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BOOK OF ABSTRACTS

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CLINICAL RESEARCH

Patterns of renal osteodystrophy one year after kidney transplantation.

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Objective: Renal osteodystrophy is considered common after kidney transplantation, but is not well characterized in the current era. This study reports bone biopsy findings in an unselected cohort of kidney transplant recipients (n=141) who underwent a transiliac bone biopsy at 12 months post-transplant.

Methods: In addition to a full bone histomorphometric analysis, biochemical parameters collected included serum biointact (1-84) parathyroid hormone (PTH), total calcium (tCa), phosphate, bicarbonate, calcidiol, and sclerostin.

Results: Bone turnover by histomorphometry was normal in 71% and low in 26% of patients, with just four cases (3%) of high turnover. Hyperparathyroidism (PTH>1.5xUNL) with hypercalcemia (tCa>10.3 mg/dL) was present in 13% of patients, of which only one had high bone turnover. Delayed bone mineralization was detected in 16% of patients, who had lower levels of bicarbonate (21.3 vs 23.3 mmol/L, p=0.004), phosphate (2.68 vs 3.18 mg/dL, p<0.001), and calcidiol (29 vs. 37 ng/mL, p=0.02) as compared to patients with normal bone mineralization.

Conclusions: Although the majority of kidney transplant recipients have normal bone turnover 1 year post-transplant, low bone turnover remains an issue for a substantial subset of patients. The value of PTH in guiding treatment decisions is low. Metabolic acidosis, vitamin D deficiency, and hypophosphatemia represent potential interventional targets to improve bone health post-transplant.

Robot-Assisted Management of Ureteral Complications in Kidney Transplant Patients.

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OBJECTIVE: Ureteral complications following renal transplant procedures are common and mainly include urinary leaks, ureteral stenosis, vesicoureteral reflux (VUR) and acute graft pyelonephritis. First approaches for the management of stricture and VUR include, respectively, percutaneous balloon dilation with or without laser incision and endoscopic injection of dextranomer/hyaluronic acid copolymer. In case of recurrence after a primary endourological approach, a stricture >1cm or complex anatomy in transplant patients, ureteral reimplantation should be performed. A robotic approach may reduce morbidity in a fragile transplant population. We describe our case series and surgical technique of robot-assisted ureteral reimplantation in kidney transplant patients.

METHODS: We present 20 renal transplant patients who suffered from ureteral complications: 15 with VUR and 5 with ureteral stenosis. Given the complex anatomy and/or failed first endoscopic treatments, ureteral reimplantation was indicated in all cases. As each case had a unique indication and anatomy, five different surgical approaches were used: Lich-Gregoir non-dismembered or dismembered vesico-ureteral reimplantation, uretero-ureterostomy, and ipsilateral or contralateral pyelo-ureterostomy using the native ureter. All surgeries were performed using the Da Vinci Xi® robot by a single surgeon.

RESULTS: All surgeries were completed successfully without intraoperative complications. Median pre- and postoperative (3 months) GFR values were 53 ml/min (IQR 30-70) and 55 ml/min (IQR 43-66) respectively in

patients who suffered from VUR and 29 ml/min (IQR 22-36) and 35 ml/min (IQR 29-49) in patients who suffered from stenosis. Median hospital stay was 3 days (IQR 2-4). One patient had postoperative laryngeal edema requiring intensive care admission (Clavien- Dindo grade 4), one patient needed repositioning of a dislocated JJ stent (grade 3b), one patient had erysipelas of the left arm and one patient had febrile urinary tract infection within 90 days requiring antibiotics (both grade 2). No other complications occurred and all patients were free from nephrostomy tube or double J stent at a median follow-up of 12 months (IQR 7-19).

CONCLUSION: We demonstrate the safety, feasibility and surgical technique of robot-assisted ureteral reimplantation options in kidney transplant patients. This approach allows for high-quality realignment of the urinary tract, a quick recovery with low complication rate and preserved renal function in a fragile renal transplant population.

ILLUMINATE-B, a Phase 3 open-label study to evaluate lumasiran, an RNAi therapeutic, in young children with primary hyperoxaluria type 1 (PH1).

A. Devresse, G. Deschenes, P. Cochat, D. Magen, W. van't Hoff, M. Michael, D. Sas, G. Schalk, H. Shasha-Lavsky, W. Hayes, K. Bae, A. Seddighzadeh, P. Garg, A. Vaishnaw, T. McGregor, K. Fujita, Y. Frishberg

ADPedKD: A global online platform to explore the childhood phenotype of Autosomal Dominant Polycystic Kidney Disease.

A. Dachy, S. De Rechter, L.M. Guay-Woodford, A.J. Mallet, T. Harris, D. Bockenhauer, F. Schaefer, M.C. Liebau, D. Mekahli on behalf the ADPedKD consortium

Introduction: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the 4th common cause of renal replacement therapy worldwide. As the disorder has been historically considered an adult-onset disease, there is a lack of longitudinal data from large pediatric cohorts. However, evidence is growing that first manifestations of ADPKD may be detected in childhood and children represent a specific target population for future treatment, allowing a better chance of preserving long term kidney function. To better define the pediatric spectrum of the disease, a global multicenter observational study on childhood-diagnosed ADPKD was launched in 2017.

Methods: The ADPedKD registry is a worldwide web-based database, including both retrospective and prospective longitudinal data from young ADPKD patients (≤19 years). Australia, North-America and the United Kingdom joined the initiative with their source databases, namely the KidGen Collaborative (KidGen), NIH-funded Hepato-Renal Fibrocystic Disease (HRFD) and National Registry of Rare Kidney Diseases (RaDaR). Under informed consent, de-identified patient data, including genetics, radiological and laboratory findings, treatments and follow-up were enrolled in the database accessible via https://www.ADPedKd.org/.

Results: 1019 ADPKD children (from 89 centers and 33 countries) are enrolled in the registry of which 167 patients from RaDaR, 17 from KidGen, 11 from HRFD and 824 from ADPedKD (401 male/ 423 female) with a mean (± SD) age at diagnosis of 6.3 ± 5.2 years. 81 children (9.8%) were diagnosed prenatally at a mean gestational age of 26.8 ± 7.8 weeks. Reasons for initial visit were: family screening in 325 (39.4%), postnatal incidental finding in 223 (27.0%), presenting features (such as hematuria, hypertension, urinary tract

infections and flank or back pain) in 150 (18.2%) or unknown/not available in 126 (15.3%). Genetic testing was performed in 42.8% of the population, with the following results: PKD1 mutation (85.4%), PKD2 mutation (11.7%) and others (6.0%).

Conclusions: The ADPedKD registry is a unique source of clinical observational data that will provide deep phenotyping of children with ADPKD and will allow to define unified diagnostic, treatment and follow-up recommendations.

The serum levels of anti-sars-cov-2 antibodies remain detectable at 9 months post covid-19 in systematically screened kidney transplant recipients.

L. Firket, P. Huynen, A. Bouquegneau, C. Bonvoisin, S. Grosch, F. Jouret, L. Weekers

Risk for excessive anticoagulation during hemodialysis is associated with type of vascular access and bedside coagulation testing: results of a cross-sectional study.

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Objective: Recommendations and practice patterns for heparin dosing during hemodialysis show substantial heterogeneity and are scantly supported by evidence. This study was designed to evaluate the variability in unfractionated heparin (UFH) dosing during hemodialysis and its clinical and biological anticoagulant effects and to identify predictive factors of heparin dosing.

Methods: Cross-sectional study. Administered UFH dose was assessed. Coagulation times - activated partial thromboplastin time (aPTT) and activated clotting time (ACT) before dialysis start, 1h after start and at treatment end (4h) - and residual blood compartment volume of used dialyzers were measured.

Results: 101 patients, 58% male, with a median dialysis vintage of 33 (IQR 6-71) months received hemodialysis using a total UFH dose of 9306±4079 (range 3000-23050) IU/session (128±58 IU/kg/session). Use of a dialysis catheter (n=56, 55%) was associated with 1.4 times higher UFH dosing ($p<0.001$) irrespective of prior access function. Compared to baseline values, aPTT increased significantly more than ACT both 1h and 4h after dialysis start, independent of the dialysis access used. 53% of patients with catheter access and ACT ratio <1.5 one hour after dialysis start had simultaneous aPTT ratios >2.5. Similar findings were present at 1 hour for patients with AVF/AVG and at dialysis end for catheter use. There was no clinically significant clotting of the extracorporeal circuit during the studied sessions. Dialyzer's blood compartment volume was reduced with a median of 9% (IQR 6-20%) without significant association with UFH dose, aPTT or ACT measurements and vascular access type. UFH dose, aPTT, ACT and catheter use were not associated with spKt/V urea either.

