30. Histopathological atlas of renal disease: ANCA-associated vasculitis (First part)

Ferrario F, Rastaldi MP.


“ANCA-associated vasculitis are Wegener’s granulomatosis, micropolycytheritis and its renal-limited variant (previously called idiopathic necrotizing glomerulonephritis). According to the “Chapel Hill Conference” classification, ANCA associated vasculitis are characterized by prevalent involvement of small-size vessels, whereas medium and large-size arteries involvement is the marker of polyarteritis nodosa. But the vessel size-based classification is not always powerful enough, because also in ANCA-associated vasculitis the involvement of medium and large-size arteries if frequent. The distinctive marker of ANCA-associated renal vasculitis has therefore become the presence of necrotizing extracapillary glomerulonephritis, that is always absent in polyarteritis nodosa. Small vessel vasculitis is morphologically defined by massive necrosis of the vascular wall with endo- and perivascular inflammatory infiltrates. This lesion should be the diagnostic hallmark of the disease, but is histologically detected in only 20-30% of cases, confirming the diagnostic importance of necrotizing extracapillary nephritis. Furthermore, a similar arteritis can be found in other diseases, such as anti-GBM antibody disease, Henoch-Schönlein nephritis, cryoglobulinemic nephritis and lupus nephritis.

31. Antineutrophil cytoplasmic antibodies (ANCA) in Chinese patients with anti-GBM crescentic glomerulonephritis


Abstract: Objective: To study the prevalence of ANCA and their target antigen in Chinese patients with anti-GBM crescentic glomerulonephritis (CGN), and evaluate the possible role of ANCA in Chinese anti-GBM CGN patients with coexisting serum ANCA by studying clinicopathologic features of this disease. Material and methods: Twenty-three sera were collected from 23 renal biopsy-proven anti-GBM CGN patients. According to the standardized procedures, all of the sera were determined by both, indirect immunofluorescence (IIF) ANCA, and enzyme-linked immunosorbent assay (ELISA) MPO-ANCA, PR3-ANCA and BPI-ANCA. The patients were divided into two groups according to serum ANCA positivity (Group A) or negativity (Group B). Thirty-three ANCA-associated pauci-immune CGN patients were regarded as control group (Group C). Their clinicopathologic features were compared to reveal whether ANCA correlated with disease activity. Results: There were 11 (47.8%) cases with positive serum ANCA in 23 anti-GBM glomerulonephritis patients. There were 4/11 MPO-ANCA (one with positive PR3-ANCA and C-ANCA, three with negative IIF-ANCA), 1/11 PR3-ANCA (with positive MPO-ANCA and C-ANCA), 3/11 P-ANCA (with negative ELISA-ANCA) and 5/11 C-ANCA (one with positive PR3-ANCA and MPO-ANCA, and the other four with negative ELISA-ANCA). No BPI-ANCA was detected. No different clinicopathologic features were found between Groups A and B. Both were different between GrupsC in age, sex ratio, frequency of anuria and ESRD, variety of crescents,
glomerular sclerosis, vessel lesion and prognosis. Conclusion: Our data demonstrate that ANCA in Chinese patients with anti-GBM CGN is not rare. The major target antigen of ANCA is MPO. ANCA seems not to be correlated with disease activity.

32. Pathogenesis of Wegener’s granulomatosis

Sarraf P, Sneller MC.


Wegener’s granulomatosis (WG) is a complex autoimmune syndrome that is characterised by upper/lower respiratory necrotising granulomatosis, glomerulonephritis and small-vessel vasculitis. Since Wegener’s 1936 description, considerable advances in recognition and treatment have changed this disease from a rapidly and uniformly fatal illness to a chronic disease characterised by remission and relapses. The serendipitous discovery of anti-neutrophil cytoplasmic antibodies (ANCAs) as a marker associated with WG focused attention on the potential pathogenic role of these antibodies and has recently led to the development of novel animal models that might facilitate our understanding of the disease pathogenesis. Future animal models of this disease will have to account for the role of both ANCA-mediated pathology and granulomatosus inflammation to enable us to understand the chronic and persistent features of WG in humans.

33. Complex genetics of Wegener granulomatosis

Jagiello P, Gross WL, Epplen JT.


Wegener granulomatosis (WG) belongs to a heterogenous group of systemic anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (AASV). WG is characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract, glomerulonephritis and vasculitis. As a multifactorial model disease, WG is hallmarked by the presence of specific ANCA-subtypes directed against a defined antigen. WG is more predominant among Caucasians and the genetic predisposition appears quite comple. Here, we provide a brief overview concerning genetic factors in the pathogenesis of WG and discuss intricacies of molecular genetic approaches.

34. Manifestations mimicking relapsing polychondritis in a patient with microscopic polyangiitis

Ogawa H, Nishi E, Amano K, et al.
Microscopic polyangiitis (MPA) is a systemic disorder characterized by inflammation of small vessels mainly affecting the kidneys and lupus. We describe a 72-year-old woman who developed multiple cartilage involvements as well as major manifestations of MPA. The left ear biopsy demonstrated cartilaginous inflammation and small vessel vasculitis. She also had conjunctivitis, hearing impairment, interstitial lung disease, glomerulonephritis with vasculitis and mononeuritis multiplex. Serological examinations revealed a positive antineutrophil cytoplasmic antibody (PR3 ANCA). Cyclophosphamide and oral corticosteroid therapy was instituted and remission achieved. Due to lacks of nasal and bronchial involvements, as well as the evidence of auricular vasculitis, we concluded that her findings mimicking relapsing polychondritis developed as systemic manifestation of MPA.

35. Activation of lectin complement pathway in Henoch-Schönlein purpura nephritis

Hisano S, Matsushita M, Fujita T, et al.


