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Studies on Dialysate Mixing in the Genius® Single Pass Batch System for Haemodialysis Therapy

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The Genius® single pass batch system contains a closed tank with 75 l of dialysate: the fresh dialysate is withdrawn from the upper area of the reservoir and the spent fluid is drained at the bottom of the tank. It is assumed that the spent dialysate and the unused dialysate remain unmixed during the progression of dialysis. To our knowledge, this assumption has up till now never been tested. In the present study, we investigated whether mixing of the dialysate occurred during the dialysis session and if any, at which time point it started. Two different dialysate temperatures were compared. For that purpose, 10 chronic hemodialysis patients were dialysed twice, with 1 week interval, with the Genius® system. In 1 dialysis, the dialysate was prepared at a low temperature (37 °C) and in the other session the dialysate was heated to 38.5 °C. All sessions lasted 270 min; the blood/dialysate flows were set at 300 ml/min (1 double-sided peristaltic pump generates simultaneously blood and dialysate flow). Dialysate was sampled at 5, 60, 180, 210, 225, 230, 235, 240, 255, 270 min after the start, both from the inlet and outlet dialysate line and tested for urea, creatinine, p-cresol, hippuric acid and indoxyl sulfate. Blood samples were taken pre dialysis, after 4 h and post dialysis. A Kt/V of 1.17 ± 0.20 and 1.18 ± 0.26 was reached with the 37 °C and 38.5 °C dialysate temperature, respectively (not significant). Serum levels of urea, creatinine, free p-cresol and total and free hippuric acid decreased significantly during the first 4 h of dialysis. For all measured solutes, no differences in serum concentration were observed between the sessions with the two temperatures. The time point (h:min) at which uremic solutes appeared in the inlet dialysate line (mixing) and the amount of removed solute (mg) per session are displayed in the table:

	Mixing	Mixing	Removal	Removal
Dialysate at	37 °C	38.5 °C	37 °C	38.5 °C
Urea	4:01 ± 0:10	4:04 ± 0:09	31,393 ± 11,598	32,268 ± 11,790
Creatinine	4:00 ± 0:10	4:05 ± 0:10	2,080 ± 636	2,133 ± 696.3
p-Cresol	4:03 ± 0:12	4:10 ± 0:15	19.1 ± 10.4	20.8 ± 12.0
Hipp. acid	3:53 ± 0:22	3:59 ± 0:10	983.9 ± 634.0	892.8 ± 613.4
Indox. sulf.	3:50 ± 0:19	3:52 ± 0:13*	93.1 ± 52.0	85.0 ± 34.7

37 vs. 38.5 °C: not significant; * p < 0.05, vs. p-cresol.

It is demonstrated that recirculation of uremic solutes occurred at the dialysate inlet only near the end of the session when small quantities of fresh dialysate were left in the tank. Differences in dialysate temperature did not result in a different separation between used and unused dialysate, nor in differences in removal of toxins or Kt/V.

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Utility and Correlation between Vascular Access Blood Flow, Hematocrit and Mean Arterial Pressure in Detecting Vascular Access Dysfunction

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The on line measurement of vascular access blood flow (Qac) is an important clinical tool to detect access dysfunction. Some studies indicate that a reduction of Qac can be associated to increased hematocrit (Hct) or excessive reduction of the arterial pressure during hemodialysis so that the patients can be exposed at risk for subsequent access clotting. In order to study this question, we evaluated the vascular access blood flow in 25 hemodialysed patients by recirculation measurement and thermodilution technique using temperature sensors (BTM, F.M.C.). Qac was derived on-line during hemodialysis from measurements of access recirculation induced by reversing the patient's blood lines according to the Krivitsky theory. Qac (means ± SD 1,240.13 ± 727.16 ml/m) was measured over a 6-month period and correlated with Hct (means ± SD 35 ± 3.01) and mean arterial pressure (Map: means ± SD 85.71 ± 17.18). Eight patients with Qac values <650 ml/m have had angiograms. Qac was significantly correlated with Map but not with Hct. Three patients with Qac <300 ml/m were correlated with angiographic findings of stenosis. One patient with Qac >500 <650 ml/m have had thrombosis. The patients with Qac <650 ml/m have showed lower mean values of Map in comparison with the values obtained in the total sample, and the patient with thrombosis have had the most low value. This suggests that Map is a major important determinant of Qac. Hct is not associated with vascular access dysfunction. We conclude that Qac is an important predictor of access dysfunction. Hct is not useful for this purpose.

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The Toxicity of the Free Non-Protein-Bound Fraction of P-Cresol: A Prospective and Cross-Sectional Analysis

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The uremic syndrome is the consequence of the retention of solutes normally cleared by the healthy kidneys. Several of the protein-bound uremic compounds, as p-cresol (cr), have biological activity

and toxicity. Although it is conceivable, in analogy with drugs, that the free non-protein-bound fraction exerts toxicity, this aspect was never evaluated, nor the factors influencing the free fraction. We evaluated in a transectional study which clinical and biological characteristics correlated to free (F) cr and the ratio of F over total (T) cr (F/T) (n = 44). In addition, the evolution of F cr was assessed prospectively in 12 patients showing a change of albumin (alb) by at least 0.5 g/dl over time. The hospitalization days in function of the F cr were noted over a 1-year period. In vitro, the impact on leukocyte functional capacity of changes in F cr with unaltered T cr was estimated, by modifying the alb content. In vivo, a correlation was found between T and F cr ($r = 0.84$, $p < 0.001$) and between F/T and alb ($r = -0.44$, $p < 0.01$). When alb changed in the same patients, a higher F cr was found when alb was low (0.089 ± 0.05 mg/dl versus 0.064 ± 0.03 mg/dl, $p < 0.05$). F cr was significantly lower in the patients with a hospitalization period of less than one week per year (n = 16) compared to the patient group with more than 1 month hospitalization (n = 12). In vitro, F cr was higher in the 2.5 g/dl than in the 0.5 g/dl alb solution ($p < 0.05$). Leukocyte function as estimated by chemiluminescence was more inhibited in the low alb (high F cr) solution ($28 \pm 6\%$ versus $21 \pm 8\%$, $p < 0.05$). It is concluded that F cr depends on T cr, and that alb has an impact on the ratio F/T. Patients with high F cr have the highest hospitalization rate. In vitro, a high F cr has a more negative impact on leukocyte chemiluminescence production. These data suggest that hypoalbuminemia together with total p-cresol increase the free fraction of p-cresol, which results in higher toxicity.

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Evaluation of the Abdominal Aortic Calcification Index in Hemodialysis Patients

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Purpose: The abdominal aortic calcification index (ACI), which is calculated by computed tomographic scanning, is one of the most beneficial indicators for atherosclerosis. In order to clarify the factors that participate in the progression of atherosclerosis in chronic hemodialysis patients, we analyzed the relationship between several clinical factors and the increase rate of ACI. Methods: ACI was measured in 53 patients once a year between 1997 and 2002, and then the increased value of ACI at 3-year intervals was reviewed as Δ ACI. All 53 patients were divided into 3 groups according to the levels of Δ ACI as follows: low Δ ACI group (< 2.0 , 19 cases), middle Δ ACI group (< 10.0 , 17 cases), and high Δ ACI group (> 10.0 , 17 cases). Results: ACI itself significantly increased from 21.1 ± 22.6 to 28.8 ± 25.3 in 3 years ($p < 0.001$). The patients were significantly older in the high Δ ACI group than in the low Δ ACI group ($p < 0.01$). There was no significant difference in sex, duration of dialysis, blood pressure, diabetes, smoking, and blood chemistries between these three groups. Conclusion: These results suggested that aging does not only promote atherosclerosis, but also accelerates its progression velocity itself in hemodialysis patients.

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Vascular Access Flow and Haemodynamic Parameters – Interrelation and Changes during Haemodialysis

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Aim: The aim of the study was to investigate interrelation of vascular access blood flow (QVA), cardiac output (CO) and other haemodynamic parameters and their behaviour during an HD session. Material and Method: QVA, CO, peripheral resistance (PR), access resistance (AR) and other haemodynamic parameters were investigated in an unselected group of 30 chronic HD patients (so far). QVA, CO and PR were measured with HD01 monitor (Transonic Systems) at the beginning and towards the end of an HD session. Concurrently, overall extracorporeal thermal balance (TB) was measured with BTM module (Fresenius), relative blood volume changes (Δ BV) with Crit-line monitor (Hemametrics) and blood pressure (BP) and heart rate (HR) with an automatic device BP-100 (Gambro). Access-free peripheral resistance (AFPR) was evaluated from PR and access resistance (AR), where AR was taken as a quotient of the mean arterial pressure and QVA and $AFPR = PR \cdot AR / (AR - PR)$. Results: Significant correlation was found between QVA and CO ($CO = 5 \cdot QVA + 3.37$; $r = 0.45$) suggesting that CO increase after vascular access creation is several times higher than QVA itself. Significant decrease in CO (in some cases over 30%), correlating strongly with Δ BV ($r = 0.73$) was seen in majority of patients during HD. Slight increase in CO occurred in about 25% of performed measurements. Change in CO in turn induced change in QVA ($r = 0.56$). Exceptional cases of low to zero increase in PR were related to positive TB value. Mean AR and AFPR values at the start of HD were 157 and 18 mm Hg/l/min, respectively, and their ratio did not change significantly during HD. Conclusions: CO is clearly influenced by the magnitude of QVA. During dialysis, this relation is manifested in opposite way – Δ BV induces drop in CO, which in turn leads to a decrease in QVA. This process may be modulated by varying degree of vasoreactivity influenced by thermal balance.

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Acetate Free Hemodialysis (AFHD): Feasibility and Comparison with Acetate Free Biofiltration (AFB) and Bicarbonate Dialysis (BD)

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AFB is an hemodiafiltration technique, particularly suited for critical ill hemodialysis patients thanks to a better cardiovascular stability due to the acetate free bath, and a tailored correction of acidosis. These features could be extended to a wider dialysis population, less critical but still cared with BD. AFHD should represent an intermediate diffusive technique, which uses a low flux filter, an acetate

free bath and a 1 Mol substitution fluid of sodium bicarbonate at low flow rate (0.5 l/h). The study was aimed to check the feasibility of such a technique as concerns: (1) electrolyte kinetics (Na^+ , K^+ , HCO_3^- , pH, Hct); (2) dialysis adequacy (KT/V, b2-mglobulin reduction ratio, RRb2); (3) haemodynamics behaviour (blood pressure, SBP, heart rate, HR, blood volume, BV). Nine patients entered into the study (randomised crossover) and were followed for one month in each treatment. Data (reported as mean \pm SD) were analysed by an ANOVA test. All the patients received comparable treatments (QB = 325 ± 20 ml/min, WL = 2.4 ± 0.8 kg, TD = 227 ± 15 min, $p = \text{n.s.}$). Bath conductivities (in mS/cm) were 15.1 ± 0.2 in AFB, 14.2 ± 0 in BD and 13 ± 0 in AFHD. Electrolyte kinetics (intradialytic time means in mEq/l) resulted comparable ($\text{Na}^+ = 138.7 \pm 1.8$, $p = 0.12$, $\text{K}^+ = 4.0 \pm 0.4$, $p = 0.16$, $\text{HCO}_3^- = 25.6 \pm 2.2$, $p = 0.34$, pH = 7.4 ± 0.04 , $p = 0.77$, Ht = $38.3 \pm 5\%$, $p = 0.34$) with a quicker correction of acidosis in AFB. Dialysis efficiency were again comparable (KT/V = 1.5 ± 0.3 , $p = 0.44$), while AFB seems to show a higher RRb2 ($47.6 \pm 4\%$ vs. $6.8 \pm 8.4\%$, $p < 0.01$ of AFHD and BD). Even the hemodynamic behaviour seems not to differ (SBP 112.9 ± 22 mm Hg, $p = 0.74$, HR 73.8 ± 4.4 beats/min, $p = 0.74$, BV $-12.7 \pm 6.4\%$, $p = 0.82$). The pre to post infusion data showed an increase of Na^+ and HCO_3^- by 13.1 ± 3.8 and 20.7 ± 4.2 mEq/l. AFHD seems to be a safe technique but the clinical advantage and the therapeutic use must be investigated.

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Erythropoiesis and Folic Acid Supplementation in Hemodialysis Patients

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Purpose: Folate deficiency (FD) in end-stage renal disease patients may cause megaloblastic anemia and thus contribute to erythropoietin (EPO) resistance. This study was performed to evaluate the efficacy of oral folate supplementation on erythropoiesis in hemodialysis patients. Methods: A total of 81 patients were recruited (46 men, 35 women, 76 treated with EPO). Enrolled patients were not previously treated with folic acid for at least 24 months preceding the study. We measured serum folate, erythrocyte folate and serum cobalamin concentrations together with other hematological parameters. All patients received folic acid in a single oral dose of 5 mg per day and measurements were repeated at the end of a 4-week period. All patients received folic acid in a single oral dose of 5 mg per day for 4 weeks and were followed over this period of time. Throughout the study erythropoietin treatment was stable. Results: The mean level of serum folate and erythrocyte folate were 3.4 ng/ml, ranging from 0.7 to 10.2 ng/ml and 308.8 ng/ml, ranging from 133.5 to 975.5 ng/ml, respectively (respective reference intervals, 3.7–14.4 ng/ml and 192.1–577.1 ng/ml). Taking into account folate serum levels, 65% of the patients ($n = 53$) had values less than 3.7 ng/ml and therefore needed supplementary oral administration of folic acid. Conversely, only 11% of the patients ($n = 9$) demonstrated folate

deficiency according to erythrocyte folate levels. A statistical significant correlation was found between the concentration of folic acid in serum and in red blood cell ($r = 0.39$, $p < 0.001$), whereas mild cobalamin deficiency was present in just 3 patients. In 14 patients with macrocytosis (MCV > 99 fl) the cobalamin levels were reported adequate and folate values (M \pm SD) in serum were 3.8 ± 1.5 ng/ml and in red blood cell 322.2 ± 196.2 ng/ml. No correlation was found between mean corpuscular volume and cobalamin levels, folate serum levels and erythrocyte folate levels. A significant increase in folate concentration in serum (25.3 ± 10.4 ng/ml) as well as in erythrocytes ($1,117 \pm 261$ ng/ml) was evident, after one month of supplementary administration of folic acid. However, the mean value of hemoglobin and MCV remained identical throughout the study (from 10.7 to 10.6 g/dl and from 92.0 to 92.4 fl before and after folate administration, respectively). Conclusion: This study confirms that erythrocyte folate concentration is a more reliable indicator of folate status than serum folate, although the latter is the variable generally measured. Supplementary oral administration of folic acid seems to be ineffective in improving anemia of hemodialysis patients.