Conclusions: Dose adaptations of UFH based on ACT measurements frequently result in excessive anticoagulation according to aPTT results. Higher doses of UFH are used in patients with hemodialysis catheters without evidence that this reduces dialyzer clotting or improves urea clearance.

Psychological wellbeing in parents of children with chronic kidney disease.

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Patients with severe lactic acidosis on the ICU: retrospective study of contributing factors and impact of renal replacement therapy.

L. Van De Ginste, F. Vanommeslaeghea, E. Hoste, J. Krusec, W. Van Biesen, F. Verbeke

Prevalence and risk factors of sickle cell nephropathy in children living in a low-resource setting.

O. C. Adebayo, DM K. Betukumesu, A.B. Nkoy, P.M. Ekulu, L.P. Van den Heuvel, V. Labarque, E. Levtchenko

Introduction: Clinical and genetic factors have been reported to influence the development of sickle cell nephropathy (SCN). However, such data remain limited in the pediatric population. Our study aimed to determine the prevalence of markers of kidney damage and to examine the association between these markers and clinical and genetic factors in children with sickle cell anemia (SCA).

Methods: In a cross-sectional study, we enrolled 361 patients with sickle cell disease from the Democratic Republic of Congo (DRC). Participants were genotyped for □-globin gene, Apolipoprotein-L1 (APOL1) G1 and G2 variants, and Heme oxygenase-1 (HMOX1) GT dinucleotide repeats. APOL1 high-risk genotype (HRG) was defined by the presence of 2 risk variants (G1/G1, G2/G2, and G1/G2) and low risk genotype (LRG) if 0 or 1 risk variants were present. HMOX1 GT dinucleotide repeats were categorized into two allele classes (□ 25 repeats as “short” and > 25 repeats as “long”). The association of SS/SL/LL variants with the markers of kidney damage was then assessed using the dominant model. As main outcomes, albuminuria was defined as urinary albumin-to-creatinine ratio (ACR) ≥ 30mg/g, decreased estimated GFR with creatinine (eGFRcr) when <60 ml/min/1.73 m2 and hyperfiltration when eGFRcr >130 and 140 ml/min/1.73 m2 for female and male, respectively.

Results: From participants enrolled, 326 were confirmed to be SCA patients through genetic sequencing. Albuminuria, hyperfiltration and decreased eGFRcr were presented in 65 (20%), 93 (28%) and 18 (5.50%) patients, respectively. Regression analysis revealed more frequent blood transfusions, lower diastolic blood pressure and male gender as clinical determinants of kidney damage. APOL1 HRG was significantly associated with albuminuria (P = 0.04), hyperfiltration (P = 0.001) and with increasing eGFRcr (P < 0.00001). HMOX1 GT dinucleotide long repeats was significantly associated with lower eGFRcr.

Conclusion: The study revealed a high burden of kidney damage among children with SCA in the DRC. Frequent blood transfusions, male gender and lower diastolic blood pressure were found as the main clinical determinants. Evidence has been provided of possible role of APOL1 and HMOX1 in making individuals more susceptible to kidney complications.

Illness-related stress in parents of children with Chronic Kidney Disease and associations with child Quality of Life.

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Objective: In the frame of RIZIV/INAMI convention of pediatric nephrology, tertiary centers of pediatric nephrology provide multidisciplinary care for children with chronic kidney disease (CKD). This multidisciplinary care is essential, as studies have shown that CKD has an impact on the psychosocial development and Quality of Life (QoL) of these children and their families. Many studies have focused on the QoL of children with CKD. However, less is known about the illness-related stress of the parents. Therefore the aims of the present study are to investigate (1) illness-related stress in parents of children with CKD with and without kidney transplantation (Tx) and compare it to parents of children with cancer and (2) explore the associations between illness-related parental stress and child QoL.

Methods: All children with CKD included in the convention of one institution were approached. QoL was assessed by means of PedsQL Core 4.0 and illness-related parental stress by means of Pediatric Inventory for Parents (PIP). To explore differences in illness-related stress, we compared the scores on the PIP of our sample with previously published scores in a sample of pediatric cancer (Streisand et al., 2001).

Results: In total we included 49 children (30 boys; M age= 10.06, SD = 5.05) and their parents. Parents of children with Tx reported higher frequency ($t(45) = -2.40$, $p < .05$), and perceived difficulty of stress ($t(45) = -2.43$, $p < .05$), compared to parents of CKD patients with no Tx. Frequency of parental stress in parents of children with CKD did not significantly differ from parents of pediatric cancer ($t(171) = 1.85$, $p > .05$). Perceived difficulty of stress in our population was significantly lower compared to a pediatric cancer sample ($t(171) = -4.02$, $p < .001$). Finally, all scales of the PIP and PedsQL are significantly negative correlated ($p < 0.01$).

Conclusions: Our study show that CKD also affects the parents, and especially parents of children with a Tx and that parental stress is comparable to parental stress due pediatric cancer. Parental stress and QoL of the child are negative interrelated. These results show that health care services should keep providing a multidisciplinary team and focus on the entire family of children with CKD, in order to optimize their wellbeing.

CLINICAL EXPERIMENTAL RESEARCH

MTOR-activating mutations in rragd cause kidney tubulopathy and cardiomyopathy (kica) syndrome.

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Peripheral blood transcriptomics demonstrate great potential in unraveling pathophysiological pathways of kidney allograft pathology.

E. Van Loon, W. Gwinner, D. Anglicheau, P. Marquet, M. Naesens

Objective: Molecular changes in kidney allografts during inflammatory pathology can be reflected by changes in circulating immune cells. Peripheral blood signals could aid in non-invasively unraveling the underlying pathways, to improve our pathophysiological knowledge of these diseases, facilitate their diagnosis, and identify new targets for therapy.

Methods: We performed RNA-sequencing on 384 peripheral blood samples, paired with a concomitant kidney allograft biopsy, selected for their histopathological phenotype from biobanked samples from four centers. We performed differential expression and pathway analysis per phenotype and the abundance of involved cell types was quantified by xCell. Finally, we integrated our results with publicly available micro-array data from 224 kidney allograft biopsies.

Results: Differentially expressed genes (DEG) in any rejection vs. no rejection (N=72, FDR P-value <0.05) demonstrated upregulation of glucocorticoid receptor signaling and NOD-like receptor signaling. The upregulated pathways identified for histology of antibody-mediated rejection were strongly immune-specific, in contrast to less specific pathways for T cell-mediated rejection. DEG in polyomavirus viremia and nephropathy were comparable and demonstrated upregulation of mitochondrial dysfunction and interferon signaling. Presence of donor-specific antibodies was accompanied by activation of the calcineurin/NFAT-pathway. Upon integration of biopsy and blood transcriptomic data, DEG in rejection phenotypes were highly consistent across both tissues and transcriptomic platforms, further strengthening our findings. Cell enrichment analysis demonstrated only minor differences in cell type enrichment scores between rejection phenotypes in the blood, despite major differences in cell enrichment scores between rejection phenotypes in the biopsy transcriptomic data.

Conclusion: The biologically plausible immune-specific pathways uncovered in this study demonstrate that peripheral blood signals mirror molecular changes in the graft, thereby non-invasively providing novel pathophysiological insights.

Sparse intragraft molecular classifiers for antibody-mediated and T-cell mediated kidney transplant rejection: development and validation.

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Objective: Although the distinct transcriptional landscapes of antibody-mediated rejection (ABMR) and T-cell mediated rejection (TCMR) have been largely elucidated, applying these gene expression signatures in transplant clinics is hampered by the large number of features, unclear cut-off values and difficult integration with histological findings. We aimed to develop and validate a sparse molecular classifier for ABMR and TCMR.

Methods: In a discovery cohort of 224 prospectively collected kidney transplant biopsies, microarray gene expression was used to build two separate prediction models for presence of ABMR or TCMR, as assessed according to the Banff classification. Class imbalance was addressed by SMOTE, and variable selection for logistic regression was performed by lasso regularization. The diagnostic accuracy and prognostic value of the obtained ABMR and TCMR classifiers were assessed in two external validation cohorts.

Results: From the discovery cohort, a 2-gene ABMR classifier and 3-gene TCMR classifier were derived. In the first validation cohort (N=403 biopsies), very good diagnostic accuracy was retained for ABMR (ROC-AUC 0.80, 95% CI 0.75-0.85) and TCMR (ROC-AUC 0.84, 95% CI 0.79-0.90), also allowing discrimination between pure and mixed phenotypes. In the second validation cohort (N=282 biopsies), ABMR and TCMR scores predicted graft failure (respective time-integrated AUC of 0.82 and 0.80) and identified a group of biopsies at risk without proven histological rejection.

