sodium intakes while in sodium-depleted subjects kaliuresis decreases in response to high sodium intake. We also show that the thiazide-sensitive sodium reabsorption is proportionate to dietary system and that this study suggests that high salt intake induces a redistribution of sodium reabsorption from proximal to distal tubules.
Phenotype of kidney stone formers with renal phosphate leak

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Background: A renal phosphate leak is believed to promote hypercalciuria in calcareous stone formers (SF). However, the phenotype of SF with a renal phosphate leak remains poorly defined and its association with stone history, stone composition and bone mineral density has not been studied.

Methods: A comprehensive cross sectional analysis of multiple phenotypes in relation to renal phosphate transport, represented by TMP/GFR, was conducted in 586 calcareous SF of the Bern Kidney Stone Registry. Mixed effects linear and logistic regression models included adjustment for age, sex, BMI, eGFR, diabetes, hypertension, and thiazide medication.

Results: Male sex and a higher blood pressure is significantly associated with a renal phosphate leak in calcareous SF. SF with a renal phosphate leak have their first stone event at a younger age (fig. 1) and have more frequently a positive family history for nephrolithiasis. They excrete less oxalate but more calcium in 24 hours urine and have a lower prevalence of calcium oxalate stones (fig. 2) whereas brushite stones (fig. 3) are more prevalent. Dual-energy x-ray absorptiometry (DEXA)-based bone mineral density measurement revealed no differences of T- and Z- scores at the lumbar spine, femoral neck, tibia diaphysis and epiphysis. In addition, calcareous SF with a renal phosphate leak have higher plasma levels for PTH and lower levels for 25-ViD and 1,25-ViD, whereas no changes were found for FGF23.

Conclusions: We find that renal phosphate handling in calcareous SF is associated with PTH, 25-ViD and 1,25-ViD, but not with FGF23. Our data further indicate, that a renal phosphate leak is a risk factor for brushite stones and has a strong heritable component.

Prediction of kidney function after nephrectomy in donor and recipient

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Background: In living kidney donors expected post-donation kidney function is largely dependent on pre-donation glomerular filtration rate. Post-transplant renal function in living kidney transplant recipients is impacted by various variables, predominantly by donor graft nephron supply, recipient metabolic demand and transplant specific factors such as immunosuppression and possible complications. This study aimed to assess accuracy and applicability of prediction of post-transplant kidney function based on donor and recipient age, weight and gender, as well as donor’s pre-donation serum creatinine values in donors and recipients.

Methods: Retrospectively pre- and post-transplantation markers reflecting kidney function and demographic data were analyzed during the first year before and after transplantation in 68 donors and 48 recipients. Expected serum creatinine and glomerular filtration rates were calculated using a recently published formula by Al-Sehli et al. To test this formula’s predictive capability, expected and observed serum creatinine values and glomerular filtration rate were compared.

Results: Expected and observed glomerular filtration rate and serum creatinine Levels correlated significantly, whereby correlation was stronger in the donors (r = 0.9 in donors, r = 0.6 in recipients, p <0.00001). Mean difference between observed and expected serum creatinine was 5 ± 11 μmol/l in donors and 9 ± 35 μmol/l in recipients. In donors 78% and in recipients 46% of the observed serum creatinine values ranged within ±15% of the expected serum creatinine. Adaptive increase of the remaining kidney in donors was 33 ± 15%. Differing body weights of donors and recipients were significantly associated with diverging predicted and observed serum creatinine Levels in recipients (r = 0.55, p <0.00001).

Conclusions: In living donors post-donation kidney function can be predicted with high accuracy. In contrast, renal function in the recipients is less predictable. The significant impact of donor to recipient weight indicates the importance of metabolic demand on the degree of hyperfiltration in the transplanted kidney.
Low β-catenin expression levels during development alter renal morphology and function (NCGR Project)
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Background: During kidney development, segmental identity of the future nephron is laid down by a proximal-distal β-catenin gradient. Ex-vivo chemical stimulation of β-catenin activity leads to an expansion of distal segment identity, whereas suppression of β-catenin activity promotes proximal positional identity. In this project, we reduced β-catenin expression levels along the entire nephron during nephrogenesis in-vivo or in murine distal convoluted tubule (DCT) cell lines in-vitro. We hypothesize that upon this restriction the DCT adapts properties of more proximal nephron segments, which further affects renal function.

Methods: β-catenin expression in embryonic kidneys was reduced to 12.5% or 25% compared to wild type using 2 different Cre-lines. Kidneys were isolated before (Cdx1::Cre) or after birth (Pax8::Cre) and analyzed histologically, by qRT-PCR or Western blot. Furthermore, biochemical parameters in urine and serum, as well as blood pressure were determined of Pax8::Cre mice. In vitro, β-catenin was knocked down in murine DCT cells with siRNA and the expression of specific nephron markers was assessed.

Results: β-catenin knock-down kidneys were smaller in size, displaying multiple cysts. The expression of DCT markers was significantly reduced, whereas transcription of TAL markers was enhanced. Furthermore, Pax8::Cre mice displayed polyuria with an elevated protein:creatinine ratio, and had higher blood pressure than controls. Lastly, knock-down of β-catenin in DCT cells increased the expression of proximal nephron marker genes in these cells.

Conclusions: Reducing β-catenin profoundly alters renal morphology and function, which is reflected by multiple phenotypes including cysts, polyuria or hypertension. Furthermore, the altered specification of intermediate nephron segments (DCT and TAL) provides a possible explanation for polyuria and hypertension in these mice. Whether the cystic transformation is also a consequence of the distorted pattern of nephron segments remains to be investigated.

Protein phosphatase 1 inhibitor 1 mediates cAMP-dependent stimulation of the renal NaCl cotransporter
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Background: The thiazide-sensitive NaCl cotransporter (NCC) in the distal convoluted tubule (DCT) is critical for renal Na+-reabsorption and blood pressure control. Several cAMP-elevating hormones, including aldosterone, stimulate NCC activity. Here, we tested the hypothesis that the DCT-enriched protein phosphatase 1 inhibitor 1 (I1) mediates the effects of cAMP on NCC.

Methods: In addition to MDCK cells stably transfected with NCC, several ex vivo approaches such as isolated mouse DCTs, mouse kidney slices and isolated perfused mouse kidneys were used. The expression and phosphorylation of NCC and I1 were assessed by immunoblotting and immunohistochemistry.

Results: Exposure of isolated DCTs to cAMP-elevating agents forskolin and IBMX rapidly increased the phosphorylation of NCC via a protein kinase A (PKA)-dependent pathway. The forskolin/IBMX-induced NCC phosphorylation was paralleled by phosphorylation of I1 at its PKA-consensus phosphorylation site (T35). Forskolin/IBMX-induced phosphorylation of NCC was diminished in MDCK cell slices from I1-knockout mice (I1-KO), while transgenic overexpression of a phosphomimetic I1 mutant (T35D) in kidneys of I1-KO mice restored NCC phosphorylation, but made NCC resistant to forskolin/IBMX stimulation. Yeast two-hybrid and co-immunoprecipitation experiments in MDCK cells stably transfected with NCC indicated a physical interaction between NCC and the I1-target PP1. Pharmacological inhibition of PP1 by calyculin A increased NCC phosphorylation. Finally, studies on kidney slices and isolated perfused kidneys from control and I1-KO mice demonstrated that I1 is critical for the beta-adrenergic stimulation of NCC.

Conclusions: Our data establish a complete signal transduction pathway by which cAMP, via a PKA-dependent phosphorylation of I1 and subsequent inhibition of PP1, increases NCC phosphorylation. This pathway likely accounts for beta-adrenergic NCC activation and may hence contribute to salt-sensitive hypertension in patients with sympathetic hyperactivity.
expression of the main renal uric acid transporters. SLC22A12 (URAT1), involved in urate reabsorption, was strongly down regulated in the female kidney, while SLC22A9 (GLUT9) was unchanged. In the liver, we observed a significant increase of SLC22A9 in female mice, allowing urate intake into the hepatocyte and its degradation by the intracellular uricase which was unchanged by istself. Preliminary results also showed decreased xanthine oxidase activity in the liver of females. In the intestine, uric acid is rapidly degraded in the lumen by the uricase expressed by the intestinal microbiota. We showed that females had a higher intestinal uricase activity than males, particularly in the caecum.

Conclusions: Overall, these results showed co-operation between multiple organs to differentially regulate urate homeostasis between males and females. In females, (i) urate renal reabsorption is decreased, potentially through lower URAT1 expression, favoring renal excretion; (ii) GLUT9-mediated urate transport in the hepatocyte is increased, facilitating urate degradation by the intracellular uricase; (iv) uric acid synthesis by xanthine oxidase is decreased; (v) finally, intestinal uricase activity is higher in females. These observations will be of particular interest to personalize treatments for hyperuricemia, gout and kidney stones between genders.

ORAL COMMUNICATIONS – HEMODIALYSIS / PERITONEAL DIALYSIS

Implementation of remote patient management in the care of automated peritoneal dialysis patients in Switzerland: 18 months experience
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Background: Given the remote nature of peritoneal dialysis (PD), nephrologist visibility to patient and therapy-related issues can be problematic. Remote patient management (RPM) enables monitoring of patients outside of conventional clinical settings and has already been implemented in many other medical fields including oncology, cardiology, diabetology and neurology with significant positive impact on patient outcomes but only scarce data exist up to now in nephrology.

Methods: A newly available automated peritoneal dialysis (APD) RPM system (Claria Sharesource) with cloud-based connectivity was implemented in our department in December 2015. We present here our 18 months experience (up to August 2017).

Results: 11 patients were started on RPM up to August 2017. PD team had to face a learning curve to instaure a systematic analysis of the transmitted data. In the first patient, RPM helped to recognize prolonged drained times (fig. 1) and led to early clinical evaluation with ensuing diagnosis and correction of PD catheter migration. Identification of <90% adherence to prescribed PD therapy was then documented with the RPM system (fig. 2), alerting the clinical staff to address this important issue given its association with significant negative clinical outcomes1. RPM also allows clinicians to remotely alter PD prescription, which proved very useful in one peculiar oliguric patient with ultrafiltration and subsequent overhydration problems necessitating weekly therapy adaptation. Some specific populations such as people with reduced mobility could also particularly benefit from RPM.

Conclusions: RPM of APD patients with a two-way cloud-based connectivity platform allows for monitoring and quick adjustment of therapy, as well as early recognition and timely management of adverse clinical issues. It is therefore a promising new tool that may help clinicians to improve PD therapy outcomes and both patient and clinician confidence in embracing home dialysis.

1 Jotterand Drepper et al., PDI, in press.
Experience with rivaroxaban treatment in 10 haemodialysis patients

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Background: Using a direct factor Xa inhibitor such as rivaroxaban in haemodialysis patients has theoretical advantages, because in contrast to the vitamin K antagonists it lacks the risk of promoting arterial calcification and calciphylaxis. No data on efficacy and safety of this therapy exist in haemodialysis patients, and their use in this group is therefore discouraged.

Methods: We retrospectively collected data on indication, duration of treatment, adverse events, and reasons for discontinuation in 10 haemodialysis patients treated with rivaroxaban (10 mg morning dose) over the past two years at our unit. Peak rivaroxaban concentrations (approximately 4 hours after intake) were measured at the beginning of afternoon haemodialysis sessions using the BIOPHEN DiXal kit (HYPHEN BioMed France), which measures anti-factor Xa activity using a chromogenic method.