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Effects of a Vitamin E-Bonded Hemodialyzer on Iron Infusion Induced Oxidative Stress during a Hemodialysis Session

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Purpose: Intravenous iron administration to haemodialysis patients deteriorates oxidative stress. The aim of this study was to investigate the effects of a vitamin E-coated regenerated cellulose hollow fiber dialyzer (VED) on oxidative stress compared with a polysulfone hollow fiber dialyzer (PSD). Methods: In 9 patients receiving hemodialysis, plasma malondialdehyde (MDA) and total cholesterol (TC) levels were determined, during two successive sessions with and without iron supplementation for every dialyzer. Intravenous iron was administered during the second half hour of the dialysis session. Measurements were made before and 30, 60, 90, 120, 180 and 240 min after the session started. Results: Areas under curve (AUC 0–24 min) of ratios of plasma MDA to cholesterol were determined. In sessions where iron was given, patients receiving hemodialysis with PSD showed a significant increase in (AUC 0–24 min) of MDA to cholesterol, compared to those sessions where no iron was administered (15.5 ± 7.0 vs. 5.4 ± 2.5 , $p < 0.009$). On the other hand, in patients receiving hemodialysis with VED, there was no significant increase in (AUC 0–24 min) levels of MDA to cholesterol between sessions with and without iron administration (11.2 ± 5.8 vs. 8.4 ± 4.2 , $p = \text{NS}$). Conclusions: Iron infusion deteriorates oxidative stress in PSD hemodialysis, but not in VED hemodialysis.

Medical Quality Management in Hemodialysis

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Introduction: After more than 30 years, hemodialysis (HD) still is an empirical form of treatment with extensive variation in practice patterns. Under growing medical and economic constraints, a medical quality management project of hemodialysis was initiated by the largest German non-profit dialysis provider, KfH. **Methods:** According to standardized operating procedures, each dialysis-unit voluntarily collects patient information (demography, comorbidity, hemodialysis process data, biochemical data, medication, quality of life, hospital admissions and mortality) in a unique database. Electronically, data are transferred to a central and independent institution (^{a, b}). Every 4 months unit-specific quality reports are generated and sent back to the facilities within short time. Benchmarking enables anonymous comparison of each unit's parameters (e.g. hematocrit, Kt/V) to the rest. **Results:** As of April 30, 2002, 55 facilities with 6,084 patients participated. Anemia management (56% reduction of low hematocrit values (<30 volume %)), dialysis adequacy (73% reduction of short dialysis time <4 h) and phosphate control (31% reduction of high calcium phosphate product >5.8 mmol/l) were most prominently improved. **Conclusions:** Using evidence-based (process-/outcome-) parameters, medical quality management in hemodialysis is feasible and improves quality in German dialysis facilities.

Biocompatibility of the New Diapes® LF100 Low Flux Dialysis Membrane

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There is an increasing number of synthetic membranes available for low-flux hemodialysis. In a prospective cross-over study with 10 ESRD patients, the new synthetic low-flux dialysis membrane DIAPES® LF100 (Bellco BLS 517 SD, 1.7 m²) was compared to low-flux F8 HPS (Fresenius, 1.8 m²) and low-flux Polyflux 8L (Gambro, 1.8 m²), concerning biocompatibility. Each patient was hemodialyzed with each membrane for 4 h (Q_B 250 ml/min; Q_D 500 ml/min). Blood samples were drawn at 0, 15, 30, 60 and 240 min. All membranes had a modest white blood cell drop (maximum after 15 min DIAPES® LF100 82 ± 11%, F8 HPS 84 ± 12%, Polyflux 8L 75 ± 8%, p < 0.05) which was significantly higher for Polyflux 8L in comparison to the other two membranes. Decrease of the platelet count detected after 30 min was low for all membranes (DIAPES® LF100

90 ± 8%, F8 HPS 96 ± 6%, Polyflux 8L 95 ± 8%). Complement factor C5a was below 4 ng/ml after 15 min for all membranes indicating no activation of the complement system. There was also no difference between the membranes in the activation of blood coagulation. Thrombin-antithrombin III complex formation after 240 min was below 7 ng/ml for all membranes. We conclude that DIAPES® LF100 is a new synthetic dialysis membrane with excellent biocompatibility properties.

Clinical Performance of DIAPES® LF100, a New Synthetic Low-Flux Dialysis Membrane

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DIAPES® LF100 is a new synthetic low-flux membrane, designed to remove low molecular weight (LMW) proteins. In a prospective cross-over study with 7 ESRD patients, DIAPES LF100 (Bellco BLS 517G, 1.7 m²) was compared to F7 HPS (Fresenius, 1.6 m²) regarding small molecule and LMW protein (β₂-microglobulin (β₂m), cystatin c (cys c)) elimination. HD duration was 4 h, QB 350 ml/min and QB 500 ml/min. Clearances after 30, 240 min and removal rates (RR) were determined in plasma. LMW proteins were measured in continuously collected dialysate. Both dialyzers revealed comparable small molecule (urea/creatinine/phosphate) clearances (DIAPES 250/235/244 ml/min; F7HPS 258/236/231 ml/min) and RR (DIAPES 79/73/65%; F7HPS 79/72/62%). β₂m/cys c clearance (DIAPES 12/7 ml/min; F7HPS -2/-7 mL/min) and RR (DIAPES 27/24%; F7HPS 10/3%) was significantly (p < 0.05) higher for DIAPES LF100. β₂m/cys c in dialysate was detected only for DIAPES (33/4.1 mg) (p < 0.05), while no albumin was observed in dialysate with both membranes. DIAPES LF100 demonstrates superior LMW protein removal and comparable small molecule clearances compared to F7 HPS. The advantages for DIAPES LF100 regarding the LMW protein elimination can be explained by a different membrane structure compared to conventional low-flux polysulfone.

Hemodialysis Membrane and Dialysate Fluid Biocompatibility

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Purpose: In this data we studied the interleukin production (IL-1β, IL-2, IL-6, TNFα), the platelets and the white blood count during the dialysis procedure. The purpose of the study was the implication

of two main reasons in biocompatibility: (1) the type of dialyser and (2) the dialysate fluid. Methods: We studied 30 patients on dialysis program and 15 normal volunteers. 10 were in dialysis with acetate fluid with cuprophane membrane (CU) initially and after with polysulfone (PS), 10 in bicarbonate at first with CU and after in PS, and 10 in biofiltration with polyacrylonitrile. Results: We did not find any significant difference in IL-1 β and IL-2 production in anyone hemodialysing group. In biofiltration in IL-6 production we found significant decrease. In acetate fluid with both CU and PS membrane we found significant elevation in TNF α production. White blood count and platelets in 10 min showed decrease especially with CU membrane. Conclusion: Biofiltration and bicarbonate dialysis with PS membrane seem to be more biocompatible because of the phenomenon of less interleukin production.

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Vitamin B₆ Serum and Erythrocyte Index in Hemodialysis Patients

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Vitamin B₆ deficiency was recognized as a risk factor for hyperhomocysteinemia and cardiovascular disease. Chronic hemodialysis patients (HD) are especially susceptible to impairment in pyridoxine status, as well as to cardiovascular complications. It is established that vitamin B₆ status in humans is influenced by nutritional and environmental factors. Little is known about the need of individualization of pyridoxine doses in HD patients. The dose of 10 mg pyridoxine hydrochloride daily is regarded as safe and sufficient, but there are cases of vitamin B₆ accumulation and the risk of neurotoxicity in HD patients. Objective of this study was the evaluation of vitamin B₆ status in local population of HD patients supplemented with pyridoxine in the weekly dose of 50 mg. Second purpose was to compare serum and erythrocyte vitamin B₆ indexes in HD patients as predictors of pyridoxine status. 55 HD patients (33 M/22 F), aged from 22 to 77 years, mean age 52 years, treated in our center and 52 healthy volunteers (14 M/38 F), mean age 39 years, were studied. Vitamin B₆ serum and erythrocyte indexes were assessed by calculation of the ratio of AST activity stimulated with pyridoxine to basal AST activity in serum and hemolysate respectively. Serum vitamin B₆ index was 1.27 \pm 0.26 in HD group vs. 1.21 \pm 0.23 in controls (p = 0.01). Erythrocyte vitamin B₆ index was 2.24 \pm 0.57 in HD patients and 1.42 \pm 0.33 in control (p = 0.0000). The correlation between serum and erythrocyte indexes of vitamin B₆ was negligible (r = 0.124, p < 0.05). We conclude that erythrocyte vitamin B₆ index predicts pyridoxine status in HD patients better than serum vitamin B₆ index. Serum index has advantage of simplicity in performing but does not reflect tissue pyridoxine status and probably underestimates its deficiency. Increase of vitamin B₆ supplement dose, diet counseling and better compliance will be advisable in reducing vitamin B₆ deficiency in our patients.

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Heart Rate Variability in Chronic Hemodialysed Patients

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Chronic renal failure leads to autonomic neuropathy (AN). Heart Rate Variability (HRV) is a non-invasive method of assessment of AN. Depressed parameters of HRV are poor prognostic factors. Purpose: The aim of the study was to investigate the influence of hemodialysis on HRV parameters in chronic hemodialysed patients. Methods: Two 24-hour ECGs (in the day with HD and in the next day – without HD) were performed in 35 HD patients (F = 17, M = 18), aged 49 \pm 10 years, duration of HD therapy 37 \pm 31 months. Time domain measures of HRV were obtained according to ESC recommendations: SDNN, SDANN, SDNNi, rMSSD, pNN50 and mean RR (mRR). Results: In the day with HD the values of SDNNi, rMSSD and pNN50 were lower than in the day without HD: SDNNi 36.8 (SD 8.9) vs. 38.6 (SD 10.5) ms, p < 0.05; rMSSD 19.7 (SD 6.4) vs. 22.0 (SD 6.6) ms, p < 0.02; pNN50 2.16 (SD 2.03) vs. 2.83 (SD 2.34)%, p < 0.05. There were no differences between the values of SDNN, SDANN and mRR in the day with and without HD. Conclusion: In conclusion, parasympathetic activity is decreased in the day with hemodialysis.

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Timing of Nephrology Referral

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Purpose: More than 10,000 patients with end-stage renal disease initiate hemodialysis (HD) in Japan each year. However, the optimal time at which time to refer patients to nephrologists remains unclear. To evaluate the effects of different referral patterns on morbidity and mortality, we retrospectively studied 206 patients who entered our chronic HD program from 1998 to 2000. Methods: Patients were classified early referral (ER) if they were referred to a nephrologist at least 1 year before the start of HD, to late referral (LR) if they were referred less than 1 month, and to intermediate referral (IR) if they were referred from 1 month to 1 year. We compared risk for death, days of hospitalization, complications at the first HD, and referral source in three groups. Results: ER is associated with a higher proportion with a permanent vascular access, shorter duration of hospital stay and early creation of permanent vascular access, and decreased short-term mortality. Conclusion: We conclude it is necessary to focus on continuing medical education initiatives for early referral of patients with progressive renal insufficiency among primary care physicians.

Evaluation of Fiber Length and Fiber Filling – Rate of Reduction of Low Molecular Weight Proteins in Dialyzer Housing

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A new polysulfone dialyzer (BS-1.6UL: BSL), characterized by a longer fiber length and an increased fiber-filling rate, recently has been developed by Toray Medical (Tokyo). To determine the significance of the fiber length and the fiber filling rate, the reduction of the serum low molecular weight proteins were compared among BSL and two conventional dialyzers. The dialyzers tested were BSL, BS-1.6U (BSU, Toray) with a shorter fiber length compared to BSL, and PS-1.6UW (PSW, Kawasumi, Tokyo), a polysulfone dialyzer with a similar fiber length as BSL. In *in vitro* studies, discarded plasma from end stage renal disease (ESRD) patients and a familial hypercholesterolemia patients were dialyzed in a recirculation batch system. The 6 ESRD patients were used for this procedure. Both of the *in vitro* and clinical studies showed that the reduction rate of low molecular weight proteins was higher in BSL than in other dialyzers, whereas the reduction rate of small molecular substances were similar among three dialyzers. Adsorption of small proteins and lipids were not significantly different among three dialyzers. Pressure drop was significantly higher in BSL (BSL > PSW > BSU) both in blood and dialysate compartments. Our results suggest that a longer fiber length and an increased fiber-filling rate in dialyzer housing are efficient for the removal of low molecular weight proteins. The efficiency is presumably attributable to the fiber dependent internal filtration accomplished by the high blood pressure drop in blood and dialysate compartments.

A Case of Severe Mechanical Hemolysis in the Extracorporeal Blood Circuit in Hemodialysis

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Today, hemolysis is a rare acute complication of hemodialysis. We here describe a case of blood stream obstruction in the blood tubing as the cause of severe hemolysis in hemodialysis. Case Report: A male patient, age 72 years, chronic glomerulonephritis, arteriosclerosis. Low-flux polysulfone hemodialysis (3 × 5 h/week) for 4 years, ultrafiltered bicarbonate-buffered dialysate. On the day of the event, 1 h after start of dialysis, increasing abdominal pain, nausea, a rise in blood pressure to 200/100 mm Hg, and tachycardia occurred. Dialysis was stopped, and a blood test revealed a drop in hematocrit from 32 to 16% in the presence of hemolytic serum. Additional tests excluded high dialysate temperature, hypotonic dialysis fluid and residual disinfectants as possible causes of hemolysis.

Therefore, mechanical obstruction of the blood flow was the most likely cause of hemolysis. Examination of the blood tubing identified a mass of glue at the entrance of an extension chamber between the blood pump and the dialyser blood inlet. The glue obstructed the blood flow almost completely except for a central hole of approximately 1 mm in diameter. The blood pump was strong enough to pump against the obstruction without giving an alarm because this segment of the blood line is not monitored by pressure control devices of the dialysis monitor. Using a similar pump speed compared to previous sessions, a significantly lower venous pressure was measured which may suggest obstruction. The patient developed dyspnoea because of lung oedema and signs of a severe pancreatitis. He was submitted to the intensive care unit for further surveillance and needed 4 weeks for full recovery. Conclusion: Severe mechanical hemolysis may occur in modern hemodialysis and may be difficult to identify because of a gap in the monitoring system of the extracorporeal blood circuit.