Conclusions: We identified and validated an intragraft 2-gene ABMR classifier and 3-gene TCMR classifier that can be used as diagnostic, discriminatory and prognostic tools. The clinical value of the classifiers was most apparent in the prediction of outcome beyond the histological diagnosis of rejection. Robust variable selection models can yield parsimonious molecular classifiers for kidney transplant rejection with preserved accuracy, which may facilitate their interpretation and clinical implementation.

Gut microbiota and their derived metabolites, a search for potential targets to limit accumulation of protein-bound uremic toxins in chronic kidney disease

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Objective. Chronic kidney disease (CKD) is characterized by gut dysbiosis. We recently demonstrated a decrease of short-chain fatty acid (SCFA) producing bacterial species in CKD. Besides, levels of protein-bound uremic toxins (PBUTs) and post-translational modifications (PTMs) of albumin are increased in CKD, both are risk factors for accelerated cardiovascular morbidity and mortality. The aim of the study was to explore the relation between the abundance of SCFA producing gut microbiota, fecal levels of SCFAs and precursors of PBUTs and plasma concentrations of PBUTs in different stages of CKD (1-5).

Methods. The study cohort includes 103 non-dialyzed CKD patients (stages 1-5). Quantification of PBUTs in plasma and their precursors and SCFAs in fecal suspension was performed by validated UPLC/Fluorescence detection methods. Serum proteins were detected by capillary electrophoresis and UV absorbance at 214 nm with the symmetry factor as a marker of albumin PTMs [the lower the symmetry factor, the more PTMs of albumin].

Results. Kidney function (eGFR) is associated with fecal butyrate concentrations (r_s=0.212; $p<0.05$). The latter is associated with the abundance of the SCFA producing gut bacteria Butyricicoccus spp. (r_s=0.332; $p<0.001$), Faecalibacterium prausnitzii (r=0.424; $p<0.001$) and Roseburia spp. (r=0.580; $p<0.001$). Fecal butyrate concentrations are also associated with fecal concentrations of indole (r_s=0.401; $p<0.001$) and plasma p-cresyl conjugates (r_s=-0.422; $p<0.001$) but not with fecal p-cresol.

Conclusions. The decreased abundance of SCFA producing gut bacteria and, in parallel, of fecal concentration of butyrate and indole, can compromise the intestinal epithelial barrier function in CKD. This can contribute to increased plasma levels of PBUTs potentially playing a role in PTMs of albumin. This justifies further evaluation of SCFA producing bacteria and fecal butyrate as potential targets to restore both gut dysbiosis and uremia.

Peripheral blood inflammatory chemokines uncover allo-immune inflammation in the absence of histological lesions.

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Objective: Cytokines and chemokines play a critical role in the pathophysiology of allograft rejection, but the relation of peripheral blood cytokine expression profiles to clinical kidney transplant rejection is insufficiently investigated.

Methods: Levels of 28 cytokines, chemokines and growth factors were assessed using multiplexed Luminex magnetic bead testing in 293 peripheral blood samples. Blood samples were collected between 2012 and 2016, at time of a kidney allograft biopsy for graft dysfunction within the first year after transplantation in a cohort of 192 consecutive transplants at a single kidney transplant center.

Results: Principal component analysis and hierarchical clustering uncovered two clusters, distinct in their pro-inflammatory cytokine level. Patients in Cluster I (N=20) had higher pro-inflammatory protein expression compared to patients in Cluster II (N=172). Cluster I was hallmarked by a higher prevalence of donor-specific anti-HLA antibodies (HLA-DSA) (75%), and higher incidence of histopathological rejection (70%) compared to Cluster II (HLA-DSA in 1.7% and rejection in 33.7%) . Serum C-reactive protein and polyomavirus and/or CMV viremia did not differ between the two clusters. In 30% of biopsies in Cluster I, there was no histological evidence of rejection. Cluster I had a worse graft survival independent of clinical confounders and histological evidence of ongoing rejection (adjusted hazard ratio 3.31, 95% CI 1.09 -10.03, p=0.03). In silico analysis of publicly available single-cell RNAseq data from kidney transplant biopsies demonstrated expression of the observed cytokines in endothelial cells, monocytes and NK cells. Furthermore, the observed inflammatory cytokine profiles were confirmed in in vitro models of DSA-mediated NK cell and/or monocyte activation.

Conclusion: The expression of pro-inflammatory cytokines is increased in peripheral blood of kidney transplant patients with circulating HLA-DSA, even in the absence of histopathology of rejection. These results challenge the vision that kidney transplant histology is the gold standard for identification of ongoing allo-immune processes.

BASIC RESEARCH

Exposure to the toxic calcineurin-inhibitor cyclosporine, but not dehydration, mimics histopathology of chronic interstitial nephritis in agricultural communities.

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Objective: In the past 30 years, a significant increase in the prevalence of chronic kidney disease, mainly in young male agricultural workers, has been observed in Central America, Sri Lanka, and other tropical regions. Based on the histopathological characteristics and epidemiology, it was named chronic interstitial nephritis in agricultural communities (CINAC). Ever since its detection, the etiology is still enigmatic, with heat stress/dehydration and toxic exposure postulated as possible causes. Recently, in our lab, a peculiar proximal tubular lysosomal lesion was discovered in association with more unspecific features such as tubular atrophy, basement membrane thickening and tubulo-interstitial fibrosis. These lysosomes were enlarged, dysmorphic and contain dispersed aggregates. Remarkably, they were also observed in transplant patients experiencing calcineurin inhibitor (CNI) nephrotoxicity, after treatment with cyclosporine or tacrolimus, suggesting that CINAC is a toxin-induced nephropathy involving calcineurin inhibition. We

evaluated in rats to what extent heat stress/dehydration versus CNI exposure reflects proximal tubular CINAC histopathology.

Methods: Wistar rats were divided in 3 groups. Group 1 (n=6) was given water ad libitum (control group). Group 2 (n=8) was water deprived for 10 hours per 24h, 5 days/week and were placed in an incubator (37°C) for 30 min/hour during the water deprivation period. Group 3 (n=8) underwent daily oral gavage with cyclosporine (50mg/kg body weight). Animals were weighed daily, and urine was collected at day 1, 17 and 28. After 28 days, rats were sacrificed, and kidneys were collected for light- and electron microscopic histopathological analysis.

Results: Cyclosporine rats developed focal cortical lesions mimicking those of CINAC patients: i.e., atrophic proximal tubuli with thickened basement membranes and associated tubulo-interstitial fibrosis. Periodic acid silver methenamine staining demonstrated enlarged argyrophyllic granules in proximal tubuli, which were confirmed to be lysosomes by Cathepsin B immunofluorescent staining. Electron microscopy confirmed the presence of enlarged, somewhat dysmorphic, lysosomes resembling those of CINAC patients, however, without electrodense aggregates. No such lesions were observed in rats in which dehydration was confirmed by urinary osmolality and fluctuating body weight due to water deprivation.

Conclusion: Dehydration/heat stress alone did not lead to the constellation of proximal tubular lesions as observed in CINAC patients. The histopathological analogy, however, between CNI nephrotoxicity in rats and CINAC-patients advocates a toxicological etiology for CINAC.

Delayed nephrectomy after unilateral ischemia enhances epithelial repair by stimulating proliferation of renal progenitor cells.

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Objective: Acute kidney injury (AKI) is a global health concern affecting 13.3 million patients per year and is an important risk factor for the development of chronic kidney disease (CKD). Crucial for successful renal recovery after AKI is the proliferative capacity of surviving tubular epithelial cells (TECs). We established a murine model in which the functional and histological recovery of a kidney, injured by ischemia, is enhanced by removal of the unharmed contralateral kidney, i.e. nephrectomy-induced recovery. The renal epithelial reparative response in this unique model has not been investigated, yet can provide important new insights in unlocking the inherent physiological regenerative potential of the renal epithelium.

Methods: AKI was induced in R26RtdTomato and PAX2/Confetti mice by left unilateral ischemia/reperfusion (UIRI) for 21 min at 34°C, after which either right nephrectomy (Nx) or no Nx was performed 3 days later. Mice were euthanized 6 weeks and 28 days after UIRI, respectively. At week 6, kidneys were weighted and renal function and fibrosis was assessed by serum creatinine and Sirius Red histology, respectively. At 28 days, renal tissue of PAX2/Confetti mice was processed to study histological clonal expansion by lineage pattern analysis of PAX2+ renal progenitor cells.