Results: Drug exposure time, mean rivaroxaban plasma concentration (μg/l), indications for rivaroxaban, reasons for discontinuation and adverse events are listed in table 1. No patient had a major bleeding. One of 10 patients suffered from a cardioembolic stroke. The two deaths were related to death episodes at home. Two patients were switched to vitamin K antagonists at the time of listing for kidney transplantation, where rivaroxaban is impractical, because there currently is no antagonist available.

Conclusions: In the haemodialysis patients exposed to rivaroxaban 10 mg/d during a total of 1817 days, the drug was well tolerated without any bleeding complication. If the mean rivaroxaban levels in this small group of haemodialysis patients are considered as CMax levels, they fell below the mean CMax levels found in phase 2 studies for VTE prevention after hip replacement (125 μg/l) and for stroke prevention in atrial fibrillation (229–249 μg/l). This may be appropriate for this group at high risk for bleeding but obviously requires prospective studies.

Table 1

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Do measurements of serum ferritin and TSAT as performed in clinical practice accurately guide IV iron therapy with ferrum carboxymaltose in haemodialysis patients?

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Background: Most chronic haemodialysis patients are in negative iron balance due various reasons. Iron is supplemented with doses of 100–200 mg every 2–4 weeks. While no laboratory parameters have been shown to reliably reflect total body iron stores, serum ferritin and transthyretin saturation (TSAT) are generally used to assess the iron status of dialysis patients and to adjust maintenance iron dosing. The rationale of this study is to evaluate whether variations in the timing of blood sampling relative to the iron dosing schedule influences these laboratory parameters to a relevant degree and whether a certain amount of time should elapse between the last maintenance FCM dose and evaluation of iron Status.

Methods: Patients are recruited from the outpatient haemodialysis population treated at the dialysis units in Frauenfeld and Münsterlingen. At the beginning of a dialysis session during which patients receive their FCM dose as well as at days 2, 4, 7, 14, 21 and 28, the following laboratory parameters are assessed: serum ferritin, TSAT, hematogram, CRP, reticulocyte count. The values will be compared to their baseline value using a two-sided paired t-test. Main inclusion criteria are stable dosing of FCM for the last 12 weeks, of ePO (+/-25%) for the last 2 months, stable Hb values and normal CRP.

Results: By September 05, 2017, 13 patients have been included and 37 are planned to be enrolled by November. A first interim data analysis revealed a great interpatient variability in the rise of ferritin. Maximum peak values are reached between 4–7 days after FCM injection. In particular a dose of 200 mg FCM led to a significant transient rise of serum ferritin values.

Conclusions: The timing of iron status evaluation has to be coordinated to FCM injection. An analysis of all patients completing the study by November will be presented at the Meeting.

The role of ISO-9001:2008 certification for management and quality control in dialysis: the experience of a Swiss centre

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Background: Worldwide government and health insurances are striving to contain increasing healthcare costs. In front of an aging population, providing high-quality haemodialysis therapy could be challenging in the near future. Therefore, an efficient, cost-effective organization able to remove inefficiencies by maintaining the quality of care is of major importance. The aim of this study was to analyse patients outcome and dialysis unit performance at different reorganization stages aimed to implement ISO-9001:2008 during the period 2000–2015.

Methods: The “clinical-process indicators” (patients outcome) were measured using the yearly mean values of systolic blood pressure (SBP), urea reduction rate (URR%), haemoglobin (Hb), serum phosphate (P), calcium/phosphate product (Ca²⁺P), albumin, ferritin and transferrin saturation (StTrans). The targets were defined as SBP <160 mm Hg, URR >65%, Hb range 10–12 g/dL, P <1.8 mmol/L, Ca²⁺P <4.5, albumin >34 g/L, ferritin <150 mg/L, StTrans >200. The clinical quality goal is the achievement of the target in 80% of the patients. “Structure-results indicators” (dialysis unit performance) were analysed in terms of mortality and growth over 12 months. The target for mortality was <15% and for growth >4%. The collected outcome and performance data were analysed according to each reorganization design model (e.g. elementary), following Mintzberg’s typology.

Results: Our data, collected over 15 years, were compared with the “Swiss renal registry and quality assessment program” (swrmap). All clinical-process and structure-results targets were reached with the advocacy model. Compared to other models, advocacy reached an higher number of patients with a lower employment rate and no increase in mortality. Notwithstanding the older age of our patients, we found a similar mortality rate (15%) to swrmap. Challenging the patient population.

Conclusions: Our results suggest that the organization developments pursued to implement ISO-9001:2008 had a positive influence on the management and quality control in dialysis. Advocacy model displayed the highest efficiency. Whether this model is applicable to larger centres needs further evaluation.

Risk factors for community-acquired Acute Kidney Injury in patients with and without chronic kidney injury and impact of its initial management on prognosis: a prospective observational study

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Background: We aimed to describe clinical characteristics of patients with community-acquired acute kidney injury (CA-AKI), the effectiveness of initial management of CA-AKI, its prognosis and the impact of medication on its occurrence in patients with previous chronic kidney injury (CKI).

Methods: We undertook a prospective observational study within the Emergency Department (ED) of a University Hospital, screening for any patient >16 years admitted with an eGFR <60 ml/min/1.73 m² and a rise in serum creatinine as compared to previous values. Patients’ medical files were reviewed by a panel of nephrologists in the subsequent days and at one and three-years follow-up.

Results: From May 1st to June 21st 2013, there were 8464 admissions in the ED, of which 653 had an eGFR <60 ml/min/1.73 m². Of these, 352 had previous CKI, 341 had CA-AKI, and 104 had
CA-ACKI (community-acquired acute on chronic kidney injury). Occurrence of CA-ACKI was associated with male gender and with use of diuretics, but not with use of ARBs or ACEIs. Adequate management of CA-ACKI defined as identification, diagnostic procedures and therapeutic intervention within 24 hours, was recorded in 45% of the cases and was not associated with improved outcomes. Three-year mortality was 21 and 48% in CKi patients, respectively, without or with CA-ACKI, and 40% in patients with only CA-ACKI (p <0.001). Mortality was significantly associated with age, hypertension, ischemic heart disease and CA-ACKI. Progression of renal insufficiency was associated with male gender and age.

Conclusions: CA-ACKI is more frequently encountered in male patients and those treated with diuretics and is an independent risk factor for long-term mortality. Its initial adequate management failed to improve outcomes.

Toward a better understanding of chronic kidney disease using metabolomics
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Background: Metabolomics aims to analyse comprehensively the metabolic complexity of biological systems and constitutes a potential method for assessing phenotype modifications caused environmental influences or pathologies. An extensive coverage of metabolites (mass 1000 Da) is required for relevant untargeted metabolomics. As no technique offers an exhaustive monitoring of all metabolites in a biofluid, the use of multiple analytical platforms is needed. This methodology was implemented in the context of a clinical study to detect alterations in plasma metabolic profiles due to chronic kidney disease (CKD) and allow a better understanding of the pathology.

Methods: Reversed-phase chromatography (RPLC) and hydrophilic interaction chromatography (HILIC) coupled to high resolution mass spectrometry (HRMS) are complementary techniques commonly used for their coverage of apolar and polar metabolites, respectively. A strategy based on the combination of these two analytical approaches was applied to plasma samples collected from a clinical study designed to evaluate the metabolic impact of CKD. The cohort was composed of 56 control samples, and 104 patients at several disease stages, including 35 dialysed patients before their mid-week dialysis session. Each sample and quality control (QC) was analysed by RPLC and HILIC coupled to QTOF-MS in negative and positive ESI mode.

Results: More than 230 annotated compounds were investigated thanks to the fusion of datasets generated from multiple platforms using an in-house database of 600 metabolites. The major sources of variability observed in the dataset were related to biological alterations due to the pathology that could be related to the Glomerular Filtration Rate. The multivariate analysis of the dataset showed a strong ability to stratify patients. Metabolite enrichment analysis was performed on discriminant metabolites to evaluate pathways potentially involved in the pathology.

Conclusions: The workflow developed in this study allowed patient stratification according to CKD stages and helped to generate biological hypotheses based on the metabolic profiles.

Clinical long-term outcomes of kidney transplantation from pediatric donors
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Background: The activation of aryl hydrocarbon receptor (AHR) – a transcription factor involved in drug metabolism – plays a key role in inflammation and viral tolerance through modulation of macrophages polarization. Since AHR has not been studied in kidney transplantation, our aim was to compare the AHR expression within renal grafts in BKPyV+ and T-cell mediated rejection (TCMR) as a control.

Methods: We evaluated AHR expression in kidney grafts from BKPyV+ (n = 8) and TCMR as control (n = 6) patients. Each sample and quality control (QC) was analysed by RPLC and HILIC coupled to QTOF-MS for their coverage of apolar and polar metabolites, respectively. A strategy based on the combination of these two analytical approaches was applied to plasma samples collected from a clinical study designed to evaluate the metabolic impact of CKD. The cohort was composed of 56 control samples, and 104 patients at several disease stages, including 35 dialysed patients before their mid-week dialysis session. Each sample and quality control (QC) was analysed by RPLC and HILIC coupled to QTOF-MS in negative and positive ESI mode.

Results: More than 230 annotated compounds were investigated thanks to the fusion of datasets generated from multiple platforms using an in-house database of 600 metabolites. The major sources of variability observed in the dataset were related to biological alterations due to the pathology that could be related to the Glomerular Filtration Rate. The multivariate analysis of the dataset showed a strong ability to stratify patients. Metabolite enrichment analysis was performed on discriminant metabolites to evaluate pathways potentially involved in the pathology.

Conclusions: The workflow developed in this study allowed patient stratification according to CKD stages and helped to generate biological hypotheses based on the metabolic profiles.
6.5 years. Among the 105 ‘viremia’ cases, BKPyV-viremia was first occurrence of rejection, and evolution of allograft function.

Methods: This was a multicentre, non-interventional, observational, 12-month study conducted at five sites in Switzerland. Adult stable liver and kidney transplant patients converted from IRT to PR-T in routine clinical practice, were included. Data were collected pre-conversion (Visit V1), 2 weeks, 6 and 12 months post-conversion (V2–4).

Primary composite endpoint was non-adherence by the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASSIS; V4), any investigator adherence rating of ‘poor’ (V2–4), or a subtherapeutic (investigator-defined) tacrolimus trough level (V3–4). Secondary endpoints included: components of the composite, pill burden, patient satisfaction, and adverse drug reactions (ADRs).

Results: Seventy-eight patients were enrolled; 75 received PR-T, and 68 (46 kidney, 22 liver) completed the study. Most (81.8%, 36/44) patients were non-adherent for the composite endpoint. Overall non-adherence by BAASSIS was similar at V1 (30.7%, 23/75) and V4 (38.1%, 18/47). Post-conversion, investigators rated 23 patients (46.9%) as non-adherent; 62.0% (31/50) of patients had sub-therapeutic tacrolimus trough levels. PR-T decreased tacrolimus pill burden in 66.7% (40/60) of patients; median daily number of tacrolimus capsules decreased in kidney recipients from 3.0 to 2.0 and liver recipients (4.0 to 2.0). All patients were very satisfied/satisfied with PR-T administration; 75% (48/64) of patients found it easier to remember to take PR-T versus IRT. Overall, 20.0% (15/75) of patients reported ADRs, most frequently infections (9.3%; 7/75).