Monitoring the Hemodialysis Dose by Accumulated Hemodialysis Blood Flow Amount Gives Better Dialysis Dose than Conventional Timed Dialysis

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Purpose: Intercurrent episodes during dialysis such as hypotension, vomiting, etc. during hemodialysis tend to cause early termination of dialysis session. This study is to monitor each dialysis dose. Methods: Total, accumulated, blood volume passed through the dialyser was measured indirectly by counting the number of roller rotation of blood pump. (1) The counted numbers were correlated with KT, which was derived from $(KT/V) \times V$, where KT/V was from Daugirdas equation and V from Watson's anthropometric estimates. (2) Changes of counts were compared on 18 patients between conventional 4-hour dialysis with 'blinded counting' and count-conscious dialysis. Results: (1) 56 Counting and KT were linearly related (Pearson correlation coefficient = 0.737, $p = 0.01$). (2) Average counts increased and their deviations (% of SD/average) decreased as below (paired sample tests); averages: before 5,446, after 5,806, $n = 10$ to 15, $p = 0.000$; %, SD/average: before 7,511, after 5,644, $n = 10$ to 15, $p = 0.045$. Conclusion: (1) Once a month measurements of KT/V tend to give 'good' numbers, while measurements of each dialysis dose yield less deviations and overall increase in dialysis doses. (2) Simple way of estimating dialysis dose was innovated.

Are Disinfectants Able to Remove Cytokine-Inducing Substances (CIS) from Haemodialysis Circuits?

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The potential actions of biofilm in flowing systems represent a real problem for many industrial water applications, as biofilm represents the starting point for bacterial growing, resistance to disinfection and corrosion of surfaces. In this study we evaluated the effectiveness of various sterilisation systems on the eradication of biofilm, experimentally formed in a dialysis monitor, and on CIS removal (i.e. LAL-negative biologically active bacterial fragments). A single-pass dialysis monitor without any recirculation was employed in the 'in vitro' study. The monitor was contaminated with waterborne *Pseudomonas aeruginosa* >100,000,000 CFU/ml for 48 h (biofilm) or 1 h (without biofilm) respectively, then washed and disinfected by ten different methods: Hypochlorite, Amuchina, Peresal, Tiutol-KF, Instrunet, Amu-Safe, Oxagall, Heat Disinfection 90 °C (HDS), HDS + chemical (citric acid), HDS + chemical + Dialox dwelling (60 h) into the monitor. Disinfection procedure was followed by a final washing. Water samples from the monitor were collected at different timing: basal, at the end of contamination, at the end of disinfection, and thereafter at 24, 48 and 72 h, in order to evaluate bacteria regrowth. We evaluated CIS production by monitoring IL-1 production from PBMC cultures. Biofilm was detected by Scanning Electron Microscopy (SEM). We never observed total disappearance of CIS. The presence of biofilm interferes with effectiveness of disinfectants. The association between heat, citric acid and dwelling with 0.37% peracetic acid of disinfectant determined more CIS reduction, so as a lower reappearance of CIS, than the other protocols. This study underlines the importance of biofilm on changing the effectiveness of disinfectants, both chemical and physical, and on favouring the reappearance of CIS in the dialysis circuits. Due to a poor capacity on CIS removal by most common disinfectants, when high microbial load is present, it is important to prevent contamination in order to reduce biological activation.

Monitoring of Medical Quality of Hemodialysis Enables Patient Empowerment

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Dialysis therapy becomes increasingly complex due to medical, demographic and economic factors. Thus, effective medical monitoring is mandatory. Intelligent and fast data management as well as patient empowerment are the two most important pillars of quality management. KfH, Kuratorium für Dialyse und Nierentransplantation, Neu-Isenburg, Germany introduced in 1998 a coordinated

quality management project, termed QiN ('Quality in Nephrology'). Based on an electronical database, data are recorded according to previously defined standard operating procedures (SOP). Continuous quality improvement is the underlying principle. Dialysis adequacy, blood pressure management, anemia and bone metabolism are key issues of improvement (i.e. Kt/V +13%, hematocrit +11%). Morbidity, quality of life and mortality are the central quality parameters. Every three months, QiN generates unit-specific reports (USR) that enable dialysis facilities to anonymously compare their performance (i.e. dialysis duration, Kt/V, hemoglobin, phosphate, blood pressure) to other participating centres. USR also contain anonymous patient lists that can be instrumentalized by the medical staff to help improve patient management. Consequently, effects of interventions, i.e. prolongation of dialysis time etc. can be demonstrated to patients and their families by convincing and regularly updated parameters. Provided that SOP for data acquisition and electronical communication standards are harmonized, different monitoring systems could cooperate to cover large hemodialysis populations.

Elimination and Rebound Kinetics of Complement Factor D in Hemodialysis and Hemodiafiltration with Different Treatment Schedules

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Factor D (fD), the rate limiting protease for C3-convertase formation, is 10-fold elevated in HD patients, exposing them to increased risk of chronic complement-mediated inflammation. To optimise treatment modes we investigated removal and rebound kinetics of fD. Treatment performance was varied for 10 patients (77 ± 12 kg) by using (A) high flux HD (Polyflux 14S; $Q_B 293 \pm 9$, $Q_D 500$ ml/min) or (B) on-line HDF (Polyflux 21S; $Q_B 451 \pm 53$, $Q_D 700$, $Q_{UF} = 113$ ml/min, post-dilution). Treatment frequency was varied by applying (1) A or B for 4 h and (2) A or B 2×2 h on consecutive days. Plasma samples taken before, during and up to 90 min as well as 24 h and 48 h after treatments were analyzed for fD by specific ELISA. Data are given as concentrations (mean \pm SD) in mg/l and reduction rates (RR in %). * $p < 0.05$ vs. t0; # $p < 0.05$ A vs. B (paired t test, 2-sided).

	Pre	Post (4 h)	RR 4 h	4 h + 90 min	24 h	48 h
A1	10.7 \pm 3.7	8.2 \pm 3.3*	36 \pm 15	8.7 \pm 3.5*	9.8 \pm 4.0	9.6 \pm 3.9
B1	10.3 \pm 3.9	6.8 \pm 2.7*#	47 \pm 11*#	7.1 \pm 3.0*	9.1 \pm 4.2	8.9 \pm 4.2
	Pre [§]	Post (2 h) [§]	RR 2 h [§]	2 h + 90 min [§]	24 h [§]	48 h
A2	10.2 \pm 3.3	9.7 \pm 3.9	14 \pm 13	9.1 \pm 3.0	10.0 \pm 3.3	9.6 \pm 3.0
B2	10.2 \pm 2.8	7.9 \pm 2.8*	27 \pm 26#	9.0 \pm 2.8	10.7 \pm 2.8	10.2 \pm 3.7

[§] Means for the two 2-hour treatments.

High flux HD shows limited efficiency in reducing factor D levels with a definite effect of treatment time. Optimized HDF, i.e. using a large dialyzer, high blood flow rate and 18 l postdilution exchange, is able to significantly enhance fD removal. Detailed kinetic modelling needs to be applied to evaluate optimized treatment schedules for blood purification therapies.

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Quality Control in Paired Hemodiafiltration on Line (PHF)

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Purpose: Safety in on-line techniques remains relevant and unsolved. PHF is a innovative technique that associated a high efficient depuration with an on-line control of the dialysate infused through two ultrafilters. Methods: Four patients were treated with to PHF for 6 months with 9,984 l infused. According to the French regulation (DGS/DH/AFSSAPS 311 2000), bacteriological and endotoxin samples were performed. Every 3 months a water quality control was performed following the European Pharmacopea. Every month we performed an in vitro PHF session with infusion of 21 l. To study bacterial, disposable filters (0.45 µm) were used after the 1st and the 2nd ultrafilter. LAL tests were performed, using disposable filter (0.2 µm) after passing each ultrafilter with 10 sl infusate. Results: We found only two positive CFU and LAL tests after the 1st ultrafilter, in the first phase of the study (accidental contamination due to mistaken handling), while all tests were negative after the 2nd ultrafilter. Conclusion: PHF provides ultrapure infusate according to the French regulation. However, using a PHF system, the high cost and the heavy burden in time and effort for the staff could be reduced.

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Hemofiltration (HF) vs. Hemodiafiltration (HDF): A Multi-Centre, Prospective, Cross-Over Study

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Purpose: To compare the convective treatment modes, HF and HDF, regarding cardiovascular tolerance and effects on blood pressure, when applied under similar conditions in stable dialysis patients. Methods: 39 clinically stable dialysis patients were treated with HD for 6 months to generate baseline data followed by HF and HDF in random order for 2 × 6 months. Similar biocompatibility (same membrane and fluid quality), similar urea Kt/V (eKt/V = 1.2)

and similar treatment time (3.5 h) were achieved by using AK100/200 ULTRA machines, polyamide membranes in low-flux and high-flux versions and appropriate adjustment of blood flow rate (Qb) and dilution ratio (Qb/Qinf). Predilution was used for HDF (target dilution = 2/1) as well as for HF (target dilution = 1/1). Results: 30 patients completed the study; 5 dropped out for non-study-related reasons and 4 for non-compliance.

	HD	HF	HDF	p value for HF vs. HDF
<i>Episodes or ml/patient/month</i>				
Hypotension, intrasession	0.5	0.5	1.1	0.017
Plasma expander	32.8	35.9	103.1	0.035
Headache, intrasession	0.5	0.1	0.5	0.06
Intertreatment weight gain, kg	2.4	2.3	2.3	NS
MAP pre-session, mm Hg	95.0	98.4	93.8	0.037
MAP post-session, mm Hg	93.5	94.7	93.2	NS
p-Sodium, pre-session, mmol/l	136.9	138.0	138.0	NS

Conclusion: HF and HDF provide good control of intrasession symptoms and blood pressure in stable dialysis patients. Treatment with HF resulted in a significant reduction of intrasession hypotension and a slight but significant increase of pre-session MAP, caused by an increase of systolic BP without effect on the prevalence of hypertension and the dose of antihypertensive drugs, all in comparison to HDF.

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Effect of Ultrafiltration Rate on Filter Performance in Pre-Dilution Hemofiltration (HF)

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For critically ill patients treated with continuous HF, doses recently shown to improve survival (Ronco, Lancet 2000) can usually be achieved only in the pre-dilution (D) mode. In an isovolemic, plasma-based pre-D HF system (Qp = 200 ml/min), we measured removal parameters for a 1.2 m² polysulfone hemofilter at ultrafiltration rates (Qf) of 20, 40, and 60 ml/min, corresponding to 17, 34, and 51 ml/h/kg for a 70 kg patient (n = 3, hemofilters for each Qf). Clearances (K) of urea (U: MW 60), vancomycin (V: 1,448), inulin (I: 5,200), and β₂-microglobulin (β₂M: 11,800) were derived from plasma concentrations at 30, 60, 120, 180, and 240 min. Sieving coefficients (SC) of V, I, and β₂M were measured at the same time points and at baseline (T = 0 min). The K (ml/min) values (mean ± SD) were (p < 0.02 by ANOVA for all solutes):

Qf (ml/min)	Urea	Vancomycin	Inulin	β ₂ M
20	18.3 ± 2.0	15.3 ± 1.4	16.7 ± 3.3	17.7 ± 3.3
40	32.3 ± 1.6	28.9 ± 1.4	26.3 ± 0.8	26.3 ± 0.8
60	42.9 ± 4.6	37.4 ± 0.9	37.8 ± 2.4	29.9 ± 0.5

At QF = 20, 40, and 60 ml/min, respectively, mean SC values (average of all time points) were 0.76 ± 0.02 , 0.73 ± 0.03 , and 0.73 ± 0.03 for V, 0.80 ± 0.03 , 0.69 ± 0.03 , and 0.69 ± 0.03 , and 0.75 ± 0.03 , 0.71 ± 0.03 , and 0.75 ± 0.05 for $\beta 2M$ ($p = NS$ for differences between solutes at a given Qf and between Qf values for a given solute). In addition, for each solute, SC values did not change significantly with time at any Qf. Specifically, at Qf = 40 ml/min, SC values at T = 0 and T = 240 min, respectively, were 0.68 ± 0.07 and 0.77 ± 0.02 for V, 0.75 ± 0.03 and 0.66 ± 0.06 for I, and 0.66 ± 0.05 and 0.75 ± 0.02 for $\beta 2M$. In conclusion, a predictable effect of pre-D on solute clearances was observed. SC values were not influenced significantly by either Qf or time and the equivalence of SC values over the middle molecule range suggests attenuation of secondary membrane effects. These data indicate filter performance can be preserved despite high Qf values by use of pre-D.

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Effects of Hematocrit and Blood Flow Rate on Internal Filtration in an Experimental Dual Hemodialyzer System

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Renal replacement therapy with enhanced internal filtration (IF) dialyzers can be an alternative to standard hemodiafiltration, because it provides remarkable convective solute removal in a simple system. However, it has been assumed that the rate of IF (QIF) is difficult to be determined and significantly influenced by the properties of the blood and the operational conditions. To evaluate the effects of hematocrit (hct) level and blood flow rate (QB) on QIF, we employed an experimental dialyzer system, which consists of two sequentially placed hemodialyzers (APS-150S, Asahi Medical, Japan). In the experiment, the bovine blood and the dialysate was introduced in a countercurrent manner. This system uniquely allowed for the determination of QIF, by using the hct values before the dialyzers (pre-hct) and between the dialyzers (mid-hct). At different pre-hct and QB with zero net filtration, we determined QIF in the following equation: $QIF = QB \times (1 + \frac{pre-hct}{mid-hct})$. When pre-hct was 37% and QB was 100 ml/min, mid-hct was increased to 57%, indicating an occurrence of significant filtration. QIF was, in fact, calculated 35.1 ml/min. When QB was increased to 200 and 300 ml/min, QIF was also increased to 77.4 ml/min and 127.9 ml/min, respectively. Similarly, when pre-hct was reduced to 28% by diluting with the bovine plasma, QIF was 37.1 ml/min (QB = 100), 64.3 ml/min (QB = 200) and 97.6 ml/min (QB = 300). In this report, we demonstrated that QIF is influenced by the hct level, as well as QB, which should therefore be taken into account in clinical applications of enhanced IF dialyzers.