Results: When no Nx was performed after UIRI, a significant decrease in left kidney-to-body weight ratio and increase of serum creatinine compared to control kidneys at week 6 was observed, indicating sever atrophy and functional loss in the injured kidney. However, when Nx was performed, renal function and mass were preserved. In addition, without Nx the injured kidney became fibrotic, whereas in the solitary injured kidney fibrosis did not increase compared to control kidneys at week 6. Clonal analysis in PAX2/Confetti mice revealed a significant increase in clone size frequency from mainly monoclonal PAX2+

progenitor cells in control animals to a greater number of multicellular clones after UIRI. When Nx was performed after UIRI, this clonal expansion was further stimulated. Likewise, the percentage of clonogenic PAX2+ cells was higher when Nx was performed after UIRI as compared to when no Nx was performed.

Conclusion: Nx overcomes loss of renal mass and function after UIRI. This enhanced recovery is at least established by a stimulated clonal expansion of renal progenitor cells that surpasses that of spontaneous repair after UIRI. Getting insight in the signaling mechanisms by which nephrectomy achieves this response may open new therapeutic research avenues.

Metformin treatment is able to halt the progression of established non-diabetic chronic kidney disease in rats.

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Objective: Metformin, first-line drug for type-2 diabetes, exerts benign pleiotropic actions beyond its prescribed use and emerging data show protective effects against the development of renal impairment. Current treatment strategies for chronic kidney disease (CKD) mainly focus on controlling important risk factors, while effective treatment directly targeting the kidney is lacking. However, in 2019, the FDA approved the use of the sodium-glucose co-transporter-2 (SGLT2) inhibitor, canagliflozin, to treat diabetic nephropathy. Here, the ability of metformin to attenuate progression of established, non-diabetic CKD was investigated and compared to canagliflozin.

Methods: Adenine-induced CKD rats were assigned to different treatment groups to receive 200 mg/kg metformin, 4 or 5 weeks after the start of the adenine diet (0.25%), i.e. after CKD had developed, by daily oral gavage, during 4 weeks. Each treatment group was compared to a vehicle (1% carboxymethylcellulose) group. Additionally, a group receiving 25 mg/kg canagliflozin treatment 4 weeks after the start of the adenine diet was also included to evaluate and compare the effect of the SGLT2-inhibitor in non-diabetic CKD. Renal function was investigated by measuring serum creatinine levels. Histopathological decay of renal tissue was evaluated by quantifying the interstitial area percentage. Possible mechanisms underlying renal protection were evaluated by investigating tubular proliferation, inflammation and general protein expression.

Results: Serum creatinine levels dramatically rose in vehicle-treated CKD rats: from 0.7 ± 0.1 mg/dL (week 0) to 1.5 ± 0.1 mg/dL (week 4), 2.6 ± 1.2 mg/dL (week 5) and further to 6.2 ± 0.3 mg/dL (week 8) and 4.8 ± 1.1 mg/dL (week 9). Canagliflozin treatment did not alter the increase in serum creatinine as indicated by serum creatinine levels at week 8 (5.8 ± 0.4 mg/dL). In contrast, metformin treatment almost completely prevented the increase from week 4 or 5 on, as indicated by the serum creatinine levels after 8 (2.0 ± 0.5 mg/dL) and 9 (2.9 ± 0.5 mg/dL) weeks ($p<0.05$ vs. vehicle). Canagliflozin treatment did not alter the tubulointerstitial area percentage, while this parameter was 33% lower at week 8 and 23% lower at week 9 in metformin-treated CKD rats compared to vehicle treatment ($p<0.05$ vs. vehicle). Further histological examination revealed more tubular proliferation (PCNA positive cells) and less interstitial inflammation (CD45 positive cells) in metformin-treated rats compared to vehicle-treated animals. The proteomic screen of metformin vs vehicle treated animals revealed that increased pyruvate concentrations may underlie metformin's protective action.

Conclusion: Metformin is able to attenuate the progression of pre-existing adenine-induced CKD in rats. Our data do not present evidence for a beneficial effect of canagliflozin on progression of non-diabetic CKD.

Potential of urine-derived kidney progenitor cells for disease modeling in cystinosis and as target for gene therapy.

K. Veys, D. David, T. Bondue, S. Princiero Berlingerio, A. Reda, K. Held, J. Vriens, L. van den Heuvel, R. Gijsbers, F. Oliveira Arcolino, E. Levtchenko

Renal and extra renal manifestations in adult zebrafish model of cystinosis.

S. P. Berlingerio, J. He, L. de Groef, P. Baatsen, S. Cairoli, B. Goffredo, B. van den Heuvel, H. J Baelde, E. Levtchenko

CASE REPORT / CASE SERIES

A rare cause of distributive shock in a patient treated with flucloxacillin.

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Case description: A 48-year-old male patient was admitted with deterioration of renal function and recurrence of nephrotic syndrome due to Amyloid A (AA) amyloidosis secondary to a chronic osteomyelitis of his left hip. The patient was paraplegic for more than 25 years and had a terminal ileostomy after right hemicolectomy. Due to Staphylococcus aureus bacteremia originating from a skin wound contiguous with the nidus of infection, he received high dose flucloxacillin and was referred for extensive surgical debridement. In the postoperative period the patient initially recovered well. However, 6 weeks after the start of antibiotics, he gradually developed general malaise and progressive dyspnea. Laboratory analyses showed gradual decrease in bicarbonate levels reflecting a metabolic acidosis which appeared to be normal or high anion gap on different occasions. It was initially thought to be the consequence of gastro-intestinal loss of bicarbonate since the patient experienced persistent diarrhea under antibiotic treatment, combined with anion retention due to renal insufficiency. D-lactate was absent. The metabolic acidosis deteriorated despite high dose bicarbonate supplementation, ultimately leading to respiratory distress and distributive shock, for which the patient was transferred to the intensive care unit (ICU) 8 weeks after the start of antibiotics. At that time, arterial blood gas analysis showed a high anion gap metabolic acidosis with respiratory compensation (pH 7,44; pCO2 17 mmHg; pO2 193 mmHg; HCO3 11 mmol/L; base excess -12 mmol/L; anion gap 21,5 mmol/L). The patient was intubated and treated with vasopressors and corticosteroids to treat the shock. Additionally, continuous veno-venous hemofiltration was started in an attempt to correct the metabolic disbalance. Urinary evaluation of organic acids revealed accumulation of the metabolite 5-oxoproline as the underlying cause of the high anion gap metabolic acidosis. Therefore, additional treatment with N-acetyl cysteine (NAC) was started. The anion gap gradually declined and the patient's hemodynamic state gradually improved. After 5 days of invasive ventilation, the patient could be extubated. Intermittent hemodialysis was continued since renal function showed no significant recovery.

Discussion: Accumulation of 5-oxoproline is a rare cause of high anion gap metabolic acidosis, resulting from glutathione depletion due to pharmacotoxic interactions with enzymes in the gamma-glutamyl cycle. Physicians are typically aware of this condition when flucloxacillin and paracetamol are co-administered. Indeed, flucloxacillin is known to impair the degradation of 5-oxoproline by inhibiting 5-oxoprolinase. Furthermore, paracetamol is a well-known cause of glutathione depletion, which leads to excessive formation of the precursor metabolite gamma-glutamyl cysteine due to disinhibition of the gamma-glutamyl cysteine synthetase enzyme. Subsequently, further breakdown of gamma-glutamyl cysteine into 5-oxoproline contributes to the accumulation of this organic acid. However, in our patient no paracetamol

had been administered. This raises awareness for other conditions predisposing to glutathione depletion, such as renal insufficiency and malnutrition.

Conclusion: In cases of unexplained high anion gap metabolic acidosis in patients treated with long courses of flucloxacillin, one should be aware of conditions predisposing to glutathione depletion and perform urinary analyses to detect organic acids. Treatment with NAC restores glutathione stores, thus helping to regain the acid-base homeostasis and improving the outcome of patients admitted to the ICU with 5-oxoproline induced high anion gap metabolic acidosis.

Heparin-grafted dialyzer use is safe in case of heparin-induced thrombocytopenia.

K. François, C. Orlando, K. Jochmans, D. De Clerck, M-L Cambier, T. Robberechts, L. Pipeleers, P. Janssens, K. M. Wissing

Objective: To demonstrate the safety of heparin-grafted dialyzer use in patients presenting immune-mediated heparin-induced thrombocytopenia (HIT).

Methods: Descriptive case series of patients diagnosed with HIT and receiving hemodialysis.