Conclusions: For the kidney and liver transplant population combined, 1-year non-adherence rates were similar following conversion from IRT to PR-T; however, PR-T intake was more convenient. PR-T was well tolerated over 1 year of treatment.

Immunosuppressive drugs used to treat acute antibody-mediated rejection in kidney transplant recipients (STCS) 

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Methods: In this retrospective observational study, we included all kidney transplant recipients following two patients from the Swiss Transplant Cohort Study (STCS) from 2008 to 2014 who received a treatment for an acute AMR episode occurring in the first year post transplantation (post-Tx). The primary objective was to analyze the use of immunosuppressive (IS) drugs to treat acute AMR in a "real life" cohort setting. The secondary objectives were to analyze the efficacy (improvement in renal function at 3 months post acute AMR) and the safety (infectious complications occurring in the following 6 months) of the IS treatment used.

Results: 4148 (5.8%) patients were treated for AMR occurring in the first year post-Tx in the STCS (74 episodes in total). The median number of therapies used per acute AMR episode was two (range: 1–5 therapies). The most common bitherapy was Plasmapheresis (PPh) with methylprednisolone, and most common monotherapy was PPh, methylprednisolone and IVIG. The treatments used were effective in most cases, with full recovery of renal function in 68% of episodes. At 1-year, graft survival was 91%, and ongoing rejection was the main cause of graft loss. Four patients (4/64) died during the first year (6.2%), two because of severe infectious complications. Overall, the incidence of any infectious complication was 42% in the following 6 months post AMR treatment.

Conclusions: We found an heterogeneity in the IS drugs used to treat acute AMR within the first year post-Tx in the STCS, with an overall satisfactory response to therapy. Acute AMR remains a serious event post kidney-Tx with 9% graft loss at 1-year and with potentially severe infectious complications associated with its therapy.

Review of studies on changes in renal physiology induced by nephrectomy in living donors (NCCR project)

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Methods: In order to collect existing data on donor nephrectomy induced changes we performed a literature review on studies concerning the change in key nephrophysiology markers that occurs after kidney donation in LKD: preand post-donation glomerular filtration.
rate (GFR), renal reserve capacity (RRC), effective renal plasma flow (ERPF). The additional aim was to focus on these changes in donors with medical risks.

**Results:** We could identify a total of 35 physiology studies in LKD performed between 1956 to 2017 including a total of 4107 patients. Only two studies covered a followed-up period of more than 10 years. More than half of the studies assessed only GFR, and six studies were analysing post-nephrectomy changes in BD. The studies showed an adaptive increase in ERPF (106.64 ± 51.56 ml/min/1.73 m$^2$) and measured GFR (16.15 ± 10.39 ml/min/1.73 m$^2$) in the remaining kidney after donation. Only 11 studies investigated RRC before and after donation, here a decrease in RRC post-nephrectomy could be seen (6.00 ± 1.41%). Very few studies analysed changes in BD, indicating a significant impact of age and body weight on GFR and RRC.

**Conclusions:** Better understanding and more studies on physiology changes induced by kidney donation on key physiology markers are needed to further improve the safety of donation and a robust risk assessment for the potential LKD and to facilitate decision making in donor selection.

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**POSTER PRESENTATIONS – CLINICAL NEPHROLOGY / HYPERTENSION / MINERAL / ELECTROLYTES**

**Impact of citrate supplementation on urinary risk profile in Swiss recurrent calcium stone formers (NCCR Project)**

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**Background:** Urolithiasis is common in developed countries with a significant recurrence rate. Hypocitraturia and hypercalciuria have been reported as the most prevalent risk factors. Citrate is a strong crystallization inhibitor and citrate supplementation has been introduced for metaphylaxis in recurrent kidney stone formers (rKSF) with hypocitraturia and normocitraturia. However, only few studies have investigated the impact of citrate on urinary stone risk profile parameters. Thus, the aim of this study was to investigate the changes of urinary stone risk profile after citrate supplementation in Swiss rKSF.

**Methods:** This study is a retrospective analysis of prospectively collected data from the Swiss kidney stone cohort. 24h-urine parameters were measured at baseline, after 3 months and one year of therapy. The primary endpoint of this study is the change of urinary parameters after citrate supplementation.

**Results:** 446 participants (mean age 47 ± 14 years, 70% male) were evaluated. 95% of stones were calcium-containing, 88% consisted of oxalate, followed by 47% phosphate, 8% uric acid and 2% cysteine. Potassium citrate was administered to 52 patients (11.7%) at a mean dosage of 2523 ± 1173 mg citrate/d. Mean 24h-urine parameters at baseline were as follows: citrate 2.79 ± 1.54 mmol/d, potassium 60.12 ± 24.86 mmol/d, calcium 5.71 ± 3.27 mmol/d, sodium 164.81 ± 80.16 mmol/d, oxalate 0.21 ± 0.17 mmol/d, ammonium 19.42 ± 10.8 mmol/d, magnesium 3.84 ± 1.84 mmol/d, pH 5.99 ± 1.63, volume 1.54 ± 0.93 l/d. Treatment with potassium citrate was associated with significant changes after 3 months in the following parameters: pH (p = 0.047), citrate (p = 0.002), magnesium (p = 0.0248) and volume (p = 0.012).

Interestingly, no significant changes were found between baseline and after 1 year, however, 1-y follow-up data were only available in a small subset of patients.

**Conclusions:** Citrate supplementation in Swiss rKSF resulted in a significant increase of urinary citrate excretion, urinary magnesium excretion and urinary pH resulting in a beneficial change of urinary risk profile parameters. In addition, 24h urine volume increased significantly according to dietary recommendations.

**Zinc deficiency in chronic kidney disease is not related to increased uric acid excretion**

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**Background:** Zinc (Zn) is an essential element in human physiology. Several studies have shown a high prevalence of Zn deficiency in patients with ESRD; however data on Zn in earlier stages of chronic kidney disease (CKD) are scarce. The aim of this study was therefore to assess the Zn status in CKD patients in Switzerland.

**Methods:** Serum Zn levels and Zn excretion in 24 hour urine were measured in 220 participants of the LauBOLDcohort that includes stage 1–5 CKD patients, hypertensives without CKD and healthy controls. A total of 117 patients with CKD (eGFR [mean ± SD] 55.3 ± 2.7 ml/min/1.73 m$^2$) and 103 patients without CKD (eGFR 94.1 ± 1.5 ml/min/1.73 m$^2$) were included.

**Results:** Serum Zn levels were significantly lower in CKD patients compared to no-CKD patients (610.3 ± 105.4 μg/l versus 672.9 ± 97.4 μg/l, p < 0.05) whereas urinary zinc excretion was not statistically
different between the two groups (611.6 ± 450.4 µg/24h versus 596.7 ± 493.7 µg/24h, p = 0.473). The decrease in serum Zn level started in the early stages of kidney disease (CKD stage 1: 626.2 ± 101.5 µg/l; stage 3: 593.8 ± 98.8 µg/l; stage 5: 558.2 ± 67.0 µg/l) and correlated significantly with eGFR (CKD-EPI) (Spearman’s rho: 0.28, p < 0.05) (fig. 1). Zinc deficiency defined as serum zinc <585 µg/l in men and <638 µg/l in women was present in 64.7% of CKD patients and 35.3% of no-CKD patients (p < 0.05). There was no significant correlation between urinary Zn excretion and eGFR (Spearman’s rho: 0.04, p = 0.6) (fig. 2). Multivariate linear regression showed a significant association between serum Zn level and eGFR (coef. β = 0.95 [95%CI: 0.3–1.6], p < 0.05) (table 1).

Conclusions: Zinc deficiency in CKD patients starts as early as CKD stage 1 and correlates with eGFR. However, urinary Zn excretion remains stable in CKD patients suggesting that Zn deficiency is rather a consequence of decreased dietary Zn intake and intestinal absorption than increased urinary excretion.

Methods: Serum levels and 24 hour urine excretion of 23 trace elements (lithium, beryllium, aluminium, vanadium, chromium, manganese, cobalt, nickel, copper, arsenic, selenium, molybdenum, palladium, silver, cadmium, tin, antimony, iodine, platinum, mercury, thallium, lead, bismuth) were measured in 220 participants of the LauBOLD cohort. A total of 117 patients with CKD (eGFR [mean ± SD] 55.3 ± 2.7 ml/min/1.73 m²) and 103 participants without CKD (eGFR 94.1 ± 1.5 ml/min/1.73 m²) were included.

Results: Demographic patient characteristics are shown in table 1. In CKD patients, serum levels of aluminium, arsenic, molybdenum, palladium, mercury, lithium and iodine were significantly increased compared to no-CKD patients, whereas no differences were seen in urinary excretion, lithium excepted (63.8 ± 60.2 µg/24h versus 44.7 ± 370.4 µg/24h, p = 0.05) (table 2). Serum levels of nickel and bismuth were significantly reduced in CKD patients without increase in urinary excretion.

Conclusions: Serum levels of biologically important trace elements were substantially different in CKD patients compared with controls. The majority of serum levels were higher in CKD, at equal urinary excretion. This possibly points towards disturbed renal elimination in CKD patients. However, most serum levels of trace elements were in reference ranges for both CKD and no-CKD patients.
**Methods:** We evaluated the frequency, cause and outcome of kidney disease in patients undergoing orthotopic liver transplantations (OLT). We evaluated 279 OLT in 262 patients at the University Hospital in Bern from 01.01.2005 to 18.07.2017.

**Results:** Preexisting kidney disease was infrequent in patients during evaluation for OLT with a prevalence of 15% of patients suffering from CKD3 and higher. Perioperative AKINIII was present in 38% of patients and among those, 69% required renal replacement therapy. Preexisting CKD, perioperative AKINIII and perioperative RRT were strong predictors for inferior patient outcome after OLT. Among the patients with at least one month of follow-up, median Creatinine at the end of follow up was 106 umol/l (range 24–779) with a eGFR-EPI of 55 ml/min/1.73 m² (range 16–88 ml/min/1.73 m²). 51.7% of patients suffered from CKD3 and eGFR <60 ml/min/1.73 m², old age at transplantation, perioperative AKIN III and hypertension were strongly associated with the development of chronic CKD in the OLT cohort.

**Conclusions:** In conclusion, concomitant kidney disease in the pre- or post-transplant period is a highly relevant co-morbidity in the OLT cohort in need of more specific attention.

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**Change in V-ATPase B1 but not B2 subunit abundance in human urinary exosomes in response to acute acid/alkali loading and distal renal tubular acidosis**

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**Background:** In the kidney, final urinary acidification is achieved by V-ATPases expressed in type A intercalated cells. The B1 subunit of the V-ATPase is required for maximal urinary acidification, while the V-ATPases expressed in type A intercalated cells. The B1 subunit of

**Methods:** We examined the effect of acute acid/alkali loading in humans on B1 and B2 subunit abundance in human urinary exosomes in normal subjects and of acid loading in patients with distal renal tubular acidosis (dRTA). Specificities of B1 and B2 subunit antibodies were verified by yeast heterologously expressing human B1 and B2 subunits, and murine WT and B1-deleted kidney lysates.