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Nano- and Microporous Membranes for Medical Applications: Morphology and Performance

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Today, nanoporous and microporous membranes are extensively used in extracorporeal devices for blood purification. Different treatment modes in hemodialysis, as well as plasma fractionation, and plasma separation have become state-of-the-art. The polymer membranes used for these applications are produced by two different phase inversion processes (TIPS/DIPS). In our contribution we will present a novel platform technology based on DIPS, which allows to tailor the pore size from the nanometer up to the micrometer range to prepare Low Flux, High Flux, High Cut-Off and different Microporous membranes. A novel polymeric blend is used to minimize the blood/material interaction. Direct methods (permporometry/liquid displacement) have been applied to determine the pore size distribution and the number of pores in the selective layer. Field Emission SEM is used to characterize the selective membrane layer consisting of a nanoporous nodular channel structure, which allows a selective separation. To study the roughness and the pore geometry scanning probe microscopy techniques are applied.

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Serum PI Control in RDT PTS Undergoing On-Line HDF

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High sPi, sCaxPi and the therapy of mineral abnormalities are correlated with vascular risk in RDT patients. We reexamined Ca-Pi status in 54 stable RDT patients on free diet, on HDF in our unit. The patients (age 66 ± 14 years, BW 67 ± 13 kg, dialytic age 68 ± 56 months) underwent for at least 6 months on-line HDF as follows: polyamide m 1.4 (24%), 1.7 (54%), 2.1 (22%) m², QB 400, QD 500 ml/min, reinfusate volume 17 ± 2 l, session length 260 ± 12 min; reinfusate and dialysate had a Ca level of 1.25 (19%), 1.5 (52%), 1.75 (29%) mmol/l. Only 41 patients (76%) received 7 ± 4 g of CaCO₃ in the interdialytic period before the meals, 30 patients (56%) received 0.9 ± 0.4 μ g/week of calcitriol per os, 8 patients (15%) 1.1 ± 0.8 g/session of phosphate salts i.v. to avoid hyposPi. 6 patients had undergone PTX. Pre-post sPi and sCa, pre sCr and sPTH, postHb were measured in a mid-week session of 2 consecutive winter months. Mean pre-post sPi was 4.9 ± 0.8 , 2.1 ± 0.4 , sCa 9.6 ± 0.5 , 10.6 ± 0.6 , sCr 8.6 ± 1.6 mg/dl; sCaxPi 47 ± 9 ; sPTH 365 ± 324 pg/ml (except PTX patients); Hb 12.1 ± 1.1 g/dl. sPi was >6 mg/dl in 1 patient, sCaxPi >60 (63 ± 1.5) in 4 patients who had sPTH (683 ± 205), sCa (10.7 ± 0.2), sPi (5.8 ± 0.1) higher than the average of all patients, on a similar dose of CaCO₃ and calcitriol; whereas PTX patients had lower sPTH (14 ± 9), sCa (9.2 ± 0.1), sPi (3.8 ± 1), sCaxPi (35 ± 8). The HDF schedule resulted in a fair sPi, using low CaCO₃ dose which also necessary to keep normal sCa. PTX should be recommended for high levels of sPTH.

New Model to Predict the Performance of High Flux Dialysers

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Purpose: Mass transfer of large solutes like β_2 -microglobulin (β_2 -M) across dialysis membranes occurs primarily by convection. High convective transport requires membranes with high hydraulic permeability. Low net ultrafiltration with a high-flux dialyzer is, therefore, a result of a balance between internal forward- and backfiltration. This effect is influenced mainly by fibre dimensions (e.g. inner diameter, length) and by the intrinsic membrane parameter hydraulic permeability. To predict both convective and diffusive transport, a model would be useful to calculate the local transport performance along the length of the fibres within the dialyzer. **Methods:** Our semi-empirical model is based on the theories of mass transfer resistances and concentration polarization. We propose to correlate the factors 'a_k' and 'b' of the dialysate Sherwood functions as follows: $Sh_{Dk}(x) = a_k Re(x)^b (d_i/x)^{1/3}$, where factor 'a_k' is specific for each solute ('k'), since the dimensionless Schmidt number is included, factor 'b', however, is influenced by dialysate flow conditions. **Results:** We validated this model in vitro with the standard high-flux dialyser Gambro-Polyflux 24S and found an excellent correlation for creatinine and cytochrome C (submitted to J Mem Sc). In a clinical study with modifications (inner diameter of fibres, hydraulic permeability, packing density, cut-off) of the standard dialyzer Polyflux P24S, the respective effects on total removal of β_2 -M were analyzed. We found that β_2 -M clearance increased, with diminished fiber inner diameter and higher hydraulic permeability. Fitting these in-vivo experimental results with our model by adjusting the fluid data to that of whole blood, we found a good correlation ($r = 0.992$). **Conclusion:** This newly developed model extends previously published ones and allows to predict local transport and clinical performance data.

Effects of Low Dose of Simvastatin on Increased Levels of C-Reactive Protein (CRP) in Hypercholesterolemic Hemodialysis Patients

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Recent study has showed a short-term cholesterol-independent effect of simvastatin on reduction of CRP levels in hemodialysis patients. The aim of our study was to evaluate the long-term effects of simvastatin on increased CRP levels in aspirin-free hypercholesterolemic hemodialysis patients. The effects of low dose of simvastatin (10 mg/day p.o.) (nephelometric method: range <0.8 mg/dl) have been studied in 11 hypercholesterolemic patients with increased basal levels of CRP (group A), while 17 untreated normocholesterolemic hemodialysis patients with increased CRP levels were considered as

control group (group B). Exclusion criteria were presence of permanent venous catheter, chronic inflammatory or neoplastic diseases, aspirin and antilipidemic drugs or drugs that modified lipid levels. CRP, total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglyceride (TG) and albumin (Alb) levels were measured every three months during one year. The results after one year of observation expressed as mean \pm SD, and p value (less than 0.05 considered to be statistically significant using Student's test), were:

	T:0	T:12	p
<i>Group A</i>			
CRP (mg/dl)	3.33 \pm 3.41	0.63 \pm 0.2	<0.005
TC (mg/dl)	227 \pm 21	177 \pm 26	0.006
HDL-C (mg/dl)	35 \pm 10	47 \pm 11	0.004
LDL-C (mg/dl)	112 \pm 33	96 \pm 29	NS
TG (mg/dl)	205 \pm 57	168 \pm 87	NS
Alb (g/dl)	3.5 \pm 0.2	3.8 \pm 0.2	0.06
<i>Group B</i>			
CRP (mg/dl)	1.96 \pm 1.36	1.36 \pm 0.6	NS
TC (mg/dl)	152 \pm 34	151 \pm 23	NS
HDL-C (mg/dl)	29 \pm 11	34 \pm 14	NS
LDL-C (mg/dl)	104 \pm 47	98 \pm 25	NS
TG (mg/dl)	162 \pm 107	175 \pm 81	NS
Alb (g/dl)	3.5 \pm 0.2	3.5 \pm 0.2	NS

Our preliminary results confirm literature data, on long-term effects of statin on reduction of CRP levels and on increasing of HDL-C levels in hemodialysis patients. We have not observed statistically significant modifications of TG, LDL-C levels while we have observed a mild but not significant modifications of albumin levels. Low doses of statins reduce cholesterol levels in treated patients. Our conclusions are that simvastatin can reduce the increased CRP levels in hemodialysis patients.

Associations between Dialysate CA125, IL-6 and VEGF in a Longitudinal Study

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CA125 is a marker of mesothelial cell mass and of remesothelization, and the mesothelium is capable of secreting various cytokines and growth factors in vitro. The clinical relevance of these findings is unknown. To evaluate the associations between CA125, vascular endothelial growth factor (VEGF), interleukin-6 (IL-6) and peritoneal solute transport rate (PSTR; 4-hour D/Pcreat), we studied 31 patients in the first month of PD and after 12 \pm 2 months of PD. PSTR (0.67 \pm 0.19 vs. 0.80 \pm 0.12; $p = 0.001$) and IL-6 (63 pg/min; 20–603 pg/min vs. 107 pg/min; 19–546 pg/min; $p < 0.01$) increased over time. There was a correlation between CA125 and VEGF at baseline ($Rho = 0.54$; $p < 0.005$), whereas after 1 year there were correlations between CA125 and VEGF, and CA125 and IL-6 ($r = 0.59$, $p < 0.005$, and $r = 0.79$, $p < 0.0001$). After 1 year VEGF was

correlated with IL-6 ($r = 0.64$; $p < 0.0001$). Changes in CA125 correlated with changes of VEGF and IL-6 ($r = 0.53$, $p = 0.01$, and $r = 0.49$, $p < 0.05$, respectively). Besides a correlation between IL-6 and D/Pcreat at baseline ($r = 0.66$; $p < 0.0001$) no other correlation between the effluent markers and PSTR were found. Our study suggests that mesothelial cells produce growth factors and cytokines *in vivo*, and/or that inflammation can result in a high turnover or breakdown of mesothelial cells.

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Asymptomatic Ischaemic Heart Disease in Peritoneal Dialysis (PD) Patients – A Need for Invasive Approach

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Coronary artery disease (CAD) is the most frequent reason of death of PD patients in Poland. There is a need for creating and implementing a standard of diagnostic and therapeutic interventions in this group of patients. We have followed 15 of our PD patients who underwent coronary angiography. There were 12 M, 3 F, aged 35–70 (mean 56) years, 22 ± 18 months on dialysis. 4 of them were diabetics. Only one third of them presented symptoms of angina, in the majority CAD was suspected because of pathology in the resting ECG and/or echocardiography. Nine patients underwent exercise testing, but more than 50% of the results were non-diagnostic due to impaired overall exercise capacity and not achieving heart rate limits. Dobutamine stress testing performed in 4 patients showed variable results. Coronary angiography detected multiple lesions in two thirds of patients. As a result, 6 patients underwent coronary artery bypass graft (CABG), 2 percutaneous coronary angioplasty (PTCA) and 3 PTCA with stent implantation. All patients except one continued PD treatment peri- and postoperatively. One CABG patient died during the perioperative period. The mean time of observation without symptoms of CAD is 15.5 months. Conclusions: PD patients frequently present with asymptomatic CAD. Coronary angiography appears to be a reliable procedure to diagnose these patients. Invasive therapeutic approach should be implemented as the short- and long-term outcome seems to be satisfactory.

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Plasma Levels of von Willebrand Factor (vWF), Metabolic Disorders and Inflammation Markers in Peritoneal Dialysis (PD) Patients

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The plasma levels of the vWF adhesion protein reflect endothelial dysfunction and, in some studies, are an independent predictor of coronary artery disease. The aim of the study was (1) to determine whether or not there is a difference in vWF levels between PD patients with ESRD with and without diabetes mellitus (DM), and (2) to identify the factors affecting vWF levels. The plasma levels of vWF (ELISA, Imubind vWF, American Diagnostica Inc.) differed significantly among the 21 healthy individuals, 11 non-DM patients, and 10 DM patients (Kruskal-Wallis test, $p < 0.001$). Compared with healthy individuals (740.0 mU/ml, median), the levels were significantly higher both in non-DM patients on PD (1,977 mU/ml; $p < 0.001$, Wilcoxon's test), and in DM patients on PD (1,992 mU/ml; $p < 0.001$). The difference between DM and non-DM patients showed significantly positive correlation with serum urea, creatinine, phosphates, $Ca \times P$ product, CRP, homocysteine, iPTH, glycemia, C peptide, insulin, triglycerides, fibrinogen, white blood cell count, and a negative correlation with serum albumin, HDL-cholesterol, apolipoprotein AI and hematocrit. Stepwise regression analysis revealed vWF levels are best predicted by the presence of ESRD treated with PD ($p < 0.01$, partial correlation 0.44) regardless of the presence or absence of DM. Conclusions: The plasma levels of vWF are significantly increased in ESRD patients treated by PD. There is no difference between patients with and without DM. vWF levels correlate with metabolic disorders characteristic of ESRD and inflammation markers.

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Pulse Wave Velocity (PWV) in Diabetic and Non-Diabetic Patients on Long-Term Peritoneal Dialysis (PD)

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PWV reflecting the elasticity and stiffness of the large arteries is regarded, in various populations, as a marker of atherosclerosis and cardiovascular disease in diabetics (DM) and non-diabetics (nonDM) on PD, and (2) determine the relationship between PWV and some factors potentially affecting the development of atherosclerosis in these patients. Aortic PWV (measured between carotid and femoral artery) was investigated non-invasively using a Sphygmocor system (PWV Medical Ltd., Sydney, Australia) with the pencil-like Millar pressure tonometer in 11 nonDM patients on PD, 10 DM patients on PD, and in 21 healthy individuals. Aortic PWV differed

significantly among the three subgroups investigated ($p < 0.01$; Kruskal-Wallis test). PWV was significantly higher in DM (12.0 m/s; $p < 0.01$, median, Wilcoxon's test) as well as in nonDM (9.2 m/s; $p < 0.05$) patients compared with a control group of healthy individuals (6.5 m/s). Univariate analysis (Spearman's test) revealed a significant direct correlation of aortic PWV with age, BMI, blood pressure, serum urea levels, creatinine, phosphate, $\text{Ca} \times \text{P}$ product, iPTH, glycemias, glycosylated hemoglobin, C peptide, total homocysteine, insulin, fibrinogen, and white blood cell count; and an inverse correlation with albumin, HDL cholesterol, and hematocrit. Using stepwise regression analysis, PWV can be predicted by a linear combination of age ($p < 0.001$; partial correlation coefficient 0.60) and serum urea ($p < 0.001$; 0.70). Conclusion: DM and nonDM patients treated by long-term PD show higher pulse wave velocity and, hence, lower aortic elasticity and higher stiffness compared with healthy individuals. These changes depend primarily on age and serum urea levels.