Results: Five patients were diagnosed with HIT within our hemodialysis cohort over the last 11 years. All developed acute thrombocytopenia after exposure to heparin and showed positivity for immunoglobulins against heparin-platelet factor 4 (PF4) complex on a particle gel immunoassay. An IgG-specific ELISA confirmed the presence of HIT antibodies in subjects n° 1, 3 and 5. Following the diagnosis of HIT, systemic heparin administration was stopped in all patients. Subjects 1-4 were immediately converted to hemodialysis without systemic heparin administration and using a heparin-grafted dialyzer for 452, 2, 15 and 3 consecutive hemodialysis sessions respectively. Despite the exposure to the heparin-grafted dialyzer, platelet counts normalized rapidly in all 4 patients. Subject n° 4 received a second period of 17 consecutive hemodialysis sessions using a heparin-grafted dialyzer 19 months after the initial diagnosis of HIT, without recurrence of thrombocytopenia. Subject n° 5 was never dialyzed using a heparin-grafted dialyzer once HIT was established.

Discussion and conclusions: HIT is a serious and eventually life-threatening condition associated with thrombocytopenia and thrombosis after heparin exposure. Platelets activated during hemodialysis secrete platelet factor 4 (PF4) which binds polyanions such as heparin. In patients with HIT, IgG antibodies against the heparin-PF4 complex are formed. The immune complex of heparin-PF4-IgG causes platelet activation by crosslinking receptors on platelets and monocytes. Both platelet consumption due to platelet aggregation and removal of antibody coated platelets by the reticuloendothelial system lead to thrombocytopenia. The activation of platelets and monocytes results in tissue factor expression initiating the coagulation system, leading to a hypercoagulable state.
Systemic heparinization is the standard of care to avoid clotting of the hemodialysis circuit. In case of HIT, an alternative strategy to prevent extracorporeal circuit clotting has to be adopted.
Pre-clinical and clinical trials with heparin-grafted dialyzers showed that heparin remains coated onto the dialyzer membrane during hemodialysis. We hypothesize that the lack of circulating heparin in case of heparin-grafted dialyzer use without systemic heparin administration explains why further pathological heparin-PF4-IgG immune complex formation was prevented in our cases.
We conclude that the use of a heparin-grafted dialyzer is safe for patients presenting HIT.

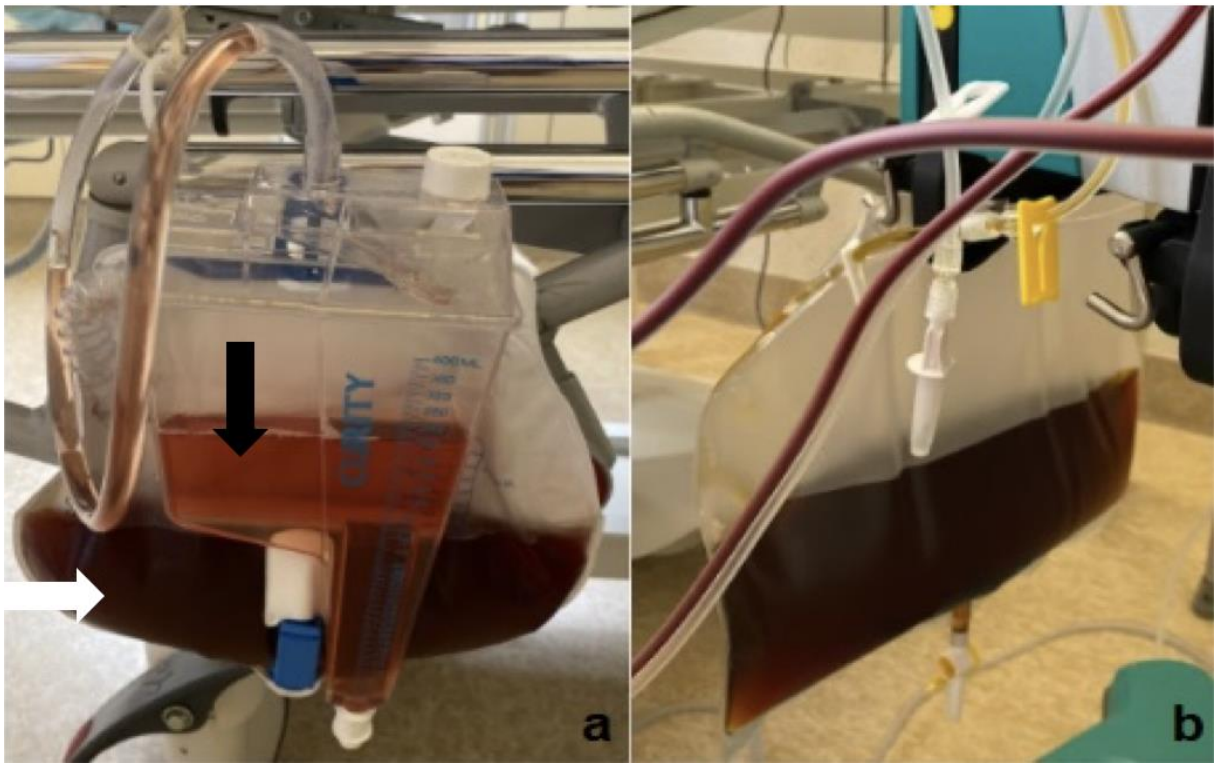
Rescue plasmapheresis for massive shear-stress induced hemolysis following closure of a paravalvular leak.

T. Couck, P. De Meester, K. Claes, C. Vandenbriele

In the new era of mechanical circulatory support (MCS) and percutaneous interventional closure devices, shear-stress induced, intravascular destruction of red blood cells or hemolysis is often a challenge for ICU-physicians. Plasma levels of free hemoglobin (pfHb) and hemoglobinuria should be carefully monitored in those patients. Circulating free hemoglobin is prothrombotic and can cause acute kidney injury through pleiotropic mechanisms, one of which is depletion of nitric oxide with resultant vasoconstriction and clot formation. Only few therapeutic options are available: optimization of device position, volume status and anticoagulation in MCS, forced diuresis and afterload reduction in valvular heart disease. For massive hemolysis, plasmapheresis is a less known but often very effective method to reverse the renal failure, as we demonstrate in this 82-year old woman presenting with dark-red urine and oliguric renal failure shortly after transapical closure of a large paraprosthetic mitral leak. Levels of pfHb peaked up to 190 mg/dl. Plasmapheresis (with combined albumin and fresh-frozen plasma) was initiated, with rapid recovery of diuresis, urine color returning back to normal and normalization of pfHb-levels. The effluent was notable for the same initially dark-red urine color, indicating efficient removal of pfHb from the patient's circulation.

* Figure legends:

Fig. 1 a. Dark urine before (white arrow) and after (black arrow) the initiation of plasmapheresis; color attenuation was in parallel with a decrease in plasma free hemoglobin levels. b. Plasmapheresis effluent (plasma) collector.



E-POSTERS

Contribution of measuring complement regulatory factors in blood as part of the evaluation of patients with thrombotic microangiopathy

S. Bisselele, P. Stordeur, J. Smet, J. Gleeson, D. Abramowicz, A. Massart

The choice between deceased and living donor kidney transplantation in children and adolescents: a multicentric cross-sectional study.

L. Dierickx, L. Willem, A. Raes, K. Van Hoeck, K. Van Cauwenberghe, J. Vande Walle, E. Swauwaert, E. Levtchenko, N. Knops, A. Prytula

Variability of bioimpedance measurements in hemodialysis patients.

F.Collart, M.Taghavi, T.Salaouatchi, G.Musigazi, M.Mesquita

Renal outcome and life expectancy in a Belgian elderly population with chronic kidney failure; a retrospective study.

R. Vleut, L. de Waele, K. Wouters, R. Hellemans, A. Massart, E. Philipse, K. Leyssens, D. Abramowicz, M.M. Couttenye

"Is polyomavirus associated nephropathy more common in kidney transplant recipients exposed to valganciclovir?" ~ A retrospective single center analysis ~

A. Bertels, K. Wouters, V. Wijtvliet, A. Massart, K. Bergs, V. Mattheeussen, D. Abramowicz, R. Hellemans

Human stool metabolome differs upon 24-hour blood pressure levels and blood ressure dipping status: a prespective longitudinal study.

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Objective: Dysbiosis of gut microbiota (GM) has been involved in the pathophysiology of arterial hypertension (HT), via a putative role of short chain fatty acids (SCFAs). The non-dipping blood pressure (BP) profile confers a higher cardiovascular risk. Its link with GM is unknown.