**Results:** Acute NH4Cl loading elicited systemic acidemia, drop in urinary pH, and increase in urinary NH4 excretion. Nadir urinary pH was achieved in 4–5 hrs, and exosomal B1 abundance was significantly increased at 2, 3 and 4 hrs after NH4Cl loading. After acute equimolar NaHCO3 loading, blood and urinary pH rose rapidly, with concomitant reduction of exosomal B1 abundance within 2 hrs and B1 abundance remained lower throughout the test. In contrast, no changes in exosomal B2 abundance were observed following acid or alkali loading. In patients with inherited or acquired dRTA, urinary B1 subunit was extremely low or undetectable and did not respond to acid loading in urine, whereas no change in B2 subunit was observed.

**Conclusions:** In conclusion, both B1 and B2 subunits of the V-ATPase are detected in human urinary exosomes, and acid and alkali loading or dRTA cause changes in the B1 but not B2 subunit abundance in urinary exosomes.

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**Lipodystrophy increases the risk of developing chronic kidney disease in HIV- positive patients in Switzerland: the LIPOKID study**

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**Background:** Antiretroviral therapy (ART) improved HIV positive patient survival. However, those patients developed metabolic complications such as lipodystrophy (LD) which is the hallmark of first generation ART. LD is defined as body shape abnormalities such as central fat accumulation and peripheral fat loss, has been associated with modifications in adipokines and may be related to alterations of mitochondrial metabolism. Abdominal obesity, adipokines and alterations of kidney fatty acid metabolism are risk factors for CKD progression. We hypothesized that the abdominal fat distribution found in HIV positive patients with LD may be an independent risk factor to develop CKD.

**Methods:** All patients from the Swiss HIV Cohort Study with an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m² at entry in the cohort from 2002 to 2015 with a minimal follow-up of 3 months were included. The primary endpoint was defined as a sustained eGFR <60 ml/min/1.73 m². Cox regression models were used to measure the risk to develop CKD associated with different patterns of LD.

**Results:** Among the 5384 patients included, 4246 did not have LD at entry in the cohort. 31.0% developed LD during their follow-up after a median existing time of 7½ months (IQR: 0–45.2 months) and 252 (4.7%) reached the studied endpoint after a median follow-up time of 43.7 months from baseline (IQR: 18.5–89.3 months). Overall LD increased significantly the risk of an eGFR <60 ml/min/1.73 m² in univariate analysis with a hazard ratio (HR) 2.25 (95% confidence interval (CI): 1.68–3.00; p <0.001). After adjustment for main confounders (such as age, sex, hypertension, diabetes, baseline eGFR and viral load), LD increased the risk of eGFR <60 ml/min/1.73 m² by a HR 1.98 (95% CI: 1.31–2.99; p < 0.001).

**Conclusions:** LD might be a risk factor for eGFR decline in HIV positive patients independently of previously reported CKD risk factors.
Renal Amyloidosis is not sufficiently prevented in patients with FMF in Armenia
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Background: Familial Mediterranean fever (FMF) is a serious health problem in Armenia. Although amyloidosis – a potentially fatal complication of FMF – can largely be prevented by colchicine administration, we are still confronted with real cases. The aim was to analyze the demographics and reasons for biopsy-proven amyloid nephropathy.
Methods: The National Pediatric Center for FMF (NPC FMF) was established in 1998 to allow early diagnosis, treatment, follow-up and wide dissemination of information on FMF. Since 2003 NPC FMF has implemented the long term program and provided regularly colchicine to over 3000 children <16 years, but not to adults. Diagnosis of FMF is based on Tel-Hashomer criteria and molecular genetic analysis (since 1998). Amyloid nephropathy was confirmed by renal biopsy (Congo Red). Patients with biopsies 1993–2004 (group 1; n = 206) are compared with those 2005–2016 (group 2; n = 475).
Results: Amyloid nephropathy due to FMF in group 1 was detected in 47 pts (38 children, 9 adults) = 23% of all biopsies, as compared to 42 pts (22 children, 20 adults) in group 2 (=9% of biopsies; p <0.05). The second group was further analyzed: On admission 6 children versus 7 adults had proteinuria, 14 versus 10 were nephrotic and 2 versus 3 had CKD (stage 3). FMF was diagnosed late in 18 pediatric patients, one was noncompliant, three were partially resistant to colchicine. In adults, FMF was diagnosed late in 16, whereas in 4 colchicine was not sufficiently effective (low dose?). Late administration of colchicine could not reverse the course.
Conclusions: In contrast to the absolute number of patients the proportion of biopsies showing amyloid nephropathy has significantly dropped. The National FMF program in Armenia is only partly effective in prevention of renal amyloidosis and requires additional efforts. Colchicine is not able to reverse advanced amyloid nephropathy.
Hypokalemic metabolic alkalosis, hypertension and diabetes – what is the link?

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Background: The triad of hypokalemia, metabolic alkalosis and hypertension is highly suspicious for mineralocorticoid excess and demands further evaluation. As the differential diagnosis is broad, further diagnostics should be chosen according to the patient’s individual clinical presentation.

Methods: All data was obtained by reviewing medical reports, laboratory results as well as histological and radiological findings from the Kantonsspital Graubünden and University Hospital of Basel. Current literature available on the topic was reviewed.

Results: Two years after diagnosis of a metastatic neuroendocrine gastrin-secreting tumour and after several cycles of chemotherapy and targeted radionuclide therapy, a 56-year-old woman presented with hypokalemic metabolic alkalosis, hypertension and new-onset diabetes mellitus. Further investigations revealed renal potassium loss as shown by a transtubular potassium gradient of 16, fully suppressed diabetes mellitus. Further investigations revealed renal potassium loss and new-onset hypokalemic metabolic alkalosis, hypertension and diabetes – what is the link?高血压是高度怀疑的原发性醛固酮增多症和新的临床表现。进一步的调查发现，由于转移性肿瘤而造成的钾离子丢失， hypokalemic metabolic alkalosis, hypertension and diabetes – what is the link? 

Conclusions: The initial work-up of hypokalemic metabolic alkalosis with hypertension should include measurement of the aldosterone-renin ratio and the transtubular potassium gradient. In cancer patients with diabetes mellitus in addition to signs of mineralocorticoid excess, paraneoplastic hypercortisolism should be considered. Symptoms can occur late in the course of disease, as tumour progression and therapy may lead to selection of new cell clones. Measurement of urinary cortisol metabolites detects excessive production of clinically active metabolites not captured by routine serum-cortisol tests. In our case, ectopic secretion of ACTH was found to be catecholaminergic and led to clinical signs of both hyperglycemia- and mineralocorticoidism. Metyrapone proved to be a highly effective symptomatic therapy in our patient.

Single center experience with tolvaptan in nine patients with autosomal dominant polycystic kidney disease (ADPKD)

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Background: Tolvaptan is a selective vasopressin V2 receptor antagonist which was introduced in Switzerland in November 2016 to slow renal disease progression in patients with ADPKD.

Methods: We investigated the initial clinical course of nine patients with ADPKD and CKD stages 2 and 3 in whom treatment with tolvaptan was initiated at our center. The indication for treatment was primarily based on the Mayo classification. The standard initial dose was 45/15 mg/d. If tolerated, the dose was increased to 60/30 mg/d and subsequently to the maximum dose of 90/30 mg/d.

Results: The nine patients (eight male and one female) had a mean age of 46 ± 12 years, a baseline eGFR of 67 ± 15 ml/min/1.73 m² and a TKV of 1576 ± 635 cm³. Three patients were in Mayo class 1C and six patients in class 1D. Side effects included polyuria and nocturia, fatigue (4/9), intermittent headache (2/9) and stomach pain (2/9). Younger patients tended to cope better with polyuria and nocturia. As expected, tolvaptan led to a 52 ± 33% reduction of urine creatinine concentration (p = 0.0075). A mild increase in serum creatinine after initiation of tolvaptan was seen in 9/9 patients. Two patients (62 and 64 years old) experienced an acute kidney injury stage 1 after start of the medication which was reversible after increasing fluid intake and reducing antihypertensive medication. One patient (62 years old) had to discontinue treatment due to new urge incontinence. Liver function parameters were unaltered in all patients, but one patient showed a slight increase after heavy alcohol intake the previous day.

Conclusions: Decreased urine creatinine concentration represents a useful marker for the initial treatment efficacy of tolvaptan, paralleling the increased thirst and fluid intake which appeared to have a relevant impact on everyday life and wellbeing of the patients. Transient deranged liver function parameters were seen in 1/9 patients. The long-term tolerability of tolvaptan remains to be determined.
Could polymerase chain reaction (PCR) avert worsening acute kidney injury? A case of leptospirosis in a regional hospital

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Background: Leptospirosis is a frequent zoonotic disease with high mortality from sepsis and multiorgan dysfunction including renal failure. Renal manifestations vary from mild urine abnormalities to severe acute kidney injury sometimes requiring hemodialysis. Due to high case fatality rate, early diagnosis during the initial phase of the disease (first 3 to 7 days) may guide early treatment with an influence on patient outcome. We report the case of severe non-oliguric acute kidney injury in a patient with fever myalgia and severe thrombocytopenia. Despite a negative ELISA test, PCR was positive for leptospirosis.

Methods: A 7-year-old male presented with fever and myalgia. He had hypertension managed with telmisartan. He denied swimming or water related activities. Physical examination was unremarkable except for dry oral mucosa. Laboratory findings included severe renal failure, thrombocytopenia, raised CRP and altered liver enzymes. Urinalysis showed only mild hematuria. Fractional excretion of sodium was low. With a suspicion of leptospirosis and pre renal AKI, intravenous fluids were commenced alongside broad spectrum antibiotics. Clinical course was marked by worsening thrombocytopenia and renal failure resulting in further immunologic work up which returned unremarkable. Further history revealed patient kept rats and mice.

Results: ELISA (IgM) for Leptospira sp was negative but further serum PCR revealed positive for leptospirosis and the patient was commenced followed by out patient amoxicillin with improved clinical course alongside renal function. A couple of weeks following discharge, repeat ELISA was positive suggesting seroconversion.

Conclusions: The incidence of leptospirosis associated AKI varies with disease severity. Several mechanisms of renal damage exists. However, the diagnosis of leptospirosis can be difficult during the initial phase. Although ELISA antibody testing is highly recommended with its high sensitivity and specificity, when negative, this can present a diagnostic dilemma. Our Case highlights this and underpins the role of PCR for early diagnosis to avert worsening AKI.

Vascular aging processes accelerate during the whole life following an alarming kinetic: Pulse Wave Velocity as an objective counterpart that time flies

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Background: Arterial stiffness mainly measured by Pulse Wave Velocity (PWV) is a reliable marker of vascular aging and is considered to be the only parameter quantifying the consequences, on the vascular wall, of whole life cumulated cardiovascular risk factors. The acceleration in arterial stiffness progression related to age can be worsened by different acquired factors that translate into the concept of early vascular aging.

Methods: Pulling together the data of three epidemiological studies concerning the normal population, we aimed to calculate the age specific relative amount of time (in days or fractions of year) equivalent to that necessary to progress one year in vascular age at 20. A population of 3724 subjects classified in 5 age groups was analysed. A polynomial function and its derivative, expressing the instantaneous PWV acceleration, were calculated.

Results: The number of days (if 365 at 20 years) necessary at 30, 50 and 70 years to produce the same amount of PWV progression observed in one year at 20 is respectively 318, 170 and 69. The age related increase in PWV does not follow a kinetic of constant acceleration; this means that vascular aging processes accelerate during the whole life. Our data confirmed that acceleration in PWV has dramatic consequences producing, comparing to the age of 20, the same amount of structural changes at 50 in half of the time and at 70 in a fifth.