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A Novel Salvage Technique to Exit-Site Infection That Does Not Require Catheter Removal

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Purpose: We are doing the partial substitution and the catheter exit-site partial exchange for the rescue of an infected PD catheter. Method: The PD exit-site was first incised in a spindle-shape and a further incision was made right above the outer cuff and the catheter. The outer cuff and the extraperitoneal part of the catheter is dissected and removed with infected tissue. Otherwise, a new extraperitoneal catheter is connected to the remaining part of the old catheter. A new exit-site was then made using the tunneler and the titanium extender was fixed to the abdominal wall fascia with nylon thread in such a way that the extender was not excessively bent. Results: This salvage technique has been performed twenty-two times in 22 patients. Only one patient developed a recurrent tunnel infection with the same strain (*Pseudomonas aeruginosa*) after a period of four months. Conclusion: This technique can be performed in cases of persistent exit-site infection or tunnel infection that is limited to the outer cuff without the discontinuation of PD therapy. We believe that this technique is useful and efficacious in such problematic patients.

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The Clinical and Pharmacological Effectiveness of Hemoperfusion in the Management of Acute Theophyllin Poisoning

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Purpose: In order to clarify the clinical and pharmacological effects of direct hemoperfusion (DHP) in three episodes of two patients with severe acute theophyllin poisoning, we retrospectively analyzed the clinical course and the pharmacokinetics of theophyllin removal via DHP. Methods: DHP was begun for 3 to 6 h, using a double-lumen femoral catheter, a DHP-1® cartridge (Kuraray, Japan) on a KM-8500 dialysis machine (Japan), with a constant blood flow rate (QB) of 150 ml/min. We observed the clinical course of consciousness level, blood pressure, heart rate and so on. The plasma theophyllin levels were determined both at inflow (Ci) and outflow (Co) of the cartridge. The hemoperfusion cartridge extraction fraction (EF = $100 [C_i - C_o]/C_o$) and theophyllin clearance ($K = \text{QB} \times \text{EF}$ ml/min) were continuously calculated. Results: (1) The plasma theophyllin levels fell rapidly from 150.9 to 60.4 µg/ml, 134.0 to 46.2 µg/ml and 287.6 to 63.0 µg/ml, respectively. (2) EF and K at 1, 2, 3 and 6 h after DHP had been started ranged from 0.944 to 0.960 and from 144.0 to 159.0 ml/min, respectively. (3) At the end of DHP, the clinical findings such as hypotension, tachycardia and alimentary tract disorders had markedly improved in all cases. Conclusion: The results indicated that DHP was quite an effective and useful extracorporeal elimination technique for both the improvement of clinical outcome and the clearance of toxins in the treatment of severe acute theophyllin poisoning.

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Evaluation of New Algorithms for the Estimation of Continuous Systolic Blood Pressure Using Electrocardiogram and Pulse Oximeter on Hemodialysis Patients

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Purpose: Blood pressure (BP) significant varies during hemodialysis. Continuous estimation of blood pressure might be very useful for the management of the hemodialysis patients. We evaluated the new algorithms for the estimation of systolic BP (Esys) using electrocardiogram and pulse oximeter (SpO_2) with the invasive blood pressure measurements (Isys). Methods: Isys and Esys by the new algorithm was measured during hemodialysis data of Isys, Esys and non-invasive BP (NIBP) data were stored in external MO disk drive. Automatically identified significant cardiovascular change identified by Esys (HASTE trigger) were compared by those by Isys. Results: Esys was correlated to Isys ($r = 0.79$). HASTE trigger provided time-

ly marker of blood pressure events in the cardiovascular system. When the systolic blood pressure was under 90 mm Hg, blood pressure change rate was $28.3 \pm 8.3\%$ in Esys, $27.9 \pm 8.7\%$ in Isys, and $46.1 \pm 2.2\%$ in NIBP. When the systolic blood pressure was in the range of 100 to 180, they were $25.0 \pm 0.0\%$ in Esys, $25.3 \pm 12.4\%$ in Isys, and $20.5 \pm 11.5\%$ in NIBP. Conclusion: Esys estimated by new algorithm was the reliable estimation of the blood pressure events of patients during hemodialysis therapy.

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Statins Reduce Tissue Injury in Acute Ischemia Reperfusion Injury in Rat Kidneys

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It has been shown that apart from lipid lowering effects HMG CoA reductase inhibitors (statins) have direct effects on signaling events in cell culture. We tested the hypothesis that statins reduce inflammatory responses caused by ischemia reperfusion (I/R) injury the rat kidney by direct cellular effects. Male Sprague-Dawley rats were pretreated with 0.5 mg/kg Cerivastatin over a period of 3 days. Renal ischemia reperfusion (I/R) injury was induced by clipping the left renal artery for 45 min, meanwhile the right kidney was removed. Animals were sacrificed 24 h after operation and kidneys were examined immunohistologically for infiltrating cells, adhesion molecules and MAP kinase activation (ED-1, ICAM-1, Erk1/2). NF kappa B DNA binding assay was performed. Plasma creatinine was measured spectrophotometrically. I/R injury caused a 7.5-fold increase in creatinine levels within 24 h. Pretreatment with Cerivastatin reduced the creatinine elevation by 40%. The same effects were seen when glomerular filtration rate was measured, statins ameliorated renal function after IR injury. The inflammatory reaction was significantly reduced, monocyte and macrophage infiltration was almost completely abolished. The upregulation of Erk1/2 and ICAM-1 was greatly diminished. NF kappa B DNA binding activity was partially reduced compared to placebo-treated animals. Short-term Cerivastatin treatment ameliorated renal function after I/R injury in rats by reducing cell infiltration, inhibiting the upregulation of Erk1/2 and of adhesion molecules due to direct cellular effects of statins.

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Asymmetric Dimethylarginine Is a Potent and Long-Lasting Endogenous Inhibitor of Nitric Oxide Synthase

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Increased blood concentrations of asymmetric dimethylarginine (ADMA), i.e. an endogenous nitric oxide (NO) synthase inhibitor, have been linked to hypertension and to excess cardiovascular morbidity and mortality. A direct biological action of ADMA in humans has not, however, been documented so far. We assessed the effect of escalating intravenous ADMA doses on renal perfusion and NO production in healthy subjects. In addition, the effect of ADMA was compared with that of L-NAME, a potent NO synthase inhibitor with a long-lasting action. We observed a definite effect on renal perfusion, that is on effective renal plasma flow (ERPF), with an ADMA infusion rate of 0.075 mg/kg/min which yielded plasma levels above 10.0 $\mu\text{mol/l}$. Both with infusion of 3.0 mg L-NAME/kg/min and 0.25 mg ADMA/kg/min ERPF decreased significantly (placebo: from 665 ± 38 to 668 ± 41 ml/min/1.73 m²; L-NAME: from 668 ± 30 to 594 ± 31 ; ADMA: from 669 ± 34 to 600 ± 25 ; both $p < 0.01$ vs. placebo). In addition, urinary excretion of cGMP, i.e. an indicator of NO production, decreased significantly with infusion of both NO synthase inhibitors. Thus, a comparable effect on renal perfusion and NO production was achieved with a more than 10 times smaller dose of ADMA. Similarly as with L-NAME the effect of ADMA on renal perfusion was sustained due to a relatively long plasma half-life that was calculated from the plasma ADMA concentration decay profiles in healthy volunteers. Asymmetric dimethylarginine is a potent inhibitor of NO synthase with a long-lasting action. Thus chronically elevated ADMA blood levels may contribute to vascular damage and cardiovascular morbidity via perpetuating endothelial injury.

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Asymmetric Dimethylarginine, Renal Perfusion, and Blood Pressure in the Elderly

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Reduced availability of nitric oxide (NO) is thought to contribute to the age-associated increase of renovascular tone and blood pressure. The link between the endogenous NO-synthase inhibitor asymmetric dimethylarginine (ADMA) with changes of renal hemodynamics in the elderly has not, however, been elucidated so far. We assessed blood concentrations of L-arginine, dimethylarginine and homocysteine, as well as renal hemodynamics comparing young ($n = 24$, 13 m, 25 ± 2 years) and elderly ($n = 24$, 13 m, 69 ± 6 years)

healthy normotensive subjects, and elderly patients with essential hypertension ($n = 24$, 13 m, 70 ± 5 years). Mean plasma ADMA concentration was significantly higher ($p < 0.01$) in elderly ($2.77 \pm 0.61 \mu\text{mol/l}$) than in young ($1.30 \pm 0.32 \mu\text{mol/l}$) healthy normotensive subjects, and it was even markedly higher in the hypertensive elderly ($3.53 \pm 0.68 \mu\text{mol/l}$; $p < 0.01$ vs. both groups). In contrast, mean plasma concentrations of the biologically inactive stereoisomer symmetric dimethylarginine (SDMA), L-arginine and homocysteine were similar in all three groups studied. Plasma ADMA levels were strongly correlated with age ($r = 0.79$, $p < 0.001$), effective renal plasma flow ($r = -0.78$, $p < 0.001$), filtration fraction ($r = 0.79$, $p < 0.001$), calculated renovascular resistance ($r = 0.71$, $p < 0.001$), and blood pressure ($r = 0.61$, $p < 0.005$), but not with body weight ($r = 0.07$, $p = 0.57$). In contrast to ADMA, plasma SDMA concentrations did not correlate with any of these variables. Multiple regression analysis revealed that age and ADMA were independently related to effective renal plasma flow, whereas only ADMA was independently related to blood pressure. Plasma ADMA concentrations are markedly increased in the normotensive elderly and particularly in the elderly patient with essential hypertension. Plasma ADMA concentrations correlate significantly with effective renal plasma flow and with blood pressure. Thus, accumulation of this endogenous NO-synthase inhibitor with senescence may be involved in the reduction of renal perfusion and increase of blood pressure.

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Evaluation for Diagnosing Blood Vessels Using a Fast Three-Dimensional (3-D) Ultrasound Imaging System in Hemodialysis Patients

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Objectives: In this study we evaluated the efficacy of a fast 3-D ultrasound imaging system in HD patients. **Materials and Methods:** Five HD patients with hemodialysis access failure were enrolled in this study. Mean age was 43.6 years, with 3 males and 2 females. We have observed 3-D ultrasound images of vessels in 5 HD patients using an ultrasound data acquisition system (SSD-1000, Aloka). In the system, an ultrasonic probe is automatically scanned along the forearm of the patient in a constant speed. At the same time of the scanning, vessel portions are extracted from the acquired echo signals and 3-D images of the vessels are rendered to display with volume rendering technology in real-time. After 3-D ultrasound images were observed, an intra-arterial digital subtraction angiography (IADSA) was also examined in all HD patients. 3-D ultrasound images were compared with IADSA in 1 cm interval. **Results:** All patients had a stenosis of an artery-vein (A-V) anastomosis. Out of 5, 3 patients had a vein stenosis, too. One patient had an artery stenosis because of arteriosclerosis. In 4 HD patients percutaneous transluminal angiography (PTA) was performed at the same time. One patient was not able to perform PTA because of severe blood vessel stenosis. The total number of 148 points in 1 cm interval in all patients compared between 3-D ultrasound images and IADSA. Out

of 148 points, 145 points (98.0%) were detected in a vein by 3-D ultrasound imaging system. Although 17 points were detected in vein stenosis by 3-D ultrasound imaging system, actually 12 points (70.6%) were detected in vein stenosis by IADSA. **Conclusion:** 3-D ultrasound imaging system seemed to be effective for screening of a vein stenosis and management of blood vessels in HD patients.

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Interleukin-6 System Is Associated with Renal Function in End-Stage Renal Disease (ESRD)

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ESRD patients present signs of inflammation, but it is not clear if the impairment of renal function per se is involved in the genesis of the pro-inflammatory milieu. To analyze the relationship between the IL-6 system and GFR, we studied 179 ESRD patients. GFR was evaluated close to the initiation of dialysis ($6.7 \pm 0.2 \text{ ml/min}$) and after 1 year in a subgroup ($n = 31$). Progression rate was estimated by the slope of the curve generated by $1/\text{creatinine}$ (median of 9 determinations), during the prior 12 months in 78 patients. IL-6 ($n = 142$) and its soluble receptor (sIL-6R; $n = 118$) were measured using ELISA. Negative correlations were noted between GFR and IL-6 in the cross-sectional analysis ($\text{Rho} = -0.18$; $p < 0.05$), and the progression rate was correlated to sIL-6R ($\text{Rho} = 0.27$; $p < 0.05$). IL-6 increased over time (6.4 pg/ml ; $0.1\text{--}45 \text{ pg/ml}$ vs. 9.9 pg/ml ; $2.2\text{--}20 \text{ pg/ml}$; $p < 0.001$). Although sIL-6R did not increase significantly during the follow-up, changes in sIL-6R were associated with changes in GFR ($\text{Rho} = 0.57$; $p < 0.05$). These results suggest that GFR is linked to systemic inflammation. The IL-6 system may play a role in the progression of renal disease, or reflect deterioration of the kidney capacity to eliminate cytokines. These mechanisms may contribute to the association between GFR, inflammation, and high mortality in ESRD.

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The Results of Patients with History of Positive Anti-Donor Antibody (ADA) after Living Related Renal Transplantations

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Objectives: To study the relevance of transient anti-donor antibody (ADA) to the graft survival after living renal transplantations, we retrospectively examined the short- and long-term results of 1,333 recipients who underwent living donor kidney transplantations at our institution between 1983 and 2001. **Materials:** The subjects

included patients with no history of ADA-positive (n = 1,221, group 1) and patients with a history of ADA-positive (n = 112, group 2). Patients who were ADA positive for both donor T and B cells by cytotoxic assay were judged as ADA-positive patients. All patients received renal transplantations after the conversion of ADA to negative just before surgery. Results: The patients' survival rate in group 2 was not significantly different from that in group 1. The graft survival rate in group 2 was less than that in group 1. During short-term follow-up of 7 days, the rate of accelerated acute rejection after renal transplantation was 32% (36/112) in group 2, but only 14% (177/1,221) in group 1 patients. After the long-term follow-up at least 10 months, the frequency of chronic rejection was more in group 2 (29/112, 26%) than that in group 1 (248/1,221, 20%). Renal biopsy showed accelerated acute and chronic rejection in the biopsy specimens. Conclusions: This study demonstrated that the rate of graft survival in ADA-positive patients was less compared with that in ADA-negative patients. In particular, these patients should be monitored for the detection for ADA during the early time after transplantation.