Methods: Sixteen male volunteers and 10 female partners were subjected to 24h-ambulatory BP monitoring and were categorized in normotensive (NT) versus HT, as well as in dippers versus non-dippers. NMR-based metabolomics was performed on stool samples. A 5-year comparative follow-up of BP profiles and stool metabolomes was done for male patients.

Results: Significant correlations between stool metabolomes and 24h-mean BP levels were found in male cohort, female cohort and in the entire cohort (R^2=0.63; R^2=0.79 and R^2=0.54, respectively). Multivariate analysis discriminated dippers versus non-dippers in male cohort, female cohort and in the entire cohort (Q^2=0.87; Q^2=0.98 and Q^2=0.68, respectively). Fecal amounts of acetate, propionate and butyrate were

higher in HT versus NT patients (p=0.027; p=0.015 and p=0.015, respectively), as well as in non-dippers versus dippers (p=0.027; p=0.038 and p=0.036, respectively) in the entire cohort. SCFA levels were significantly different in patients changing of dipping status over the 5-year follow-up.

Conclusion: stool metabolome changes upon BP profiles in both genders.

Colon transporters in chronic kidney disease: a potential target to reduce microbiome-derived uremic toxins?

M. Lauriola, S. Dejongh, B. Meijers

Effect of kidney stone prevention on urinary risk factors for kidney stone formation and new stone formation: a single centre retrospective cohort study.

F. Janssens, C. Tielemans, L. Vonckx, KM. Wissing, E. Van de Perre

Objective: Nephrolithiasis is a highly prevalent and recurrent disease. Prophylactic treatment to prevent recurrent kidney stone formation is recommended. We evaluated the effect of combined preventive measures on the urinary risk factors for kidney stone formation, renal colic rate, stone formation rate and rate of urological interventions in a single centre retrospective cohort study.

Methods: In all nephrolithiasis and nephrocalcinosis patients attending our kidney stone prevention clinic between 22/12/2004 and 31/12/2020, baseline metabolic evaluation was performed and renal colic rate, stone formation rate and urological intervention rate before the first consultation was calculated. In patients with at least 6 months follow-up, effect of combined preventive measures on urinary risk factors during follow-up was analysed. In all nephrolithiasis patients with at least 12 months follow-up, effect of combined preventive measures on renal colic rate, stone formation rate and urological intervention rate during follow-up was evaluated.

Results: 835 nephrolithiasis and nephrocalcinosis patients (537 males, 298 females) were evaluated at baseline. 98.4% presented with at least one urinary risk factor, with increased protein intake in 77.0%, increased sodium excretion in 59.9%, low urinary volume in 59.0%, hyperoxaluria in 36.5%, low urinary pH in 27.9% hypercalciuria in 27.8%, hyperuricosuria in 24.2%, hypocitraturia in 20.0% and hyperphosphaturia in 15.3%. In 355 patients with median follow-up of 2.3 years, effect of combined preventive measures on urinary risk factors was evaluated. Combined preventive measures significantly reduced median sodium excretion ($p<0.05$), calciuria (0.08 (IQR 0.05-0.11) vs 0.07 (IQR 0.04-0.09) mmol/kg ideal weight/24h, $p<0.0001$), uricosuria ($p<0.0001$) and phosphaturia ($p<0.05$) and significantly increased median urinary volume (1950 (IQR 1400-2600) vs 2300 (IQR 1790-2850) ml/24h, $p<0.0001$). In patients with hyperoxaluria, increased protein intake, hypocitraturia and low urinary pH at baseline evaluation, combined preventive measures significantly reduced median oxalate excretion (65 (IQR 59-73) vs 46 (IQR 36-57) mg/24h, $p<0.0001$) and protein intake ($p<0.001$) and significantly increased median citrate excretion (723 (IQR 254-1220) vs 1480 (IQR 643-2339) µmol/24h, $p<0.0001$) and urinary pH ($p<0.0001$), respectively. Combined preventive measures significantly reduced median renal colic rate in 257 patients with median follow-up of 2.9 years (0.09 (IQR 0.00-0.40) vs 0.00 (IQR 0.00-0.12), $p<0.0001$) and median urological intervention rate in 254 patients with median follow-up of 3.0 years (0.00 (IQR 0.00-0.20) vs 0.00 (IQR 0.00-0.00), $p<0.0001$). Stone formation rate did not change significantly in 142 patients with median follow-up of 3.1 years, (0.40 (IQR 0.19-0.80) vs 0.36 (IQR 0.00-0.99), $p=0.23$).

Conclusion: Combined preventive measures significantly impact on urinary risk factors for kidney stone formation, especially when tailored to the patient's initial metabolic evaluation. Additionally, prophylactic treatment significantly reduces symptomatic renal colic rate and urological intervention rate, outcomes that are clinically significant for the patient and will likely reduce kidney stone disease-related health care costs.

Dietary fibre intake is associated with serum levels of uraemic toxins in children with Chronic Kidney Disease.

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Objective: Unbalanced colonic microbial metabolism plays a pivotal role in generating protein-bound uraemic toxins (PBUTs), accumulating with deteriorating kidney function and contributing to the uraemic burden of children with chronic kidney disease (CKD). Dietary choices impact the gut microbiome and metabolism. The aim of this study was to investigate the relation between dietary fibre and gut-derived PBUTs in paediatric CKD.

Methods: Sixty-one (44 male) CKD children 9 [5;14] years were prospectively followed at 3-month intervals for 2 years. Dietary fibre intake was evaluated by either 24-h recalls (73%) or 3-day food records (27%) at the same time of blood sampling for assessment of total and free serum levels of different PBUTs (mg/dL) using liquid chromatography. Linear mixed models for (natural) log-transformed plasma concentrations were fitted with a random intercept for the patient and with fibre intake (g/day), protein intake (g/day), BSA as a proxy for age (m^2), eGFR (mL/min/1.73 m^2) to assess associations between fibre intake and PBUT levels.

Results: For every g/day increase in fibre consumption, mixed-model analysis revealed a 1.6% [−3.0%; −0.3%] lower total IAA concentration ($p = 0.020$), whereas free IAA levels were 6.6% [−9.3%; −3.7%] ($p < 0.001$) lower. Further, total pCG levels were 3.0% [−5.6%; −0.5%] ($p = 0.021$) lower, and free serum pCG 3.3% [−5.8%; −0.8%] ($p = 0.010$) lower per g/day increase in daily fibre consumption. For every gram of increment in daily fibre intake, free IxS levels were 3.1% [−5.9%; −0.3%] ($p = 0.035$) lower, and free pCS were 2.5% [−4.7%; −0.3%] ($p = 0.034$) lower. In contrast, total IxS and pCS serum concentrations were not associated with daily fibre intake

Conclusions: The observed associations between dietary fibre intake and the investigated PBUTs highlight potential benefits of fibre intake in the paediatric CKD population. The present observational findings should inform and guide adaptations of dietary prescriptions in children with CKD.

Peritoneal dialysis initiation to treat end stage kidney disease during pregnancy: a report of 2 cases.

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Introduction. Despite strong evidence suggesting that peritoneal dialysis (PD) is as efficient as long-hour hemodialysis (HD) in pregnant patients, few cases are described in the current literature.
Patients on PD usually have a higher residual renal function (RRF) and a more stable metabolic environment. They also undergo less hypotensions during dialysis sessions potentially causing fetal growth

retardation or even fetal death. RRF seems to play an important role in successful pregnancy. Furthermore, peritonitis rates are not described higher in pregnant patients.
Yet, initiating PD in a pregnant woman needing extrarenal epuration is rarely described if at all. In this study, we report two cases of patients who started PD being already multiple months pregnant: the first case was 14 years ago and the second one nowadays.

Case report. Our two patients are in their thirties, are respectively 16 and 10 weeks pregnant upon admission. Both have a history of anti-phospholipid syndrome, and the second one a known reduction of renal mass. PD was started based on high urea levels in the context of end-stage kidney disease (ESKD) for both patients. PD could significantly reduce serum urea levels. Our first patient suffered from a germ-free peritonitis complication, successfully treated by intraperitoneal antibiotics. She had to switch to manual PD for a short period of time due to catheter misplacement causing inefficient dialysis and non-stopping alarms on the cycler. We later performed the adhesiolysis of the peritoneal catheter. She finally gave birth (vaginally) to a healthy 2.5 kg and 45 cm daughter at 38 weeks of amenorrhea. Our second patient is currently on dialysis without complications and is now 29 weeks pregnant with a healthy monitored fetus.