Conclusions: The results confirm the subjective perception, that time is running faster and faster; perception that can be translated into two special concepts: shorter times later in life to reach the same amount of vascular structural changes or more years of life if the age related changes at 20 are used as the reference to calculate the progression. Once again we can choose: half empty or half full?
Diabetic muscle infarction: a diagnostic challenge for clinicians and radiologists

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Background: Diabetic muscle infarction (DMI) is a rare and probably underdiagnosed complication of diabetes mellitus. Risk factors are poor glycemic control and the presence of diabetic complications, especially diabetic nephropathy.

Methods: Case report.

Results: Case 1: A 44-year old female patient with insulin dependent diabetes mellitus (IDDM) type 2 for 11 years and diabetic nephropathy with CKD stage 5 presented with severe and disabling pain at the left thigh. Laboratory findings showed a slightly elevated C-reactive Protein (CRP) with no elevation of leukocytes, Creatinin-Kinase (CK) or Lactat-Dehydrogenase (LDH). MRI of the hip, however, demonstrated hyperintensity of the T-2and STIR (short tau inversion recovery) sequences with enhancement after gadolinium administration, compatible with necrosis of the adductor muscles due to DMI. The condition was managed conservatively with rest and analgesics. Case 2: A 59-years old female with a 15-years history of IDDM type 2 and diabetic nephropathy with CKD stage 5 presented with severe and disabling pain in the left thigh. Laboratory findings showed an elevation of CRP and LDH with no leukocytosis or elevation in CK. CT and MRI revealed severe muscular atrophy. The postoperative course was complicated by multiple atelectasias and fascia lata with features suggesting necrotizing fasciitis. Intravenous antibiotics were initiated immediately after diagnosis and a fasciotomy was performed. Histologic examination revealed non-specific muscular atrophy. The postoperative course was complicated by multiple atelectasias and fascial necrosis. A muscular biopsy was repeated and histologic examination revealed necrosis of muscle and fascia due to DMI.

Conclusions: We have therefore a proofe of principle for mTOR inhibition in this individual case of fibrotic disorder.

Unexplained severe lactic acidosis in a non-diabetic chronic hemodialysis patient: do you consider to make a phone call to the pharmacy?

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Background: Metformin is acknowledged worldwide as having a central role in the primary treatment of type 2 diabetes mellitus. The drug has been used since 1957. The mean plasma elimination half-life of metformin after oral administration is 4.0–8.7 h, and since it is cleared almost exclusively by the kidneys, its elimination is prolonged in persons with CKD. Among these adverse effects, the lactate acidosis defined as an elevated lactate level (>5 mmol/L) along with a decreased blood pH (<7.35) and an increase anion gap, is most dangerous. This condition has a mortality of up to 50% per episode.

The incidence of lactate acidosis varied between 2.5 to 10 cases/100 000 patient-years1. In Switzerland Bailey and Nattrass have reported 2cases until 1972 to 1977 means an incidence of 6.7/100 000 patient-years.

Methods: Hemodialysis is an efficient method to treat metformin intoxication and correct the metabolic abnormalities. Lalau and al.1 have reported two unusual cases: metformin accumulation in the absence of hyperlacteacima and, metformin– induced hyperlacteemia in the absence of metformin accumulation.

Results: We report a case of metformin-associated severe lactic acidosis (pH = 7.20, lactate 11.4 mmol/L) in a 33-years old non-diabetic HD patient that remained initially unexplained. In this patient aluminium hydroxide (Phosphonorm 3 × 300 mg/day) had been prescribed but the pharmacy, by mistake, delivered instead metformin that the patient took at a dose of 3 × 500 mg/day for 10 days before hospitalisation.

Conclusions: Toxicology blood analysis was negative in our patient, but it is important to know that depending on the analytical technique used metformin is not always detectable in blood.
Prevalence rates and risk factors for chronic kidney disease in sub-Saharan Africa: A pilot study in a semirural region of Tanzania

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Background: In developing countries, data about prevalence rates and risk factors for chronic kidney disease (CKD) are scarce. The aim of our study was to provide data on CKD prevalence rates and to explore the impact of cardiovascular risk factors and communicable diseases on CKD in a region of sub-Saharan Africa (SSA).

Methods: We conducted a single center cross-sectional study at the outpatient clinic of the Bagamoyo District Hospital in Tanzania. For the classification, according to KDIGO 2012, we measured albumin to creatinine ratio and calculated eGFR with the CKD-EPI formula. Uni- and multivariate logistic regression was used to determine independent predictors for CKD.

Results: Patient characteristics were described from n = 945 cases (table 1). Overall, prevalence of CKD was 13.6% (n = 119) (95% CI 11–16%). Of them, 98 patients (11.2%) were categorised as moderate risk, 12 (1.4%) as high-risk, and 9 (1%) as very high-risk regarding prognosis (fig. 1). In multivariate logistic regression analysis, diabetes (OR 2.20, 95% CI 0.98–4.71; p = 0.05), history of tuberculosis (OR 3.75, 95% CI 1.66–8.18; p = 0.001), and history of schistosomiasis (OR 2.49, 95% CI 1.13–5.18; p = 0.02) were associated with CKD. A strong trend was also seen for increasing systolic blood pressure (per 1 mm Hg) (OR 1.02, 95% CI 1.00–1.03; p = 0.01). An increase in BMI (per 1 kg/m²) and in haemoglobin (per 1 g/dL) was associated with risk reduction (OR 0.92, 95% CI 0.86–0.96; p <0.001 and OR 0.82, 95% CI 0.72–0.94 per; p = 0.004, respectively) (table 2).

Conclusions: This is the first study which provides prevalence data on CKD according to KDIGO 2012 in a SSA region. In contrast to industrialised countries people living in SSA are affected by a double burden of non-communicable and infectious diseases, both with impact on the development of CKD.

Lack of Fetuin-A exacerbates interstitial kidney fibrosis (NCCR project)

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Background: Fetuin-A (FetA) is a circulating glycoprotein principally secreted by the liver into the circulation, mainly known for his inhibiting role in calcification processes. Chronic kidney diseases (CKD) patients display low levels of serum FetA which is a predictor of poor outcomes. FetA has also been shown to mimic TGF-β receptor and therefore has the potential to compete with epithelial cells and fibroblasts for the profibrotic cytokine TGF-β. In CKD, renal fibrosis is one of the main features correlating with kidney function impairment.

Methods: Kidneys, liver and blood of FetA -/-, +/- and +/+ were harvested 1–2 weeks after unilateral ureter obstruction (UUO) or 35 days after folic acid (FA) injection then prepared for IHC, WB and qPCR analysis.

Results: IHC showed that FetA -/- obstructed kidneys displayed a higher increase of collagen (Sirius red), α-SMA and Ncadherin after 1 and 2 weeks of UUO compared to wild-type or heterozygotes. Western blots, showed a higher upregulation of mesenchymal and fibrotic markers (vimentin, α-SMA and N-cadherin) in obstructed kidneys of FetA -/- than wild-type or heterozygotes, as well we a more pronounced increase of Smad3 expression and phosphorylation. Our preliminary results with folic acid nephropathy showed – similarly to the UUO model – higher increase of collagen (Sirius red) and α-SMA in kidneys of FetA -/- than wildtype mice 35 days after FA injection.

Conclusions: In two different models of fibrosis we observed a more pronounced kidney interstitial fibrosis in the absence of FetA, thus lower FetA levels, which can be encountered in CKD patients, could facilitate the progression of kidney fibrosis. Next, we plan to decipher the mechanisms regulating FetA expression in our models of fibrosis. Also we will try to counteract fibrosis progression by reconstitution of FetA, either by injection of recombinant FetA or in vivo transfection of plasmid coding for FetA.
Impact of Dietary Amino Acids on CKD Progression in Rats (NCCR project)

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Background: Our study aims to address the impact that specific dietary amino acids or groups of amino acids might have on the progression of chronic kidney disease.

Methods: We utilised the well-established 5/6th Nephrectomy (5/6th Nx) model to induce CKD. 5/6th Nx Wistar Han rats were randomly divided into groups receiving either the control diet (18% protein) or one of different diets, in each case containing 8% protein supplemented with 10% of a mix of free amino acids (AAs); Essential (EAA)s, Non-Essential (NEAAs), Branched Chain- (BCAAs), Aromatic- (AAs) or all AAs in the same proportion as in the protein mix. In addition to this we also had a group that was fed a diet containing 18% protein supplemented with 1.82% L-arginine. Both GFR and RPF were measured in free moving animals, GFR transcutaneously using FITC-sinistrin, and RPF by using radiolabelled para-aminohippurate (PAH).

Results: None of the modified diets did cause any decrease in body weight, food and water consumption in the different groups. However, the pace of RPF and GFR alteration was diet-dependent. Animals receiving AAs and EAA showed the fastest progression whereas the most dramatic reduction was in case of the animals on the BCAA diet. The kidney of these BCAAs receiving rats also showed the strongest increase in smooth muscle actin and collagen mRNA expression in their kidney, as expected for a higher level of inflammation and fibrosis. The SMA levels were increased 2-fold and the collagen levels were increased more than 3-fold compared to animals on control diet. On the other hand, the AAA receiving group showed an improvement in both GFR and RPF.

Conclusions: Taken together these results suggest that high levels of BCAAs contained in the diet have a deleterious effect on the progression of CKD whereas high levels of EAAAs, in particular AAAs have a beneficial effect.

Podocyte damage is induced by aberrantly glycosylated anti-PLA2R-IgG via the lectin complement pathway in membranous nephropathy

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Background: Primary membranous nephropathy (pMN) is an autoimmune kidney disease that usually manifests as nephrotic syndrome through damage of podocytes and leads to progressive renal failure in a significant proportion of patients. Recently, the target antigen of autoantibodies in the majority of patients with iMN has been identified as the phospholipase A2 receptor (PLA2R). However, mechanisms of podocyte injury remain elusive, although subclinical complement injury has been proposed. In this study, we developed an in vitro model for pMN and determined mechanisms of anti-PLA2R1-antibody mediated injury to podocytes.

Methods: PLA-R expression levels in human podocytes were modulated by lentiviral infection or siRNA knock down. Podocytes were treated with sera from PLA2R-IgG positive patients and human complement in the presence of various conditions activating or inhibiting specific complement components and proteinases, followed by immunofluorescence and western blot analysis. Human kidney biopsies were stained for synaptopodin, NEPH1, C3aR1, and C5aR1. Isolated IgG4 from patient and control sera was assayed by MALDI-TOF for alterations in their glycosylation pattern.

Results: As reported at the previous meeting, anti-PLA2R-positive sera induce proteolysis of synaptopodin and NEPH1 in PLA2R-expressing cells in a complement-dependent fashion. This effect was mediated by two distinct proteolytic pathways via coincident insertion of the membrane attack complex (C5b-9) and C3aR1 and C5aR1 activation. Here, we report rescue of the phenotype by specific blockade of the lectin pathway. Isolated IgG4 from pMN patients showed an altered glycosylation pattern that allows for complement activation. Finally, C3aR1 and C5aR1 were up-regulated and synaptopodin and NEPH1 expression decreased in human pMN kidney biopsies, supporting in vivo relevance of the reported pathway.