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Acute Rejections Occur Most Often during the First 6 Months after Renal Transplantation and May Promote the Development of Later Chronic Allograft Nephropathy (CAN). In Order to Identify Early Transplant Changes, We Established a Protocol Biopsy Program

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Since December 2000 we have performed 318 routine protocol renal allograft biopsies on a day-care basis in 139 patients at 6, 12 and 26 weeks after renal transplantation (B1 n = 120, B2 n = 115, B3 n = 83). The biopsy was followed by 4-hour bed rest and renal allograft ultrasound. Biopsies were analysed using light microscopy, immunohistochemistry, microdissection and quantitative RT-PCR. The patient acceptance rate of the program was 96%. We found acute interstitial rejection in 21/139 patients (15%), with a creatinine increase in only 4 cases; borderline changes in 57 patients (41%), with a creatinine increase in 5 cases, and acute tubular changes in 73 patients (53%). Chronic tubulo-interstitial changes were seen in 75 patients (54%). Acute rejections were found most often in the first of the 3 biopsies (16 vs. 8 vs. 7%, n.s.), while chronic changes were most often found in the third biopsy (4 vs. 15 vs. 53%, p < 0.0001). All patients with acute rejection and those with borderline changes accompanied by creatinine increase were treated with steroid boli. Four patients with biopsy complications had to be observed overnight (protracted vasovagal reaction 2, perirenal hematoma 1, macrohematuria 1). Other complications were slight macrohematuria 4, small hematoma 11, and small av-fistula in ultrasound 34. Outpatient protocol renal allograft biopsies can be performed safely and

result in diagnosis of clinically silent acute rejection episodes. Early treatment of infiltrates may interfere with the pathophysiologic mechanisms of chronic allograft nephropathy.

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Platelet Purine and Pyrimidine Nucleotides in Chronic Renal Failure

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Purpose: The aim of this study was to examine the concentration of purine and pyrimidine nucleotides in human platelets and to determinate the impact of treatment method on their concentration. We studied 79 patients: 20 CRF treated conservatively (CRF-C), 28 hemodialysed (CRE-HD), 31 after renal transplantation (16 azathioprine treated, 16 mycophenolate mofetil treated). Methods: Anion exchange high performance liquid chromatography technique, which differentiates between purine and pyrimidine ribonucleoside triphosphates, was used to quantify platelets nucleotide pools. Results: Concentration of nucleotides in platelets from CRF-HD patients was higher (p < 0.05) than in other groups. We also observed reduction of adenine and guanine nucleotides concentration in both transplanted groups comparing CRF-HD patients (p < 0.05). There were no differences in UTP and CTP concentrations between groups. We found higher (p < 0.05) mean platelet volume (MPV) in CRF-HD group which correlates with measured nucleotide levels. No correlation was found between measured nucleotide concentrations and sex, time of treatment, serum urine and creatinine levels as well as with immunosuppressive drug cumulative dose. Conclusion: Higher platelet concentration of adenine and guanine nucleotides in hemodialysed patients was shown. It may depend on the higher MPV value of platelets in that group. There is no clear consensus if reduction of adenine and guanine nucleotides concentration in both transplanted groups depends on immunosuppressive regimen.

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Dose Capabilities of Renal Replacement Therapies in Acute Renal Failure (ARF)

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Based on recent clinical outcome data, dialysis dose delivery in ARF is likely to increase. Using kinetic modeling, we compared small solute and middle molecule dose capabilities of three approaches: CVVH; slow low efficiency dialysis (SLED), and intermittent HD

(IHD). For a 70 kg patient (10 l initial volume excess; nPCR, 1.8 g/kg/day), concentration profiles of urea, inulin, and β 2-microglobulin (β 2M) were modeled and time-averaged concentrations (TAC) and equivalent renal clearances (EKR) determined. The following was assumed: initial BUN, 90 mg/dl; initial inulin/ β 2M concentration, 100/20 mg/l; inulin/ β 2M generation rate, 0.3/0.17 mg/min (former simulated by continuous infusion), and β 2M non-renal clearance, 3 ml/min. CVVH, at an ultrafiltration rate of 3 l/h, was modeled by direct quantification (Clar, JASN 1997) while a two-compartment variable volume model (Clark, JASN 1999) was used for both SLED and IHD, with treatment characteristics very closely following those reported by Marshall (AJKD 2002) and Schiffl (NEJM 2002). The TAC/EKR values (TAC in mg/dl for BUN and mg/l for inulin and β 2M; EKR in ml/min) were:

	CVVH	SLED	IHD
Urea	40.3/33.8	43.4/31.3	64.6/21.1
Inulin	25.4/11.8	99.4/3.0	55.5/5.4
β 2M	9.4/18.2	40.3/4.2	24.2/7.0

Relative to SLED and IHD, effective small solute clearance in CVVH was 8% and 60% higher, respectively. These differences were more pronounced for the middle molecule (MM) surrogates, determined to have an effective clearance in CVVH approximately 2-fold and 4-fold greater than the corresponding values in IHD and SLED, respectively. In conclusion, small solute dose capabilities for both CVVH and SLED greatly exceed those achieved even by daily IHD. The superior MM removal for CVVH is due to the powerful combination of convection and continuous operation.

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Determinants of Effective Treatment Dose in CVVH

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Recent clinical data (Ronco, Lancet 2000) indicate both treatment dose, based on normalized ultrafiltration rate (Qf), and timing of treatment initiation, based on initial BUN (BUN_i), influence survival in critically ill patients treated with CVVH. We assessed the effect of changes in these parameters and in the degree of hypercatabolism on effective treatment dose for simulated patients (dry weight, 70 kg; initial volume excess, 10 l) treated with CVVH. Concentration profiles over a 1-week period were generated using a direct quantification method (Clark, JASN 1997) over Qf, BUN_i, and nPCR ranges of 1.5–3.5 l/h (21–50 ml/h/kg), 50–150 mg/dl, and 1.4–2.2 g/kg/day, respectively. The time-averaged concentration (TAC) from each profile, along with the urea generation rate (G), were used to determine the equivalent renal clearance (EKR = G/TAC). The TAC (mg/dl)/EKR (ml/min) values were (BUN_i; mg/dl; nPCR: g/kg/day; # nPCR = 1.8 g/kg/day; *: BUN_i = 90 mg/dl):

Qf (l/h)	BUN _i = 50#	BUN _i = 100#	BUN _i = 150#
1.5	58.5/23.3	69.4/19.6	80.3/17.0
2.0	47.6/28.6	56.2/24.2	64.7/21.0
2.5	40.5/33.7	47.6/28.6	54.7/24.9
3.0	35.4/38.4	41.6/32.8	47.7/28.6
3.5	31.7/43.0	37.1/36.7	42.6/32.0

Qf (l/h)	nPCR = 1.4*	nPCR = 1.8*	nPCR = 2.2*
1.5	55.6/18.5	67.2/20.3	78.9/21.5
2.0	44.9/22.9	54.5/25.0	64.0/26.5
2.5	38.0/27.1	46.2/29.5	54.3/31.2
3.0	33.2/31.0	40.3/33.8	47.5/35.7
3.5	29.6/34.7	36.1/37.8	42.5/39.9

In conclusion, the EKR approach, by accounting for non-steady-state effects, provides a time-integrated estimate of effective CVVH dose in ARF.

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Blood Purification in Septic Shock: Preliminary Results Obtained with Coupled Plasma Filtration Adsorption (CPFA)

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Sepsis is the leading cause of acute renal failure and mortality in intensive care units (ICU). In physiological conditions, the biological activity of sepsis-associated mediators is under control of specific inhibitors that may act at different levels. With the progression of sepsis, and in septic shock, this homeostatic balance becomes altered; therefore the pathogenesis of sepsis might be described as a severe unbalance between pro- and anti-inflammatory factors in the host. So far, the development of the clinical picture of septic shock implies, from one side, the release of inflammatory mediators with systemic effects as endothelial damage, loss of permselectivity and vasoparalysis while, on the other hand, the lympho-monocytes show a decreased capacity to produce imcytokines. Since continuous therapies remove cytokines and inflammatory mediators, we applied CPFA for the unselective removal of mediators. CPFA is a two-step, modular system composed of plasma separation and adsorption on a hydrophobic resin, with final reinfusion of the plasmafiltrate into the patient's line before the hemofilter. Six patients, 4 males and 2 females (mean age 53.6 ± 18.2 years), all on mechanical ventilation, with a clinical picture of septic shock, underwent a mean of 9.6 ± 1.6 CPFA treatments (range 7–12, total 59 sessions). All patients presented a picture of MODS, with 3.2 ± 1.6 organs involved. The Apache II score before treatments was 24.5 ± 6.2, after 13.3 ± 4. Four patients had quite normal renal function. All patients but one were discharged from ICU after 34 ± 14.3 days (range 18–57). Labo-

ratory data showed a sharp decline of C-reactive protein along the treatment time from 30 ± 10.2 to 7.2 ± 4.3 mg/dl (-76%); data concerning IL-6, IL-10 and sICAM-1 showed, respectively, a reduction to 2.8, 36.6 and 69.2% in respect to pre-treatment values. No relevant technical failure occurred. In 15 cases (25%) the session had to be prematurely stopped (planned duration of the session: 10 h; real duration: 8.8 ± 1.5 h). Fifty-two treatments (88%) were run with unfractionated heparin (mean dose: $1,132 \pm 477$ units/h). These preliminary results underlie that CPFA is a feasible and safe treatment; it allows the unselective removal of sepsis-associated mediators, therefore avoiding dangerous peak levels and achieving a significant attenuation of the acute-phase response. Taking into consideration the high mortality rate of ICU-hospitalized septic patients, this procedure might be beneficial in improving the outcome unrelated to the presence of acute renal failure.

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Impact of Preparation Technology on Water Quality and Surrogate Parameters for Microinflammation and Outcome in ESRD Patients New on Dialysis

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There is an ongoing debate on the impact of water quality on morbidity and mortality of hemodialysis patients, esp. in relation to cardiovascular complications being closely linked to chronic inflammatory process. Bacterial products in water used for preparation of dialysis fluid have been identified as one possible source of chronic inflammatory stimuli. Therefore, we investigated whether the level of microinflammation can be influenced by technical measures, e.g. installing a new water processing system (CWP 100, Gambro), which is designed to prevent bacterial growth in the system by heat disinfection. 31 ESRD patients (58 ± 15 years, 13 female, 14 diabetics) entering a new dialysis clinic were followed for 12 months after start of hemodialysis treatment. Pre-dialysis plasma samples taken 1 week before (A) entering the clinic, 1 week, (B), 3 (C), 6 (D), 9 (E) and 12 months after (F), were analysed by specific high-sensitive ELISA for C-reactive protein (CRP 0.1 to 50 mg/l) and standard ELISA for β 2-microglobulin (β 2M, Immunodiagnostik, Germany). Absence of bacterial growth was confirmed by microbiological cultures and endotoxin analysis. Data of an intermediate analysis are reported here (means \pm STD (n) in mg/l); * $p < 0.05$ vs. A (paired t test). CRP: A 10.3 ± 11.2 (31); B 8.2 ± 10.8 (29); C $3.6 \pm 4.7^*$ (28); D 5.3 ± 5.8 (25); E 5.5 ± 5.4 (15); F $4.9 \pm 5.8^*$ (14). β 2M: A 14.2 ± 9.6 (31); B 15.0 ± 11.6 (30); C 15.8 ± 7.5 (28); D 16.3 ± 9.1 (25); E $17.8 \pm 10.2^*$ (15); F 19.0 ± 7.7 (14). After an initial drop after 3 months CRP levels remained constant at significantly lower level. β 2M slightly increased, probably due to loss in residual diuresis. Avoiding bacterial growth in water systems for dialysis fluid preparation has a significant impact on a low level of micro-inflammation as assessed by CRP in ESRD patients new on hemodialysis.

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Clinical Effects of Ultrapure Dialysate Made on Photocatalyst – A Report of New Technique

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Purpose: Photocatalyst is already used to resolve organic matters in various fields today. We applied this capability to make ultrapure dialysate for the first time, and report the result beyond our anticipation. Objects and Methods: Objects were 44 outpatients on chronic hemodialysis. We tried the new sterilization equipment with photocatalyst produced by Lizer Industries, Co., Ltd. and Mitsubishi Rayon Engineering Co., Ltd. in Japan and set it at exit-site of RO (reverse osmosis) equipment. Then we measured the concentration of endotoxin (ET) in dialysate and followed changes of clinical data. Results: Concentrations of ET were reduced through the equipment (average; 12.3 to 4.1 EU/l). Hematocrit (Hct) was increased (30.2 ± 3.9 to $33.6 \pm 2.2\%$) and concentration of beta 2 microglobulin (B2MG) was decreased (33.7 ± 7.9 to 30.2 ± 6.0 mg/dl) significantly ($p < 0.0001$) after setting of the equipment in four weeks. Concentrations of serum ferritin, serum Fe, transferrin saturation and average dose of recombinant human erythropoietin that had been required were decreased ($1,885 \pm 1,038$ to $1,680 \pm 975$ U/hemodialysis) and the count of erythrocytes was not changed. Conclusion: Considering the increase of Hct and the decrease of B2MG in short time, we presumed that half-life times of erythrocytes had been prolonged and the haematogenesis had been arisen with the ultrapure dialysate produced on the photocatalyst.

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Self Reversed Parallel Wire Technique for Dilating Unyielding Stenosis in Native Dialysis Fistulas

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Purpose: To dilate a severe stricture of dialysis fistula, the effectiveness of Self reversed parallel wire technique (SRPWT) that we designed is examined. Methods: A sheath of the required size was inserted, through which the flexible tipped guide-wire tip was passed. The tip was then turned in a 180-degree curve by pushing the tip against the region of blood bifurcation, or stricture. Next, the operator facilitated the reversal of the tip until the wire's reversed part became longer than the balloon length, by pressing the vessel from the body surface with the operator's fingers support. Then the catheter was pushed ahead, carefully, over the wire so that the guide-wire reversal would not be released. Results: In 22 cases in which this technique was applied, a good dialysis fistula dilatation was obtained. And all cases had sufficient blood flow (over 220 ml/min) on next hemodialysis. Conclusion: It is reported here that Self reversed parallel wire technique, an improvement of the conventional method, was effective in coping with even rigid strictures that could not be

dilated with the usual high-pressure resistant balloon method. It is possible to perform this modified procedure easily, safely and inexpensively. We therefore expect that this modification will come into routine clinical use. It is well worth trying this method before giving up on rigid strictures on which the usual techniques would fail.