Conclusion. Initiating PD in a pregnant patient rarely described in the current medical literature. With higher pregnancy rates than ever in the ESKD population, and considering our positive experience of safe PD initiation during pregnancy, we would suggest to consider PD as a safe alternative approach to HD in pregnant women.

A kinetics based algorithm to treat acute neonatal hyperammonemia.

E. Snauwaert, J. De Rudder, P. Verloo, E. Dhont, A. Raes, W. Van Biesen, S. Eloot

Objective: Acute neonatal hyperammonemia is associated with poor neurological outcomes and high mortality. Prompt management to achieve a fast decline in serum ammonia is therefore crucial. We developed, based on kinetic modeling, a user-friendly and widely applicable algorithm to treat acute neonatal hyperammonemia.

Methods: Four hyperammonemic patients (3.24±0.40 kg) underwent 11 hemodialysis sessions, i.e. 5 with the 4008 and FXPaed dialyzer (Fresenius Medical Care, Germany), and 6 with the CarpeDiem (Medtronic, USA) of which 2 with the 0.15m² and 4 with the 0.25m² dialyzer. Blood flows QB were in the range 22-35mL/min. Dialyzer clearance and extraction ratio were derived from the measured ammonia time-concentration curves during dialysis. Ammonia was hereby assumed being distributed in the patient in a single compartment, equal to patient's total body water. With the single compartmental models for an average child of 3, 4 and 5kg, time-concentration profiles were simulated for different start concentrations, dialysis machines/dialyzers and different dialysis settings (i.e. QB of 30-50mL/min). Based on the results of simulations, a body-weight based dialysis protocol could be derived for our clinical practice. To make the model widely beneficial, an algorithm was drawn to guide other clinicians.

Results: Extraction ratios were 38±5% in the 4008-FXPaed setup, 10±3% and 13±3% in the Carpe Diem 0.15m² and 0.25m² dialyzer, respectively. For a start concentration of e.g. 3000µmol/L in a patient of 3kg, the time to reach 400µmol/L was, with the 4008-FXPaed, 315 and 190min for a QB of 30 and 50mL/min, respectively. The CarpeDiem machine was found inadequate to decrease ammonia concentrations below 400µmol/L within 4h for start concentrations >800µmol/L. Simulations in a patient of 5kg resulted in even longer time intervals. Our institution-specific protocol therefore describes the use of the 4008/FXPaed for all ammonia concentrations >400µmol/L.

To calculate the time needed to decrease the ammonia concentration from a predialysis start concentration Cstart to a target concentration Ctarget, accounting for the patient's characteristics and dialysis setup, the following algorithm can be used: From patient's body weight, height, age and gender, total body water (V) can be calculated using Wells formula. By a single measurement of ammonia concentrations at the dialyzer inlet and outlet (in the local dialysis setup), dialyzer clearance (K) can be calculated as K = QB·[(Cinlet-Coutlet)/Cinlet]. The time (T) to target is then equal to T=(-V/K)·LN(Ctarget/Cstart).

Conclusion: By implementing these formulae in a simple spreadsheet, medical staff can draw its institution-specific flowchart for patient-tailored treatment of hyperammonemia. Since this model is based on some assumptions (i.e. single compartmental distribution equal to total body water, and no impact of generation on clearance calculation), our own institution-specific protocol will be applied and studied in a prospective study to validate the present results.

Systematic screening for sars-cov-2 s1/s2 antibodies helps to better assess the real incidence of covid-19 in kidney transplant recipients.

L. Firket, P. Huynen, C. Bonvoisin, A. Bouquegneau, M-H Delbouille, S. Grosch, F. Jouret, L. Weekers

Timing and duration of pre-transplant screening for renal transplantation: Reasons for delay and room for improvement.

M. Dirix, E. Philipse, R. Vleut, V. Hartman, B. Bracke, T. Chapelle, G. Roeyen, D. Ysebaert, G. Van Beeumen, A. Massart, K. Leyssens, M.M. Couttenye, D. Abramowicz, R. Hellemans

Objective Transplant eligibility is assessed via a range of medical examinations based on international guidelines. Since patient survival after transplantation is significantly improved with a shorter duration of pre-transplant dialysis, it is recommended to start the transplant work-up in a timely fashion to be able to register patients on the renal transplant waiting list before or at least at the moment they initiate dialysis. In this study we analysed the chronology of actions taken during the care for patients with CKD stage 5 and the time needed to complete the transplant work-up.

Methods. This study is a retrospective analysis of all the patients that were registered on our renal transplant waiting list between 2016 and 2019. We assessed how often patients started the transplant evaluation before they started dialysis and searched for potential explanatory factors by multiple logistic regression analysis. We subsequently analysed the time spent on the transplant work-up and performed a multiple linear regression analysis to identify significantly influencing variables.

Results. 161 patients were included for analysis. The median age was 53 years (IQR 43-64) and 62% were male. Diabetes mellitus and cardiovascular disease were each present in 24% of patients. The median nephrology follow-up time before the diagnosis of CKD stage 5 was 3.4 years (IQR 0.4-7.2 years). 22% of patients were late referrals (i.e. start of dialysis within the first three months after the first encounter with nephrology care). Only 43% of patients started the transplant work-up before the start of dialysis and only 33% of patients initiated the transplant work-up before their first dialysis access procedure. Multiple logistic regression analysis identified the number of hospitalisation days, language barrier and a shorter duration of nephrology care before the diagnosis of CKD stage 5 as factors having a significant negative impact on the probability of starting the transplant screening before dialysis. We observed a median

duration of 8.6 months (IQR 5-14) spent on the transplant work-up. Only the number of hospitalisation days during the screening period was identified as a significant prolonging factor.

Conclusion. The transplant work-up was often started too late to be completed before the start of dialysis. We should be planning the transplant evaluation prior or simultaneously with the planning of a dialysis access procedure and not afterwards. The median time spent on the transplant work-up was surprisingly long. By starting the transplant screening in a timely fashion and reducing the time spent on the screening examinations, we should be able to register patients with CKD stage 5 on the transplant waiting list before or at least at the start of dialysis. We estimate that such an internal audit could be of value for every transplant centre and that we should perform it regularly to permanently monitor our results.

Functional paracelular permeability of the colon in rats with kidney disease.

S. Dejongh, M. Lauriola, R. Farré, B. Meijers

Mysterious diagnosis in a child with failure to thrive.

A. Matthys, L. Gheuens, S. Karamaria, A. Prytula, E. Snauwaert, L. Dossche, J. Vande Walle, J. Dehoorne, A. Raes

Introduction: Mutations of several genes encoding the transporters involved in salt reabsorption in the thick ascending limb cause different types of Bartter syndrome (BS), with variable phenotypic expression and severity. Type I and II are the most severe presenting with polyhydramnios, prematurity and characteristically hypokalemia, metabolic alkalosis, polyuria and hypercalciuria.

Case: We report the case of a 9 month old girl referred because of fever, vomiting, dehydration and electrolyte abnormalities despite fluid administration.
Medical history revealed unexplained maternal polyhydramnios, prematurity (34weeks) and dysmaturity (birth weight 1,75kg). She was admitted in a neonatal unit and after a smooth course, was discharged after 36 days (weight 2,2kg). At 4months she presented with feeding difficulties and failure to thrive with no biochemical abnormalities or polyuria were .
At admission, laboratory examination revealed plasma potassium (K) level <3.0 mmol/L, combined with inappropriately high excretion (44%), metabolic alkalosis and hypernatremia (154 mmol/l). Despite IV fluids the biochemical abnormalities persisted but polyuria became prominent Blood pressure (BP) was 115/64mmHg with normal vital parameters. She had pronounced frontal bossing, small hands and a wide nose bridge. Neurological examination was normal.
Additional findings of hyperreninemia hyperaldosteronism, hypercalciuria and nephrocalcinosis were suggestive of a tubulopathy, namely BS. However hypernatremia and high BP are no typical features of BS. The introduction of indomethacin treatment, in addition to K supplementation, compensation of fluid losses and hypercaloric nutrition lead to a stable condition with gradual weight gain.
Mutational screening revealed a homozygous variant of unknown clinical significance of SLC12A1, a gene involved in BS type I. Interestingly there is also a heterozygous gain of function mutation of SCNN1 gene, usually associated with Liddle syndrome (LS). Further genetic testing, including of the parents, is pending.

Conclusion: This is the first report of a girl with a phenotypic overlap between BS and LS. Although genetic analysis revealed homozygosity for a SLC12A1 variant of unknown significance, clinical picture of BS indicates that this is associated with the girl's disease. The heterozygosity for SCNN1B, with subsequently

enhanced renal sodium reabsorption, leads us to hypothesize that this variant may balance the renal salt wasting caused by BS.