Conclusions: This study provides detailed insights into the mechanisms of complement activation and the complement effector pathways that lead to podocyte injury in human primary membranous nephropathy.
Role of the serine protease CAP2/Tmprss4 in renal adaptation to potassium depletion (NCCR project)

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Background: The membrane-bound serine protease CAP2/Tmprss4 was previously identified as an in vitro activator of the epithelial sodium channel (ENaC) (Vuagniaux et al. 2002), but its genetic ablation in mice revealed that CAP2/Tmprss4 is not required for ENaC-mediated sodium homeostasis in vivo (Keppner et al. 2015), leading us to explore its implication in renal potassium handling.

Methods: CAP2/Tmprss4 knockout mice were kept in metabolic cages and fed a K+-deficient diet. Urine and plasma parameters were subsequently analysed, and kidneys recovered for protein and mRNA quantifications.

Results: In this study, we show that CAP2/Tmprss4 is regulated by dietary potassium specifically in the kidney, and that upon K+-deficient diet, CAP2/Tmprss4 knockout mice display altered sodium and water handling, along with changes in the urinary osmolality and pH whereas urinary potassium excretion was preserved. We could link these parameters to differential expression of several transporters and channels, including the renal H+,K+-ATPase (HK2), NKCC2 and AQP2, as well as vascular sensitivity to vasopressin (AVP).

Conclusions: Taken together, these results suggest a new role for the serine protease CAP2/Tmprss4 in renal potassium handling, by regulating the expression of the HK2.

Salt-sensitive hypertension in a new rat model for primary generalized glucocorticoid resistance (NCCR project)

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Background: Glucocorticoids mainly act through the glucocorticoid receptor (GR) that functions as transcription factor. Glucocorticoid resistance is a condition characterized by generalized, partial target tissue resistance to glucocorticoids. Compensatory mechanisms lead to elevation in circulating adrenal steroids with mineralocorticoid and/or androgenic activity, and the clinical spectrum of this condition is broad ranging from asymptomatic to severe cases of hyperandrogenism and/or mineralocorticoid excess. So far, no animal model existed that mimics all clinical symptoms as observed in human generalized glucocorticoid resistance.

Methods: We generated the first TALEN-engineered rats carrying knockout and in-frame mutations on the GR gene locus within its coding sequence.

Results: Heterozygous mutant GR+/em4 rats reproduce all clinical features of glucocorticoid resistance and show increased size of the adrenal gland (adrenal hyperplasia), increase of mineralocorticoids (hyperminalocorticidism), corticosterone (hypercorticosteronism) and androgens (hyperandrogenism). Heterozygous mutant GR+/em4 rats, carrying deletion of the exon 3 exhibit hypercorticosteronism, but lack hypermineralocorticidism and hyperandrogenism. In summary, these rats reproduce most of the clinical signs of primary generalized glucocorticoid resistance syndrome. Moreover, all mutants develop salt-sensitive hypertension.

Conclusions: In conclusion, we show that (1) glucocorticoids induce salt-sensitive hypertension and (2) dimerization domain of the GR is likely implicated in this mechanism.

Aldosterone controls primary cilium length and Hif1β88 abundance via mineralocorticoid receptor in the distal segments of the kidney tubule *NCCR project*

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Background: The kidneys are major players in the control of body fluid homeostasis. At the cellular level, the apical single non-motile primary cilium is a signalling hub and may function as a urinary chemosensor. We hypothesized that aldosterone, a mineralocorticoid hormone that stimulates sodium reabsorption in the distal nephron, modulates cilium length and thereby its functional properties.

Methods: Experiments were performed in cultured mCCD17 cells, a model of aldosterone-responsive collecting duct principal cells, transgenic mice with inducible kidney tubule-specific knockout (KO) of the mineralocorticoid receptor (MR) and mice with randomized deletion of the MR in renal tubule cells (MRX mice). Primary cilia were detected by indirect immunofluorescence using anti-acetylated α-tubulin antibodies.

Results: In mCCD17 cells, aldosterone-stimulated Na+ transport was correlated with lengthening of primary cilia. In contrast, in MR KO mice displaying decreased sodium reabsorption along the aldosterone-sensitive distal nephron, primary cilia of distal tubules and collecting ducts were shorter compared to WT mice. The primary cilium length in
Identification of a novel hepatitis E virus-genotype 3 strain from a chronic hepatitis E virus infection in a kidney transplant recipient in Switzerland

Methods: Viral RNA extraction from patient serum and feces was performed using the High Pure Viral Nucleic Acid Kit (Roche Diagnostics, Germany) according to the manufacturer's instructions. The complete viral genome was amplified using KAPA HiFi HotStart ReadyMix PCR (Kapa Biosystems, USA). 5' and 3' sequences were determined using 5'-and 3'-rapid amplification of cDNA ends (Roche Diagnostics, Germany). Whole genome sequence and phylogenetic analyses were done using Geneious-10.0.5 and Mega-7 software.

Results: The virus was isolated from a male 57 year old kidney transplant recipient from nephrology department in Lachen, Switzerland. He presented four months after living kidney donor transplantation due to end stage kidney disease because of autosomal dominant polycystic kidney disease with itching and elevated liver enzymes treated with immunosuppressive drugs tacrolimus and mycophenolate and newly with a chinolone for urinary tract infection. No recovery was seen of liver enzyme elevation despite of stop of chinolones. Search for viral hepatitis resulted in positiv anti-HEV IgM/tg and HEV-RNA in serum and feces. Further analyses showed less than 88% homology compared to known HEV-genotype 3 strains. Patient got ribavirin for treatment seeing chronic course.

Conclusions: There was poor homology to any HEV-genotype 3 subtype usually isolated. The SW/16-0282 strain represents a new HEV subgenotype 3 by comprehensive genetic analyses of HEV strains from human and animal reservoirs. Ribavirin successfully treated this new subgenotype without recurrence within 1 year.
Methods: In patients' kidney biopsies and plasma samples were collected. In vivo, Malat1 knockout (KO) and wild-type (WT) mice were subjected to unilateral and bilateral I/R. Histopathology-, gene expression-, kidney function- and survival studies were performed. In vitro, Malat1 was silenced by antisense oligonucleotides in endothelial cells (EC) and tubular epithelial cells (TEC) subjected to hypoxia/ reoxygenation. Transcriptional activation- and functional studies were implemented. Genome-wide RNA analysis was performed.

Results: Malat1 was upregulated in human kidney biopsies and plasma and in murine kidney tissue, EC and TEC and mainly nuclear-chromatin associated. In vitro, Malat1 inhibition reduced EC in the S-phase of the cell cycle. Proliferation decreased. Less EC were apoptotic after Malat1 silencing. TEC were not functionally altered. Malat1 was transcriptionally activated in EC and TEC by hypoxia-inducible factor 1-alpha. In vivo, Malat1 KO- and WT mice showed similar degrees of tubular epithelial injuries and proliferating cells. Capillary rarefaction was not affected. Kidneys of Malat1 KO- and WT mice expressed more pro-inflammatory (IL-1beta, IL-6, MIP2a, MCP-1) and pro-fibrotic (Col1a2, Col III, TGF-beta) genes. Similar amounts of macrophage-, T-cell infiltration and tubulointerstitial collagen were detected. mRNA- and smallRNA expressions showed only minor differences. The reduced kidney function was altered by Malat1 KO. Malat1 KO mice showed no survival benefit.

Conclusions: Malat1 plays a pivotal role in hypoxia/reoxygenation induced endothelial cell pathology. Even though previous studies have suggested a prominent role of Malat1 in the induction of disease, we did not confirm an effect of Malat1 loss on the progression of renal I/R-injury.

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Antioxidative role of cytoglobin in podocytes and its association with chronic kidney disease (NCCR project)

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Background: Cytoglobin (Cygb) is an antioxidative protein that belongs to the mammalian globin family. Despite extensive research efforts, little is known about its physiological role in the kidney. Accumulating evidence suggests that oxidative stress plays a crucial role in podocyte detachment and/or apoptosis during diabetic nephropathy. In the present study we investigated if Cygb has a protective role in the kidney.

Methods: We generated stable CYGB knock-down and overexpressing cellular models in 2 independent human podocyte cell lines (A8B13 and LY), in order to investigate the Cygb-dependent transcriptome, cell viability and oxidative stress response. Additionally, we validated the results in vivo, by comparing renal function, apoptosis and gene expression of Cygb−/− and Cygb+/+ mice.

Results: Cygb-deficient podocytes displayed increased cell death and accumulation of ROS as assessed by H2-DCF-DA assays and the redox sensitive probe roGFP2-Orp1. Transcriptome analysis of control and Cygb-depleted cells identified dysregulation of multiple genes involved in apoptosis, oxidative stress and podocyte injury. Gene array data from human patients showed that CYGB is upregulated in diabetic nephropathy and GWAS analysis identified a SNP in the 3’ intergenic region of Cygb that is potentially associated with chronic kidney disease (CKD). Cygb−/− mice displayed impaired renal function and increased apoptosis compared to Cygb+/+ mice under basal conditions. Analysis of Cygb-dependent gene expression in mice is currently ongoing.

Conclusions: Data of our study demonstrate that Cygb protects podocytes from oxidative stress and apoptosis in vitro and may be involved in CKD, particularly in diabetic nephropathy. In vivo data show that Cygb deficiency is associated with worse renal clearance and increase in apoptosis, consistent with a protective role of Cygb in the kidney.

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Uromodulin excretion is modulated by the calcium-sensing receptor

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Background: Uromodulin is the most abundant urinary protein and predominantly produced in the thick ascending limb (TAL) of the Henle’s loop, a nephron segment crucial for Ca2+ homeostasis under control of the basolateral calcium-sensing receptor (CaSR). Whether the CaSR is involved in the physiological regulation of uromodulin excretion remains unknown.

Methods: We studied two mouse models with inactivating (BCH002) and activating (Nu) mutations in the Casr gene as models for the chronic modulation of CaSR activation. As an acute model, we used primary mouse TAL cells (mTAL), which endogenously express uromodulin and CaSR, exposed to specific CaSR agonist (Calindol, 100 nM) and antagonist (NPS2143, 1 μM) and to variable Ca levels (1 mM and 3 mM) in the medium.

Results: We confirmed the expected alterations in blood calcium and phosphorus levels in BCh002 and Nu mice. Interestingly, urinary uromodulin excretion was significantly increased in BCh002 mice and decreased in Nu mice, without changes in kidney expression levels. Immunostaining suggested a shift from cytoplasmic to apical localization of uromodulin pools in the kidneys of BCH002 mice contrasting with a broad cytoplasmic staining in Nu kidneys. In mTAL cells, uromodulin secretion was abolished upon treatment with Calindol for 4 hours without changes in cellular expression levels. In contrast, 6-hour NPS2143 treatment normalized the reduced uromodulin secretion induced by high Ca (3 mM) medium in mTAL cells.

Conclusions: Taken together, these results indicate that activation of CaSR modulates the release of uromodulin in the urine, probably through post-translational control of uromodulin trafficking and processing in TAL cells. Modulators of CaSR, which are used in clinical practise, are thus able to change the levels of uromodulin in urine.