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Continuous Plasmapheresis May Prevent Chronic Renal Failure in Familial Atypical Hemolytic Uremic Syndrome

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Background: Familial atypical hemolytic uremic syndrome (D-HUS) is a rare cause of HUS in children which is claimed to lead to end-stage renal failure (ESRF) despite plasmapheresis. **Case Report:** Tessa had already 2 sisters presenting with ESRF due to D-HUS. In the family, neither complement factor H, nor von Willebrand factor-cleaving protease deficiency was found. The older sister presented with an immediate relapse after transplantation leading to graft loss. She was never treated with plasmapheresis. In Tessa's identical twin, plasmapheresis was started at a GFR of 25 ml/min/1.73 m³ but was interrupted after 14 daily sessions because of lack of GFR improvement. Four months later ESRF was reached. When D-HUS was also diagnosed in Tessa 1 year later (GFR 30 ml/min/1.73 m²), intensive plasmapheresis was immediately initiated. Daily sessions (40 ml/kg fresh frozen plasma/exchange) were performed until normalization of hemolysis parameters and platelets count (2 weeks) and were progressively reduced to one session every two weeks which was pursued indefinitely. GFR improved slowly to reach normal values only after 6 weeks (90 ml/min/1.73 m³). Fourteen months after diagnosis, GFR remains normal. **Conclusions:** In familial D-HUS, other genetical deficiencies than those of complement factor H and of von Willebrand factor-cleaving protease may intervene. Intensive and indefinitely pursued plasmapheresis may prevent chronic renal failure. Prophylactic plasmapheresis should be tempted in case of transplantation.

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Complement Receptors in Blood and Dialysate of Children on Peritoneal Dialysis

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Purpose: In order to evaluate the possible role of a complement receptors (CR) dysfunction in the increased propensity to infections in chronic renal failure (CRF), the CR expression was studied in 21 children treated with peritoneal dialysis (PD). **Methods:** Lympho-

cytes (L), monocytes/macrophages (M) and neutrophils (N) in blood and peritoneal dialysis effluent (PDE) were isolated by centrifugation, incubated with FITC labeled CD11b (CR3) and CD35 (CR1) mAbs and analyzed by flow cytometry. **Results:** The % CD11b⁺ and CD34⁺ PDE N (resp. 69 and 49%) and M (80 and 59%) were lower compared to blood (all >90%) whereas the % CD11b⁺ PDE L was higher (32 vs. 19%). The MFI of CD11b and CD35 on PDE cells were all higher compared to WBCs ($p < 0.05$) except for CD35 L. CR expression on WBCs and PDE cells did not change significantly during the first year of PD treatment. During peritonitis the % CD35⁺ L in blood increased from 22% before the peritonitis episode to 30% at the first presentation ($p = 0.02$). The MFI of CD11b and CD35 M increased from 25 to 45 ($p < 0.05$). In the PDE the % CR⁺ N and M increased to 100% whereas the MFI of CD35 M only increased from 23 to 82 ($p < 0.01$). **Conclusions:** Peritoneal cells have a higher CR expression compared to WBCs, which could be related to the dialysate chemical properties or to a continuous low-grade sub-clinical peritoneal infection. During peritonitis, monocytes and macrophages, but not neutrophils, showed a CR expression upregulation. This lack of neutrophil up-regulation may impede an optimal response against infection during peritonitis.

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Altered Complement Receptor Expression in Children with Chronic Renal Failure

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Background: Cell surface receptors for complement (CR) bind opsonized bacteria and initiate the phagocytic process. Phagocytic function in uremic patients is reduced and can lead to more frequent infections. **Methods:** We measured CR1 and CR3 expression on white blood cells (WBCs) in 33 not yet dialyzed children with chronic renal failure (CRF), 26 treated with peritoneal dialysis (PD), 23 hemodialysis children (HD), and 33 healthy controls (HC). Cells were isolated by centrifugation, incubated with FITC labeled CD11b (CR3) and CD35 (CR1) monoclonal antibodies and analyzed by flow cytometry. The % CR⁺ cells and the CR numbers per cell (MFI) are expressed as medians. **Results:** CR1: monocytes (M) and neutrophils (N) were all positive compared to 20% of lymphocytes (L). The MFI of L was 29 in PD, 30 in HD and 32 in CRF versus 47 in HC ($p < 0.05$). In CRF the MFI of M and N were both 12 versus 17 and 22 respectively in HC ($p < 0.02$). CR3: The % CD11b^b cells were not different from HC expected for L: 19% in PD and 24% in CRF versus 27% in HC (both $p < 0.01$). The MFI of L was 21 in PD, 26 in HD, 32 in CRF versus 15 in HC ($p < 0.02$). The MFI of M was higher ($p < 0.02$) in HD (39) and CRF (42) versus HC (28) but not in PD. The MFI of N was 43 in PD, 42 in HD, 54 in CRF versus 25 in HC ($p < 0.01$). **Conclusions:** The CR expression in children with CRF, dialyzed or not, is altered and might result in a defective antibacterial defence. Dialysis treatment normalized the MFI of CR1 only on monocytes and neutrophils.

Increased T Cell Cytokine Production in Children with Chronic Renal Failure Normalizes after Starting Dialysis

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Purpose: As cytokines may be implicated in some complications of chronic renal failure such as impaired humoral and cellular immunity, chronic inflammatory process and arteriosclerosis, IFN- γ and IL-2 production profiles of T-helper (CD4⁺) and T-suppressor (CD8⁺) lymphocytes were analyzed in 8 children treated with hemodialysis (HD), 9 children not yet dialyzed (CRF) and 9 healthy children (HC). **Methods:** Isolated PBMC were stimulated with PMA/ionomycin, stained for intracellular cytokines (IFN- γ , IL-2) and analyzed by flow cytometry. **Results:** CRF children displayed a higher percentage of IFN- γ producing CD8⁺ T-cell (median 42%, range 23–75) compared to HC (22%, 14–72%, $p = 0.02$) and HD (27%, 16–50%, $p = 0.03$). The IL-2 producing CD4⁺ T-cell population was also higher in CRF children (median 31%, range 15–38) in comparison with HD (19%, 7–24, $p = 0.03$). **Conclusions:** The high proportion of IFN γ -producing CD8⁺ T-cells and IL-2-producing CD4⁺ T-cells found in CRF patients before starting hemodialysis is not observed in hemodialysed patients. It suggests that uremia induces an increased cytokine production which can be normalized by hemodialysis. Further studies should focus on the relation between the cytokine production profiles of circulating leucocytes in CRF, some possibly cytokine-related complications of CRF such as inflammation and arteriosclerosis and the dialysis modalities.

IgG Receptors on Phagocytic Cells in Children with Chronic Renal Failure

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Background: Bacterial infections are more frequent and more severe in chronic renal failure. As Fc γ receptors are important in the antibody mediated immune defence against infection, they were investigated in children with chronic renal failure not yet dialysed (CRF), treated with peritoneal dialysis (PD) or hemodialysis (HD) and in healthy controls (HC). **Methods:** The Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIII (CD16) expression of granulocytes (gran) and monocytes/macrophages (mo/M ϕ) was determined in 23 PD, 23 HD, 35 CRF and 30 HC children by flow cytometry after cell purification from blood and peritoneal dialysate effluent (PDE) in PD patients. **Results:** The MFIs for CD32_{mo} and of CD32_{gran} (but not of CD16 and CD64) were lower ($p < 0.05$ and $p < 0.02$, respectively) in PD, HD and CRF in comparison with HC children. MFIs of PDE cells compared to blood cells were significantly higher for

CD16_{M ϕ /mo} ($p < 0.05$), CD32_{M ϕ /mo} ($p < 0.01$), CD32_{gran} ($p < 0.05$), CD64_{M ϕ /mo} ($p < 0.02$) and CD64_{gran} ($p < 0.01$). During peritonitis episodes, the MFI of CD16_{mo} and CD64_{mo} increased in blood ($p < 0.05$) but not in PDE. **Conclusions:** Fc γ RII_{mo} and _{gran} expression in blood is lower in PD, HD and CRF children compared to HC. It may account for an impairment of the Fc γ R function and an increased risk of infections in chronic renal failure. Fc γ R of peritoneal gran or M ϕ are already fully expressed out of peritonitis episodes. This suggests a continuous cellular activation in the peritoneal fluid possibly related to the dialysate chemical features or to a continuous subclinical low-grade infectious process.

Impaired Antibody Response to Pneumococcal Polysaccharide in Chronic Renal Failure

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Purpose: Pneumococcal vaccination is recommended in children with chronic renal diseases. Protection to infections with *S. pneumoniae* is related to the post-vaccination antibody titers. We investigated the anti-pneumococcal polysaccharide antibody response in children with chronic renal disease. **Methods:** Ten children treated with peritoneal dialysis (PD) were investigated, 7 children on hemodialysis (HD), 7 children after renal transplantation and 3 children with nephrotic syndrome without renal failure. Blood samples were collected before immunization with 23-valent pneumococcal polysaccharide vaccine and at 1 and 6 months thereafter. IgG, IgG₁ and IgG₂ antibody titers against pneumococcal capsular serotypes 3, 4, 6B, 9V, 14, 19F and 23F were measured by ELISA. **Results:** Transplanted children showed a lower antibody increase after vaccination for serotypes 9V and 23F compared to PD children ($p < 0.05$). A sufficient anti-pneumococcal immune response, defined as an absolute postimmunization level of >20 U/ml in 5 or more out of seven serotypes, was found in 11 out of 27 (41%) children. No significant differences were found among the groups. Seven children (2 HD, 2 PD, 2 Tx and 1 NS) were non-responders, defined as a postimmunization level below 20 U/ml and a less than two-fold increase of the antibody titer in five or more serotypes. **Conclusion:** Non-responders after pneumococcal vaccination were found in a substantial number of children with renal disease. After renal transplantation, the increase in antibody titer was lower than in PD children for serotypes 9V and 23F.

Children with Chronic Renal Failure Have Reduced Number of Memory B-Cells

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Purpose: Reduced serum IgG and subclasses levels have been demonstrated in children with peritoneal dialysis. To study possible causes of this reduction, we analyzed B-cell subset composition, T-helper cell frequencies and immunoglobulin production capacity in vitro in children with chronic renal failure, with or without dialysis treatment. **Methods:** Eight children treated with peritoneal dialysis (PD), 8 on hemodialysis (HD), 9 children not yet dialyzed (CRF) and 9 healthy children (HC) were studied. B-cell subsets were characterized by determining CD27, IgM, IgD and CD5 expression within the CD19 population. Intracellular expression of IFN- γ , IL-2 and IL-4 in PMA/ionomycin-stimulated peripheral blood mononuclear cells (PBMC) was used to evaluate T-helper frequencies. The capacity of B-cells to secrete immunoglobulins in vitro was determined by measuring IgG₁, IgG₂ and IgM in culture supernatants of CD2/CD28- or SAC/IL-2-stimulated PBMC. **Results:** Memory B-cell numbers (identified as CD19⁺ IgM⁻ IgD⁻ or CD19⁺ CD27⁺ lymphocytes) were lower in HD compared to HC ($p < 0.05$). CD19⁺ CD27⁺ B-cells were also significantly reduced in the PD population. Compared with HC, CD5⁺ B-cells were reduced in HD-treated patients but not in PD nor CRF children. No significant differences in CD4⁺ helper cell subsets were found between the groups. However, CRF children had a higher percentage of IFN- γ producing CD8⁺ T-cell lymphocytes compared to HC ($p = 0.02$). Finally, IgG₁, IgG₂ and IgM production in vitro was similar between the groups. **Conclusions:** Significantly lower numbers of memory type B-cells were found in HD and PD children. This reduction may contribute to the low Ig levels found in these children.

Responses in Patients with Cutaneous T-Cell Lymphoma (CTCL) Treated with Photopheresis (PE). A Pilot Study

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Purpose: Four patients with pre-Sezary syndrome, 2 patients with erythrodermic Mycosis Fungoides and 2 patients with Sezary syndrome were subjected to PE on 2 consecutive days (a sequence) every 2–4 weeks for 6 months, thereafter a sequence every 1–2 months determined by skin score (Edelson) for in all 12 months. All patients were refractory to conventional treatment. Soluble IL-2 receptor (IL-2R) was recorded by ELISA (IU/l), LDH (U/l) by conventional laboratory chemistry and T-cells by flowcytometry. Pathological clones were recorded by PCR. **Results:**

	Responders (n = 4)		Non-responders (n = 4)	
	IL-2R	LDH	IL-2R	LDH
Start	189	363	337	377
3 M		280		356
6 M	195	336	645	383
12 M	68	335	450	447

Skin score improved in responders from 318 to 158 while it remained unchanged in non-responders (363–380). There were no differences in PCR findings as monoclonal clones were found in two of the patients in each group. We could neither see a difference in the course of T-cell subsets during the treatment, nor in a group or between the groups. **Conclusion:** IL-2R used in monitoring disease activity in the patients investigated clearly shows that PE has an impact on the immune system. LDH as a marker of tumor activity remained unchanged in responders and increased in non-responders. The patients' condition seemed equal at treatment start. As PE is an expensive procedure, it should be of value to find parameters telling which patient is likely to respond and who is not. This small study did not answer this, so we are still searching.

Specific Adsorption Using Functionalised S-Layer-Fusion Proteins

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Specific adsorption is still the optimal solution in extracorporeal blood purification systems, based on adsorptive or combined membrane/adsorption processes. Therefore, research and development of these systems is directed to high specificity based on functionalised adsorptive surfaces. **Aim of the Study:** Development of an S-layer-fusion protein carrying a Fc-binding region on its extended surface, which can be bound onto biocompatible microparticles as recrystallized surface layers without losing its capability to bind IgG molecules. **Methods and Results:** The synthetically produced domain Z has a length of 58 amino acids and is based on the so called B-binding domain of protein A. Using two cloning steps, 2 Z-domains can be transferred into the S-layer-fusion protein rSbp A₃₁₋₁₀₆₈/ZZ expressed from the expression trunk *E. coli* HMS 174 (DE3). After isolation and cleaning by chromatographic methods the S-layer-fusion protein can be recrystallized on peptidoglycan-containing sacculi from *Bacillus sphaericus* CCM 2177 in order to analyse the binding capacity of the fusion protein rSbp A₃₁₋₁₀₆₈/ZZ for IgG via the Fc region. It could be found that 1 g of wet pellets of structures described could bind 35 mg human IgG; this equals 80% of the theoretically possible binding capacity. **Future Development:** Our next steps will be the recrystallisation and binding of the genetically modified S-layer-protein rSbp A₃₁₋₁₀₆₈/ZZ onto microcarriers having a particle size of approximately 2 μ m in order to use them in our MDS system

(Falkenhagen D., Schima H., Loth F.; International Patent Classification: A61 M 1/34, 1994) for specific immunadsorption. Conclusion: For the first time genetically modified specific adsorbent materials could be developed which will be the basis for specific adsorption technology in order to bind IgG molecules. Additionally, further developments for different substances are on the way, using similar technology.