Reduced incidence of treated kidney failure (KF)) in 2020 : a Covid-19 effect ?

L. Jacobs, F. Collart, T. Baudoux, C. Bonvoisin, JM De Smet, A Devresse, J Mbaba, L Radermacher, JM des Grottes

Chronic acetaminophen use: a rare but emerging cause of 5-oxoproline-induced increased anion gap metabolic acidosis.

E. Devolder, W. Rosseel, A. Van Der Veen, M. Van Hemelen, P. Verschueren, A. Wilmer , P. Vermeersch, K. Claes

12-Month Analysis of ILLUMINATE-A, a Phase 3 Study of Lumasiran: Sustained Oxalate Lowering and Kidney Stone Event Rates in Primary Hyperoxaluria Type 1

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The irradiation-induced renal ischemic preconditioning is blunted by the oral administration of the anti-angiogenic agent, sunitinib

B. Khbouz, F. Lallemand, P.l Rowart, L. Poma, JM Krezenski, N. Eddine Sounni, A. Noel, F. Jouret

Objective: Irradiation has been suggested to induce renal ischemic preconditioning (RIP) in mice, possibly via angiogenesis. First, we comprehensively investigate the pathways involved in kidneys-centered irradiation. Next, we assess the functional impact of renal irradiation applied before renal ischemia/reperfusion (I/R) injury. Finally, we test whether Sunitinib-mediated inhibition of the angiogenesis prevents irradiation-associated RIP.

Methods: Exp1: Renal irradiation (8.56 Gy) was performed in male C57bl/6 mice (n=10). One month later, total kidney RNA was extracted from irradiated and control (n=5) mice for comparative RNA-Seq.
Exp2: After renal irradiation, the right kidneys were removed, and the left kidneys undergo ischemia(30min)/reperfusion(48h) at Days 7-14-28 post irradiation (n=8).
Exp3: Following the same protocol of I/R at Day14, 3 groups were compared (n=8): 1/irradiation; 2/irradiation and gavage with Sunitinib from Day2 to 13; 3/control group without irradiation or gavage.

Results: Exp1: RNA-Seq showed up-regulation of angiogenesis signaling pathways. Expressions of angiogenesis markers (CD31, VEGF) showed an increase at both mRNA and protein levels in irradiated kidneys ($p<0.01$).
Exp2: Following I/R, BUN and SCr levels were lower in the irradiated mice compared to controls: (BUN: 86.2±6.8 vs. 454.5±27.2mg/dl; SCr: 0.1±0.01 vs. 1.7±0.2mg/dl, $p<0.01$). The renal infiltration by CD11b (187±32 vs. 477±20/mm²) and F4-80 positive cells (110±22 vs.212±25/mm²) was reduced in the irradiated group. VEGF and CD31, were increased in irradiated kidneys at both mRNA and protein levels ($p<0,01$).
Exp3: One-way analysis of variance followed by Tukey's test showed that, following I/R, BUN and SCr levels were lower in irradiated group compared to controls (BUN: 106.1±33.6 vs. 352.2±54.3mg/dl; SCr: 0.3±0.13

vs. 1±0.2mg/dl), and in irradiated group compared to the irradiated-exposed group to Sunitinib (BUN: 106.1±33.6 vs. 408.4±54.9mg/dl; SCr: 0.3±0.12 vs. 1.5±0.3mg/dl; p<0.01).

Conclusions: Kidneys-centered irradiation induces the activation of angiogenesis pathways in mice. Renal irradiation leads to RIP, with preserved renal function and attenuated inflammation post I/R. Exposure to the anti-angiogenic drug Sunitinib post-irradiation prevents the irradiation-induced RIP.

ADPKD, cytopenia and transplant outcomes.

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Potassium and fibre: a controversial couple in the nutritional management of children with Chronic Kidney Disease.

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Impact of COVID-19 on the peritonitis rate in peritoneal dialysis (PD) patients (Pts); a monocentric retrospective study

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Introduction. Peritonitis is a common but serious complication of PD. Besides a mortality rate of about 16 % of PD pts, recurrent peritonitis can lead to PD failure and conversion to hemodialysis. Guidelines recommend an overall peritonitis rate of no more than 0.5 episodes per pt-year with nursing care provided by a qualified and experienced team. This has been achieved for years in our hospital thanks to rigorous follow-up protocols performed by a nursing staff fully dedicated to PD pts.

Methods. During the COVID-19 pandemic, continuous physical follow-up of PD pts was suspended from February until end-June 2020 and replaced by regular telephone calls without any access to telemedicine. Later on, the usual follow-up procedure could not be restored until the end of August, because the whole PD nursing staff (3 nurses) suffered COVID-19 with long sick leaves.
The present study aims to investigate the impact of the COVID-19 pandemic on peritonitis rates in our institution in 2020 compared to 2019. We also compared the microbiological findings of every peritonitis episode.

Results. In 2019, we observed 4 peritonitis episodes in 38 pts with an overall peritonitis rate of 0.16 per patient-year out of which 25 % were due to Gram positive cocci (GPC).
In 2020, the number rose up to 27 episodes (0.91 per pt-year) in 38 pts all being due to GPC.
The time to first peritonitis episode (days) was reduced in 2020 as compared to 2019 (233 +/-21 vs 317 +/-25 ; p=0,022)
The COVID-19 pandemic resulted in a fivefold increase of GPC peritonitis rate, 15 hospitalizations, 4 catheter changes, one shift to HD and one death.

Conclusion. In 2003, Borg D. et al demonstrated a fivefold reduction of PD peritonitis complications with a well-rounded training and retraining program. Our data show how significant this program is, as well as

having a coherent, well trained and motivated medical and nursing staff. We also demonstrate the risks of staff shortage on medical results

Optimised amoxicillin/clavulanic acid dosing in patients on chronic high-flux haemodialysis

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Objective: Amoxicillin/clavulanic acid (AMC) is frequently prescribed to haemodialysis patients, using empirical dosing regimens. The elimination pathway of both compounds differs, making dosing recommendations in ESKD challenging. Pharmacokinetic data of AMC in this patient population are scarce. Our aim was to optimise dosing regimens of AMC in patients on chronic high-flux haemodialysis.

Methods: This monocentric prospective observational study included 26 patients on high-flux haemodialysis, receiving different per oral (p.o.) and intravenous (iv) AMC dosing. Blood samples were taken inter- and intradialytic (n=247) to measure concentrations of amoxicillin (AMX) and clavulanic acid (CLA). A population pharmacokinetic (PK) model was developed using non-linear mixed effects fitting the observed time-concentration data. Different covariates were added in a stepwise fashion and, if improving the model, were retained. Monte Carlo simulations were used to simulate different dosing strategies over 1 week. The PK/pharmacodynamic (PD) target of AMX was set at 50%t>MIC=8mg/L. For CLA no PK/PD target is established, thus only occurrence of accumulation was studied.

Results: A two-compartmental model with between-subject variability for volume of distribution of central compartment (V1), total body clearance (CL) and dialysis extraction ratio (ER) fitted best the measured concentration data for both compounds. Within an individual patient, estimates for V1 and ER were highly correlated. For AMX, residual diuresis and blood flow were kept as covariates. For AMX, residual diuresis was associated with CL (p=0.027), which was 12mL/min and 22mL/min for a residual diuresis of respectively <500mL/24h and ≥500mL/24h. CL of CLA was 64mL/min. ER was high, 74% and 78% for, respectively, AMX and CLA.
All simulated AMX dosing regimens achieved adequate PD target attainment. Accumulation of AMX was observed in all simulations. CLA simulations showed only minor accumulation.

Conclusion: We propose a dosing strategy of p.o. 500mg/125mg q8h or iv 500mg/100mg q8h after an iv loading dose of 1000mg/200mg to achieve adequate exposure of CLA while minimising AMX accumulation. Considering high dialyser clearance, dosing should be scheduled post-dialysis.

The heterogenous spectrum of nephrotic syndrome in a hiv positive patient: a case report.

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HIV-associated nephropathies are rapidly evolving and the spectrum is diverse with different implications for treatment. Since the introduction of antiretroviral therapy there has been a change in pattern, and we discovered that there is a variable group of immune complex nephropathies. Furthermore, it is important to diagnose potentially treatable coincidental diseases like syphilis, a re-emerging infection in HIV patients. In this paper, we describe a case study that demonstrates the importance of a broad differential diagnosis for nephrotic syndrome, the need for the establishment of a precise etiology of the kidney disease in HIV patients, and the importance of a kidney biopsy.