The TWEAK/Fn14 pathway is required for Calcineurin Inhibitor Toxicity of the Kidneys

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Background: Calcineurin inhibitor toxicity (CNT) is a frequent occurrence in transplanted renal grafts and autochthonous kidneys from patients undergoing long-term treatment with Calcineurin inhibitors, notably Cyclosporin A (CsA) and Tacrolimus.

Methods: We studied the effect of CsA on the TWEAK/Fn14 axis of the kidney in vitro and in vivo utilizing tubular epithelial cell cultures and mice sufficient or deficient for the TWEAK gene.

Results: We show an indispensable role of the TNF superfamily molecule TWEAK (TNFSF12) in the pathogenesis of acute CNT lesions in mice. A deficiency in TWEAK resulted in limited tubulotoxicity after CsA exposure, which correlated with diminished expression of inflammatory cytokines and reduced intraparenchymal infiltration with immune cells. We further identified tubular epithelial cells of the kidney as major targets of CsA activity and found that Fn14 (TNFSF12A), the receptor for TWEAK, is a highly Ca2+-inducible gene in these cells. Correlating with this, CsA pretreatment sensitized tubular epithelial cells specifically to the pro-inflammatory activities of recombinant TWEAK in vitro. Moreover, injection of rTWEAK alone into mice induced moderate disease similar to CsA, and rTWEAK combined with CsA resulted in synergistic nephrotoxicity.

Conclusions: These findings support the importance of tubular epithelial cells as cellular targets of CsA toxicity and introduce TWEAK as a critical contributor to CNT pathogenesis.
Bone marrow transplantation improves proximal tubule dysfunction in mouse models of Dent disease

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Background: Dent disease is a rare X-linked tubulopathy caused by mutations in the endosomal chloride-proton exchanger (ClC-5, Dent 1) and in an inositol polyphosphate 5-phosphatase (OCRL; Dent 2), resulting in defective receptor-mediated endocytosis and severe proximal tubule (PT) dysfunction. Bone marrow (BM) transplantation has recently been shown to preserve kidney function in cystinosis, a lysosomal storage disease causing PT dysfunction. Here we tested the effects of BM transplantation in Cln5⁻/⁻ and Orc1⁻/⁻ mice, faithful models for Dent disease 1 and 2.

Methods: Mice were irradiated and subsequently transplanted at 10 weeks-old with wild-type GFP+ or Cln5⁻/⁻, Orc1⁻/⁻ BM cells. The kidney function was monitored during 16 weeks post-transplantation via urine and plasma analyses. To substantiate our findings in vitro, we established a system of primary cultures of mouse PT cells which were co-cultivated for 2 days with BM-derived dendritic cells/macrophages.

Results: Ionized Magnesium(ion-Mg) represents the active biological fraction of the serum magnesium content. The assessment of total serum Mg(tot-Mg) might not accurately identify patients with hypo-hyper-magnesemia. In hemodialysis, serum tot-Mg levels in the upper part of the distribution, have been associated with reduced mortality and fewer vascular calcifications; thus, resulting in the tendency to increase the Mg concentration in the dialysate, traditionally set at 0.5 mmol/L. Ion-Mg significantly correlates with tot-Mg: i) the sensitivity for pathological values of ion-Mg in patients with liver cirrhosis.

Conclusions: Bone marrow transplantation rescues the PT phenotype in mouse models of Dent disease, through the development of tunneling nanotubes between transplanted BM-derived cells and diseased PT cells. These studies open perspectives for cell-based therapy of inherited tubulopathies.

Clostridium ramosum – a rare cause of peritoneal dialysis related peritonitis

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Background: A 74-year-old patient with alcoholic liver cirrhosis was hospitalized because of abdominal pain and diarrhea for 2–3 days. He was on peritoneal dialysis (PD) for two months due to hepatorenal-syndrome. Since he never experienced spontaneous bacterial peritonitis before, he was not on antibiotic prophylaxes.

Methods: Case report.

Results: At presentation he was afebrile and confused with a low blood pressure. Abdominal examination was unremarkable, especially the exit site and the PD-catheter were without signs of infection. A white blood cell count in the dialysate was >7000/mm³ with neutrophilic predominance. Empiric antibiotic therapy was initiated for peritonitis with intraperitoneal Cefazolin and Ceftazidim. Deterioration to severe sepsis led to ICU admission the next day, where intravenous therapy with Ceftazidim and Vancomycin was added. Due to further rapid clinical deterioration the therapy regime was finally switched to comfort care due to the patient’s will. The gram-stain of the peritoneal effluent showed gram-negative rods and post-mortem cultivation revealed growth of Clostridium (C.) ramosum; blood cultures remained without growth of bacteria. Clostridium species are part of normal flora of the gastrointestinal tract and oral mucosa. They can be responsible for infections, mostly in pediatric patients with otitis media, in the elderly or immunocompromised patients. It is rarely associated with severe infection or bacteraemia. While there are single case reports about PD related peritonitis due to C. difficile or perfringens, this is the first report on PD related peritonitis due to C. ramosum. C. ramosum is mostly sensitive to amoxicillin-clavulanate, piperacillin-tazobactam, metronidazole, imipenem and vancomycin. Sensitivity to penicillin and cephalosporins, however, is variable and resistances are described in the literature. Unfortunately, it is unlikely that prophylaxes with norfloxacin would have prevented the infection with C. ramosum.

Conclusions: Although rare, we suggest, to include C. ramosum in the differential diagnosis of PD related peritonitis, particularly in patients with liver cirrhosis.
Is there a mortality paradox among diabetic patients within the Swiss dialysis population?

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Background: Diabetes is also in Switzerland the leading cause for end stage renal disease and initiation of dialysis. Various studies have shown diabetes to be a significant predictor for mortality in dialysis patients. There is little information available in Swiss dialysis patients with diabetes about their mortality early after initiation of dialysis.

Methods: Incident dialysis patients (hemo- or peritoneal dialysis; N = 895) from the Swiss dialysis registry were followed up from 2014 on until December 31 2016 (mean follow up days = 751). Deaths occurred during this time (N = 189) were recorded and mortality risk was assessed with Cox-proportional hazard models. Patients were stratified according their status regarding systemic diabetes mellitus, type either 1 or 2, regardless of renal involvement with diabetic nephropathy.

Results: Characteristics of the dialysis population are provided in table 1. Dialysis patients with diabetes are significantly older, have a higher body mass index (p = 0.068) and have been longer on dialysis. The comorbidity score and count were slightly different between the two groups, however not significant. After removing the counts attributed to diabetes, the difference between these two groups disappeared. Cox regression analyses, adjusted for age and coronary artery disease, do not show a higher mortality for diabetic patients as expected. In contrast, there is a tendency towards worse 2-year survival for dialysis patients without diabetes compared to diabetic (p < 0.269, odds ratio = 1.183; 95% percentile: 0.879–1.593).

Conclusions: Unlike many other countries who have found diabetes to be a clear mortality risk factor in dialysis patients, dialysis patients in Switzerland do not have a higher mortality risk in the early course of their dialysis therapy. It seems that they even have a better survival probability in their first two years of dialysis compared to other patients. Possible explanations are better medical management or earlier start of dialysis therapy among this population.

Evaluation of the relationship between muscle mass and serum myostatin levels in chronic hemodialysis patients

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Background: The loss of muscle mass and cachexia is commonly seen in hemodialysis (HD) patients and contribute to morbidity and mortality. The exact mechanism of this fact is multifactorial and still unclear. Myostatin, a transforming growth factor-β family ligand, is released from the skeletal and heart muscle and may be responsible for muscle degradation and atrophy. The aim of this study is evaluation of the relationship between muscle mass and serum myostatin level in chronic HD patients.

Methods: 140 HD patients (79 male, 28 diabetic, mean age; 53.96 ± 13.6) were included in this cross-sectional study and 40 healthy adult controls to observe myostatin variation. Muscle mass measurement was made with dual energy-X ray absorptiometry. Appendicular skeletal muscle index (ASMI), (ASMI: both arms and legs SMM [kg] / height [m²]), was used as a muscle mass indicator. The anthropometric and biochemistry data were obtained for each individual. Serum myostatin levels were determined by an ELISA kit (Cloud-Clone, USA).

Results: The baseline characteristics of HD patients are shown in Table 1. Serum myostatin levels were elevated when compared to controls (p < 0.001) (fig. 1) but no significant correlation with ASMI was observed (r = 0.042, p = 0.624). ASMI significantly correlated with serum creatinine (r = 0.529, p < 0.001), creatine phosphokinase (r = 0.305, P < 0.001), prealbumin (r = 0.211, p < 0.012), albumin (r = 0.2, p < 0.039), transferrin (r = 0.430, p < 0.001), phosphorus (r = 0.28, p < 0.001), Ca×P (r = 0.255, p < 0.012), inversely with Kt/V (r = 0.636, p < 0.001) (fig. 2); not with BUN (r = 0.033, p = 0.739), parathyroid hormone (r = 0.033, p = 0.698), 25 hydroxyvitamin D (r = 0.044, p = 0.603), bicarbonate (r = −0.158, p = 0.062), calcium (r = 0.055, p = 0.560), C-reactive protein (r = 0.115, p = 0.235); such that these parameters also have influence on muscle mass regulation.

Conclusions: Our study indicated that myostatin levels were high in HD patients but had no relation with ASMI. Myostatin is a well-known regulator of muscle mass so further studies are needed to demonstrate possible relationship.
Prolonged disease-free survival after treatment of a bilateral breast granulocytic sarcoma with low-dose sorafenib in a chronic hemodialyzed patient

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Background: Granulocytic sarcoma (GS), or extramedullary leukemia, is a rare manifestation of acute myelogenous leukemia (AML) and often accompanies bone marrow involvement. It is not uncommon for GS to present as an isolated disease without bone marrow involvement, in particular upon disease relapse. Certain extramedullary sites such as the central nervous system and the reproductive organs are more prone to be involved at time of relapse.

Presenting signs or symptoms are mainly due to mass effect of the tumor and dysfunction of the organ or tissue affected; the diagnosis is performed by biopsy. GS occurs in 2–9% of newly diagnosed AML patients, either isolated or in combination with bone marrow involvement. Presence of GS carries a poor prognosis with a 5-years survival of 20–30%.

Methods: The multi kinase inhibitor Sorafenib was found to inhibit proliferation and to induce apoptosis in FLT3-ITD-AML blasts at concentrations achievable in vivo. Almost all the clinical trials have exclude hemodialyzed patient, but sorafenib has already been used at reduced doses to treat dialysis patients with renal carcinoma

Results: We report the case of 45-years old woman hemodialyzed since December 2013 for renal failure due to interstitial nephritis and nephrocalcinosis complicating the induction chemotherapy of AML (idarubicine, cytarabine). AML was classified as M4/MS according to FAB classification with positive FLT3-ITD and NPM1mutation, and negative [AML1-ETO, (8;21), CBFB-MYH11, inv(16) PML, RARA, t(15;17)]. After the induction cure, she was in remission on day 17 and received 2 cures of consolidation. She refused an autograft. One year later, she developed bilateral breast GS with positive FLT3-ITD mutation

Conclusions: The treatment included four monthly cycles of azacitidine (120 mg from D1 to D5) alternating with Sorafenib (200 mg 2×day) with a good tolerance and involution of the tumors. At present time the patient is still in remission with a fairly good quality of life.

Figure 2

Safety first, fistula second!