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Peritoneal Glucose Prescription Is Strongly Related to Changes in Body Composition in CAPD Patients

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Introduction: It has been suggested that peritoneal transport characteristics may influence nutritional and metabolic state in CAPD patients because of the higher dialysate glucose concentrations needed to maintain fluid state. In the present study, the relation between peritoneal transport characteristics and peritoneal glucose prescription with body composition was assessed in stable CAPD patients. **Patients:** In a cross-sectional study which included 36 stable PD patients, followed by a longitudinal study with 4 months follow-up. The longitudinal study was completed by 24 patients. **Methods:** Body composition was assessed by dual x-ray absorptiometry (fat mass, lean body mass), with lean body mass corrected for volume status (extracellular volume (ECV): bromide dilution) [body cell mass]. **Results:** In the cross-sectional study, the daily peritoneal glucose prescription was significantly related to body mass index ($r = 0.40$; $p = 0.019$) and to protein catabolic rate ($r = -0.34$; $p = 0.045$), but not to the percentage of body fat. In contrast, daily peritoneal glucose prescription was highly significantly related to the change in body fat mass ($r = 0.53$; $p = 0.008$) and inversely to the change in body cell mass during the longitudinal part ($r = -0.44$; $p = 0.038$). D/P was not related to body composition. **Conclusion:** Peritoneal transport characteristics were not directly related to nutritional or metabolic parameters. In contrast, peritoneal glucose prescription was found to be significantly related to the increase in body fat but also to the decline in body cell mass during a four-month follow-up period. These results suggest that dialysate glucose on the one hand may lead to a decline in body protein stores by a loss of appetite and on the other hand to an increase in body fat mass by an increased calorie load.

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Fluid Status in Relation to Peritoneal Transport and Residual Function in CAPD Patients: A Longitudinal Study

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Introduction: Recently, both peritoneal transport characteristics as well as residual renal function were found to be related to outcome in patients treated with continuous ambulatory peritoneal dialysis (CAPD). It has been suggested that these relations might be due to an effect of peritoneal transport on the fluid state in CAPD patients or by the relation between inflammation and peritoneal transport. **Methods:** The relation between fluid state (extracellular volume [ECV] (bromide dilution), peritoneal transport characteristics (D/P ratio; 2.27% glucose) and residual renal function (glomerular filtration rate [rGFR] by urine collection) and inflammation (C-reactive protein (CRP)) was assessed in 37 CAPD patients, in a cross-sectional and secondly in a longitudinal design, which was completed by 25 patients. **Results:** In the cross-sectional part, ECV corrected for body surface area (BSA) (ECV/BSA) was inversely related to rGFR ($r = -0.48$; $p = 0.003$), whereas during the longitudinal part, D/P was related to the change in ECV ($r = -0.40$; $p = 0.05$). When patients were divided in 2 groups according to rGFR (<2 or >2 ml/min), a highly significant difference in fluid state was observed between both groups (ECV/BSA 11.0 ± 3.2 versus 8.2 ± 1.4 l/m²; $p = 0.001$), despite a significantly larger daily peritoneal glucose prescription (216.3 ± 60.0 versus 156.5 ± 53.0 gram) and peritoneal ultrafiltration volume ($1,856 \pm 644$ versus 658 ± 781 ml) in the group with rGFR <2 ml/min. Neither D/P nor rGFR were related to CRP, whereas a significant relation was observed between ECV/BSA and CRP ($r = 0.43$; $p = 0.007$). **Conclusion:** Fluid state was significantly related to peritoneal transport characteristics and rGFR. The increased ECV in CAPD patients with negligible GFR despite a higher peritoneal ultrafiltration volume and glucose prescription raises doubt on the fact whether fluid balance in anuric PD patients can be adequately maintained on standard glucose solutions without additional sodium and fluid restriction. The relation between CRP and fluid state might suggest a relation between overhydration and inflammation.

Effect of Icodextrin on Volume Status, Blood Pressure and Echocardiographic Parameters: A Randomised Study

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Introduction: Overhydration is a risk factor for hypertension and left ventricular hypertrophy in peritoneal dialysis (PD) patients. Recently, a high prevalence of subclinical overhydration was observed in PD patients. **Methods:** In the present open-label randomized study the effect of an icodextrin 7.5% solution on fluid status (extracellular water [ECW: bromide dilution], blood pressure regulation [24-hour ambulatory measurements] and echocardiographic parameters were studied during a four-month period, in relation to the peritoneal membrane characteristics (D/P creatinine ratio)). Forty patients (21 icodextrin, 19 controls) were randomized to either treatment with icodextrin during the long dwell or standard glucose solutions. Thirty-three patients (18 icodextrin, 14 controls) completed the study. **Results:** The use of icodextrin resulted in a significant increase in daily ultrafiltration volume [716 ± 853 ml versus $1,841 \pm 1,437$ ml; $p = 0.001$] and a decrease in ECW [17.6 ± 5.4 versus 15.7 ± 3.9 liters; $p = 0.03$]. The decline in ECW in the icodextrin-treated group was significantly related to the increase in ultrafiltration volume ($r = 0.68$; $p = 0.03$). The change in ECW between controls and patients treated with icodextrin was significant [-1.8 ± 3.4 versus $+0.8 \pm 2.2$ liters; $p = 0.011$]. The effect of icodextrin on ECW was not related to peritoneal membrane characteristics, but significantly related to the fluid state of the patients [ECW:body surface area] [$r = 0.75$; $p < 0.0001$]. Blood pressure and echocardiographic parameters did not change during the study period. **Conclusion:** The use of icodextrin led to a significant reduction in ECW. The effect of icodextrin was not related to peritoneal membrane characteristics, but more pronounced in overhydrated patients.

Influence of Fluid State on the Assessment of Body Composition in PD Patients

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Introduction: A reliable assessment of nutritional state in PD patients is of great importance. Nevertheless, techniques used to assess body composition in patients on peritoneal dialysis (PD) may be affected by abnormalities in fluid state. Aim of the study was to compare different techniques used to evaluate body composition and to assess the influence of fluid state on the assessment of body composition. **Methods:** In 41 PD patients, dual energy x-ray absorptiometry (DEXA), MF-BIA and anthropometry were compared with

regard to the evaluation of body composition (fat mass and lean body mass [LBM] (DEXA) or fat-free mass [FFM] (MF-BIA, anthropometry)) whereas the influence of the fluid state on the measurement of LBM/FFM by the various techniques was assessed by their relation to left ventricular end-diastolic diameter (LVEDD) assessed by echocardiography. **Results:** Despite highly significant correlations, wide limits of agreement were present regarding the assessment of body composition between the various techniques [Bland-Altman]: LBM [DEXA]-FFM [MF-BIA]: 1.1 ± 4.3 kg; LBM [DEXA]-FFM [Anthropometry]: -4.9 ± 6.1 kg; Fat Mass [DEXA]-[MF-BIA] -5.2 ± 4.3 kg; Fat Mass [DEXA]-[Anthropometry] 1.5 ± 5.3 kg, which were most pronounced for anthropometry. LBM/FFM measured by respectively DEXA, MF-BIA, and anthropometry were significantly related to LVEDD ($r = 0.54$, $r = 0.56$ and $r = 0.51$, respectively), suggesting an important influence of hydration state on this parameter. **Conclusion:** Wide limits of agreement were found between various techniques used to assess body composition in PD patients, in which MF-BIA appeared to be better related to DEXA than anthropometry. The assessment of body composition was found to be strongly influenced by hydration state.

Nitric Oxide Release during Hemodialysis (HD) Is Dependent upon Extracorporeal Energy Transfer (ET): Coupling the NO and Temperature Hypothesis of Dialysis Hypotension

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Introduction: During standard HD, vascular reactivity is impaired, which can be corrected by lowering dialysate temperature (T^{dial}) or the use of isolated ultrafiltration (i-UF), by which also energy loss over the extracorporeal system is induced. On the other hand, an increase in nitric oxide (NO) release has been observed during dialysis, which could also contribute to an impaired vascular response. Aim of the present study was to assess whether dialysate temperature may influence NO release during HD. **Methods:** NO release was studied by [^3H] L-citrulline formation from [^3H] L-arginine during 60 min of treatment with respectively standard bicarbonate HD ($T^{\text{dial}} 37.5^\circ\text{C}$), i-UF and HD with the same extracorporeal energy transfer (ET) as measured during i-UF ($\text{HD}^{\text{ET-set}}$) (measured and modelled by Blood Temperature Monitor; Fresenius[®]) in 12 stable HD patients. Measurements were performed with weekly intervals. Polyamide membranes and ultrapure dialysate (<1 CFU/liter, endotoxin undetectable) was used. **Results:** During 60 min of HD with $T^{\text{dial}} 37.5^\circ\text{C}$, ET was -2 ± 11 kJ, and respectively -108 ± 7 kJ during i-UF and -109 ± 15 kJ during $\text{HD}^{\text{ET-set}}$ (both $p < 0.05$ compared to $T^{\text{dial}} 37.5^\circ\text{C}$). During HD with $T^{\text{dial}} 37.5^\circ\text{C}$, [^3H] L-citrulline formation increased from 56 ± 9 to 79 ± 14 pmol/ 10^5 cells and remained stable (64 ± 16 to 68 ± 11 pmol/ 10^5 cells) during i-UF, whereas [^3H] L-citrulline formation decreased from 72 ± 11 to $56 \pm$

9 pmol/10⁵ cells during HD^{ET-set}. The change in [³H] L-citrulline during HD with T^{dial} 37.5 °C differed significantly from HD^{ET-set} (p < 0.05). Conclusion: NO release during HD is strongly influenced by extracorporeal ET. Thus, it appears to be possible to couple the 'temperature' and 'NO' hypothesis with regard to dialysis hypotension.

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Etiology of Kidney Disease Strongly Influences Arterial Wall Distensibility in Patients with Renal Failure

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Introduction: Renal patients commonly exhibit abnormalities of the arterial system, which even were found to be related to mortality. Nevertheless, as the contribution of renal failure secondary to vascular disease or diabetes mellitus is rapidly growing and the underlying disease per se may also have a strong influence on arterial wall properties, it may be of interest to focus also on arterial wall properties in relation to the etiology of kidney disease. **Methods:** Distensibility coefficient (DC) of the common carotid artery [Automated vessel wall detection system; Walltreck[®]] was used as a marker of arterial stiffening. 70 patients (age 57 ± 14 years, MAP 100 ± 18 mmHg, 30% CAPD, 46% hemodialysis [HD], 24% chronic renal failure [CRF]) with primary renal (glomerulonephritis, interstitial nephritis and polycystic disease) or urological disease and 48 patients (age 63 ± 11 years, MAP 110 ± 16 mmHg, 27% CAPD, 48% HD, 25% CRF) with secondary renal disease (vascular disease, diabetes mellitus) and 25 normotensive controls with normal renal function (age 57 ± 5 years) were studied. CCI did not differ significantly between CRF patients with renal/urological and secondary renal disease [37 ± 19 vs. 28 ± 10 ml/min]. **Results:** DC was significantly lower in patients with secondary renal disease [10.9 ± 5.5 (10⁻³/kPa)], both compared to patients with renal/urological disease [15.4 ± 7.5 (10⁻³/kPa)] and to controls [16.7 ± 4.6 (10⁻³/kPa)] (p < 0.001), whereas DC did not differ significantly between controls and patients with primary renal/urological disease (p = 0.44). **Conclusion:** The DC of the common carotid artery appears to be strongly influenced by the etiology of renal failure, which should be considered when the effect of uremia on vascular wall properties is studied.

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Randomized in vivo Study on the Elimination of Inflammatory Mediators by Modified High-Flux Dialysis Membranes

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Purpose: Inflammatory mediators such as cytokines and complement factors accumulate in renal failure and may therefore contribute to inflammation and atherosclerosis in dialysis patients. The elimination of these middle-sized proteins by conventional high-flux membranes is not satisfactory. In the present study we investigated whether there are differences between a conventional synthetic high-flux membrane (Polyflux [P11S], Gambro) and a modified synthetic membrane with a higher cut-off (Polyflux High-Cut-off [HCO], Gambro) in vivo. **Methods:** In a randomised order, 10 chronic dialysis patients were dialysed using each of the following four treatment modalities: P11S-HD, P11S-HDF, HCO-HD, HCO-HDF. Treatment time was four hours, blood flow 250 ml/min, the substitution volume for HDF was 18 litres. During these four dialysis sessions per patient, we determined plasma levels and 1-hour clearances of IL-6, TNF-R, β₂-microglobulin and factor D. In addition, the total amount of removed β₂-microglobulin and factor D was measured in spent dialysate. **Results:** The reduction of plasma levels before and after treatment paralleled the clearance values and the eliminated total amount.

	P11S HD	P11S HDF	HCO HD	HCO HDF
IL-6 clearance	-3.6 ± 7	14 ± 10	12 ± 9	39 ± 6*
TNF-R clearance	-9.7 ± 3	9 ± 14	-2.8 ± 3	23 ± 9*
β ₂ -M, mg	74 ± 14	97 ± 17	136 ± 19*	147 ± 19*
Factor D, mg	3.1 ± 0.8	6 ± 1.3	17.6 ± 3.7*#	25 ± 3.6*#

n = 10, means SEM, * = p < 0.05 vs. P11S HD, # = p < 0.05 vs. P11S HDF.

Conclusion: The use of a modified synthetic high-flux membrane with higher cut-off significantly improves removal of inflammatory mediators in vivo. In particular, there were large differences regarding factor D, the rate-limiting parameter of the initial alternative pathway of complement activation. Modification of high-flux membranes is a promising effort to dampen or to lower inflammation in selected patients and may contribute to prevent the consequences of the inflammatory response in dialysis patients.