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Background: The native arteriovenous (AV) fistulas and the AV graft are considered the best types of access for hemodialysis patients. Stenosis of fistulas is one of the most common complications in up to 80% of patients needing treatment with percutaneous transluminal balloon angioplasty (PTA) during follow-up. Stenosis is another common risk factor for acute thrombosis as well as coagulation disorder, hypotension or existing aneurysm of the venous vessel.

Methods: no methods

Results: A 77 year old patient on chronic hemodialysis presented with acute thrombosis of his fistula after a car accident. His fistula of the upper arm was created in 2008. He had several PTA of stenosis during follow-up and developed two aneurysms. The last PTA of a stenosis of the subclavian vein was performed a year before. Since then accessflow remained stable. When he suffered the car accident, the airbag was activated. As he was not severely injured, he was not sent to the hospital and presented him two days later for his regular hemodialysis session. On physical examination he had two hematomas, one in the region of the breast bone and another on his right upper arm. There was no flow detectable in the fistula and acute thrombosis was diagnosed. A revision of the fistula with resection of the aneurysm and thrombectomy was carried out. In addition angiography showed restenosis of the subclavian vein and PTA was performed. As there was no clinical sign of restenosis of the subclavian vein prior to the acute thrombosis, we suggest that due to the strong hit by the inflated airbag on the fistula, adherent thrombotic material from the aneurysm was dislodged and occluded the Fistula.

Conclusions: In the presence of an aneurysm and/or adherent thrombotic material to the vessel wall of a fistula, strong physical energy can dislodged thrombotic material leading to acute thrombosis.
Role of Immune-Senescence in the development of de-novo Donor-Specific Antibodies after Kidney Transplantation

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Background: The concept of immune-senescence, implicating a changing immune-reactivity during lifetime, has gained increasing awareness. Higher age is associated with increased risk of infections and malignancies but reduced vaccination responses and reduced frequency of acute rejections in solid organ transplantation. Yet, the influence of immune-senescence on development of donor-specific antibodies (DSA) is unknown.

Methods: In this observational study, we included all children younger than 10 years of age and all adults older than 60 years of age, who received a kidney transplant at the University Hospital of Zurich between January 2006 and February 2015. Maximum follow-up time for occurrence of de-novo DSA as measured by Luminex-assay was until March 2016.

Results: Out of 160 elderly patients, a total of 12 patients (11%) developed de-novo DSAs compared to 6 patients out of 19 (32%) transplanted children. Risk of development of de-novo DSA was significantly higher in elderly patients (p = 0.0224), as compared to children. Median time to development of de-novoDSA was similar in both age groups (adults 720 days, children 1086 days).

Conclusions: Risk of development of de-novo DSA is lower in elderly adults as compared to in accordance with the concept of immune-senescence.

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Postoperative Seroma after Kidney Transplantation: Identification of donor-, recipient- and procedure-associated risk factors

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Background: Kidney transplantation is an efficacious and safe treatment for end stage renal disease. The early postoperative outcome of kidney transplantation has tremendously improved in the last decades and patient and allograft survival reach nearly 100% after eight years and identified donor-derived, recipient-derived and procedure-related risk factors.

Methods: In a retrospective study, we investigated the safety and outcome of RAS blockade in the early phase after kidney transplantation in 171 recipients of renal transplantations at the University Hospital in Bern.

Results: At the time of allocation, 107/170 (63%) of patients had RAS blockade implemented with a median prescription of 50% of the maximal registered dosage. Treatment was paused at time of allocation and re-implemented in 141/170 patients (82.9%) within the first six months of transplantation. 55/141 (39%) received the same RAS blocker as previously, 39/141 (28%) received a different compound and 47 (33%) received a de novo prescription of a RAS block. Median time point to start RAS blockade was 24 days post transplantation. Mean serum creatinine rose 4.9%<0.17% from baseline value and 11%±0.22% at day 7 and day 30 respectively. Serum creatinine rose more than 10% in 49/132 (37.1%) patients, more than 20% in 28 patients (20.5%) and more than 30% in 10/132 (7.6%) in the early phase after treatment implementation. Therapy was stopped in 24/141 (17%) patients within the first six months of transplantation, mostly due to excessive increase of serum creatinine or symptomatic orthostasis or hypotension. Patient and allograft survival was excellent in the observation period. For the composite endpoint of alive, functioning graft and eGFR >30 ml/min/1.73 m², no significant difference was found between patients with or without RAS blockade.

Conclusions: We conclude, that early implementation of RAS blockade is safe in kidney transplant recipients, although treatment discontinuation is necessary in up to 20% of patients.

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Safety of Early RAS Blockade in Kidney Transplant Recipients

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1University Hospital Bern, Bern, Switzerland; 2Inselspital Bern, Bern, Switzerland

Background: RAS blockade is often withheld from kidney transplant recipients due to feared deterioration of allograft function. Meanwhile, due to a high prevalence of cardiovascular co-morbidities, many transplant recipients could substantially profit from these compounds. The safety of these compound is still controversial in the early phase after transplantation.

Methods: In a retrospective study, we investigated the safety and outcome of RAS blockade in the early phase after kidney transplantation in 171 recipients of renal transplantations at the University Hospital in Bern.

Results: At the time of allocation, 107/170 (63%) of patients had RAS blockade implemented with a median prescription of 50% of the maximal registered dosage. Treatment was paused at time of allocation and re-implemented in 141/170 patients (82.9%) within the first six months of transplantation. 55/141 (39%) received the same RAS blocker as previously, 39/141 (28%) received a different compound and 47 (33%) received a de novo prescription of a RAS block. Median time point to start RAS blockade was 24 days post transplantation. Mean serum creatinine rose 4.9%<0.17% from baseline value and 11%±0.22% at day 7 and day 30 respectively. Serum creatinine rose more than 10% in 49/132 (37.1%) patients, more than 20% in 28 patients (20.5%) and more than 30% in 10/132 (7.6%) in the early phase after treatment implementation. Therapy was stopped in 24/141 (17%) patients within the first six months of transplantation, mostly due to excessive increase of serum creatinine or symptomatic orthostasis or hypotension. Patient and allograft survival was excellent in the observation period. For the composite endpoint of alive, functioning graft and eGFR >30 ml/min/1.73 m², no significant difference was found between patients with or without RAS blockade.

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Antibody-mediated rejection triggered by parvovirus B19 infection? A case report

Dr. Melanie Schönberger1, Dr. Patricia Hirt-Minkowski2, Dr. Helmut Hopfer1, Dr. Thomas Menter1, Prof. Stefan Schaub1, Dr. Katrin König1

1University Hospital Basel, Basel, Switzerland

Background: Transplant recipients can be sensitized against allo-HLA antigens by previous transplantation, blood transfusion, or pregnancy. The role of infections, especially in patients allo-HLA cross-reactive T-cells has been well described for CMV and EBV. However to far, the role of parvovirus B19 has not been considered.

Methods: A 46-year old male, suffering from ESRD due to chronic interstitial nephritis was transplanted from a pediatric deceased donor. He had no previous sensitizing events and no detectable pre-transplant HLA-antibodies by Luminex SA assays. Immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil, prednisone and basiliximab for induction. Because of delayed graft function, a biopsy was performed on day 8 which showed no rejection.

Conclusions: We conclude, that early implementation of RAS blockade is safe in kidney transplant recipients, although treatment discontinuation is necessary in up to 20% of patients.

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Conclusions: We conclude, that early implementation of RAS blockade is safe in kidney transplant recipients, although treatment discontinuation is necessary in up to 20% of patients.
whole post-transplant course, there were no signs of other infections such as CMV, EBV, and BKV.

**Conclusions:** Our patient developed early graft failure due to severe, therapy-resistant acute rejection, which was likely triggered by parvovirus B19 primoinfection.

**Conclusions:** Prevalence of metabolic acidosis was highest at baseline and decreased within the first year after transplantation. In parallel, eGFR values increased from baseline to one year. However, mean rise in eGFR was higher in KTR without MA compared to patients with MA suggesting a potential role of MA on kidney graft function.

**Results:** Chronic allograft lesions were infrequent in early biopsies within the first year of transplantation (<5%). Therefore, 48/92 (52%) showed no cg or aah lesions (group 1), 14/92 (15%) had cg<0 (group 2) and 16/92 (18%) aah<0 (group 3). At time of biopsy, serum creatinine levels were similar between the various groups. aah-lesions were associated with a further deterioration kidney function within the next six months and only limited risk for grafts loss. Meanwhile, cg lesions were associated with an increased risk for allograft failure. In composite lesions, the deteriorating kidney function was dominant.

**Conclusions:** Histopathological and Clinical Correlation of Chronic Allograft Lesions may predict allograft outcome and guide personalized treatment options.

**Results:** The humoral long-term progression of kidney function in patients with and without humoral allograft response was a major focus of current research. The typical evolution of kidney function in the patients without humoral immune activation is not well described. In the present longitudinal observational cohort study we analyzed the course of kidney function in patients stratified to those with a detectable antibody response and those without.

**Methods:** All kidney transplant patients at the University Hospital of Zurich between January 2006 and February 2015 were included and the course of kidney function was determined by slope of eGFR and the following visit (at latest February 2016). Slope of eGFR was compared between patients without development of humoral allograft immune responses and patients with development of donor specific antibodies as determined by Luminex single bead assays, which were performed at least annually.

**Results:** Patients without humoral allograft immune responses present an improvement of kidney function in the long term follow up as reflected by a positive eGFR slope. Such a continuous improvement of graft function is still present even six years after transplantation. In
Rituximab induces “false” positive complement-dependent cytotoxic B cells crossmatches

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1Geneva University Hospitals, Geneva, Switzerland; 2Geneva University Hospital and Medical School, Geneva, Switzerland; 3AMC/Geneva University Hospitals, Geneva, Switzerland

Background: ABO incompatibility (ABOi) is no more considered an immunological barrier in kidney transplantation, allowing patients with a healthy living donor to undergo transplantation. ABOi kidney transplantations are routinely performed at Geneva University Hospital since May 2008 with great success and with long-term outcomes equivalent to ABO-compatible kidney transplantations.

Methods: Before all kidney transplantations, a prospective cell-based CDC (complement-dependent cytotoxic) is performed. A single dose Rituximab 375 mg/m² is required 30 days before transplantation in the ABOi transplantation therapeutic strategy. We have observed highly positive CDC B cells crossmatch following these perfusions. This positivity is due to the link of the circulating drug to B cells. Our aim was to determine for how long Rituximab may alter crossmatch results. 13 couples were analyzed 1 month before (and therefore before Rituximab perfusion), at day 0 and 3 month post-transplantation, by performing CDC and Facs crossmatches.

Results: CDC and Facs crossmatches performed 1 month before transplantation were negative for both T and B cells in all analyzed couples. When crossmatches were performed with serum of the day of transplantation, CDC and Facs crossmatches were positive for B cells but negative for T cells. 3 months after transplantation, both CDC and Facs crossmatches were again negative for B cells. We also performed anti-HLA antibodies analyses in these sera and for each patient we did not observe major differences in anti-HLA antibodies specificities on the 3 time points.

Conclusions: The interaction of rituximab with the classical CDC crossmatch observed 1 month after Rituximab perfusion is short-lived, as at 3 month post-transplantation (and therefore 4 month post-perfusion) the interaction of Rituximab with B cells is not observed anymore. Therefore, if a CDC or Facs crossmatch should be performed after transplantation, it could be safely performed 3 month later and thereafter.
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