Background: We previously reported the existence of complement activation through the alternative and lectin pathways in patients with immunoglobulin A (IgA) glomerulonephritis (GN). The current study aims to elucidate the correlation between each complement pathway and clinicopathologic findings in patients with Henoch-Schönlein purpura nephritis (HSPN).

Methods: Immunohistologic staining was performed on renal specimens obtained from 31 patients with HSPN and 20 controls as non-IgA GN by using antibodies against IgG, IgA1, IgA2, IgM, C1q, C3c, C4, fibrinogen, factor B, C4-binding protein (C4-bp), C5b-9, CD59, mannose-binding lectin (MBL), and MBL-associated serine protease-1 (MASP-1).

Results: No control showed deposition of any antibody. In 16 patients with mesangial IgA1/IgA2 codeposits, mesangial deposits of C3c, C4, factor B, C4-bp, C4b-9, CD59, MBL, and MASP-1 were found. In the remaining 15 patients with mesangial IgA1 deposits alone, no mesangial deposits of C4 or MBL/MASP-1 were found, and mesangial deposits of C3c, factor B, C5b-9 and CD59 were evident in 11 patients. Glomerular deposits of fibrinogen were detected in 15 of 16 patients with IgA1/IgA2 codeposits and only 6 of 15 patients with IgA1 deposits. Severity of glomerular changes and degrees of of hematuria and proteinuria at latest follow-up were greater in patients with IgA1/IgA2 codeposits than in those with IgA1 deposits.

Conclusion: Complement activation through both the alternative and lectin pathways is found in patients with HSPN. Complement activation is promoted in situ in the glomerulus. MBL/MASP-1 may be associated with glomerular deposition of fibrinogen. Complement activation through the lectin pathway may contribute to the development of advanced glomerular injuries and prolonged urinary abnormalities in patients with HSPN.

36. A case of renal sarcoidosis with complement activation via the lectin pathway

37. Recurrent Goodpasture’s disease secondary to a monoclonal IgA1-kappa antibody autoreactive with the alpha1/alpha2 chains of type IV collagen

Borza DB, Chedid MF, Colon S, et al.


Goodpasture’s disease is characterized by crescentic glomerulonephritis and lung hemorrhage in the presence of anti-glomerular basement membrane (anti-GBM) antibodies. This disease usually is mediated by IgG autoantibodies directed against the noncollagenous domain of the alpha3(IV) collagen chain, the Goodpasture autoantigen. In rare cases, anti-GBM antibodies of IgA or IgM class are involved, but their specificity has not been determined, and their target antigen remains unknown. The authors present the case of a 92-year-old man with anti-GBM disease mediated by a monoclonal IgA-kappa antibody, which progressed to end-stage renal disease despite intensive immunosuppression. The patient underwent living-related kidney transplantation, but lung hemorrhage and crescentic glomerulonephritis recurred, causing the loss of the allograft 2 year later. Indirect immunofluorescence found the presence of circulating IgA antibodies reactive with a basement membrane component, identified by enzyme-linked immunoabsorbent assay and Western blot as the alpha1/alpha2(IV) collagen chains. Sensitivity to digestion with collagenase indicated that IgA bound to epitopes located in the collagenous domain. This is the first case of recurrent Goodpasture’s disease to an autoreactive IgA antibody. The specificity of an IgA antibody implicated in the pathogenesis of anti-GBM disease has been investigated for first time, identifying the alpha1/alpha2(IV) collagen chains as a novel target for nephritogenic antibodies.

38. Detection of mutations in the COL4A5 gene by analyzing cDNA of skin fibroblasts


Background: Alport syndrome is a progressive hereditary glomerulonephritis that is characterized by hematuria, sensorineural deafness, ocular lesions, and progressive renal failure. The majority of cases (about 85%) are caused by mutations in the Col4A5 gene on the X chromosome which encodes the type IV collagen alpha5 chain (X-linked Alport syndrome). Methods: In this study we performed a systematic analysis of the entire coding region of COL4A5 mRNA in 31 unrelated Chinese X-linked Alport syndrome patients and four controls by using reverse transcription-
polymerase chain reaction (RT-PCR) and direct sequencing methods. The mRNA analyzed was isolated from cultured skin fibroblasts of Alport syndrome patients. Results: The entire sequences of mRNA of the controls corresponded exactly to the published sequence. There were 28 variants detected by analyzing mRNA of COL4A5 in 28/31 patients. Of those, a total of 25 functionally significant Col4A5 mutations was confirmed in 25/31 patients by using RT-PCR method and subsequently confirmed at genomic DNA level, which included seven different mutations described in previous reports, and 18 novel mutations. The mutation detection rate was 80.6% (25/31), which is comparable with the highest previous detection sensitivity of COL4A5 mutations in evident X-linked Alport syndrome using genomic DNA. Furthermore, three splicing mutations that occurred at the cryptic splice sites and would be overlooked or simply considered as intronic sequence variation by solex analyzing genomic DNA were identified in this study. Conclusion: RT-PCR and direct sequencing using cultured fibroblasts RNA is a practical approach with high sensitivity for genetic analysis in X-linked Alport syndrome patients.

39. Thin basement membrane nephropathy in pregnancy

Packham D.


There are several published series of pregnancy in patients with nonimmunoglobulin A mesangial proliferative glomerulonephritis (most of whom have thin basement membrane nephropathy [TBMN]). The aim of the present study was to review the maternal and fetal outcomes of pregnancy in women with TBMN. The medical and obstetric histories of 86 women with TBMN and their 182 pregnancies (one Twin) were reviewed. Data were collected retrospectively in 164 pregnancies (90%) and prospectively in 18 pregnancies (10%). Hypertension (alone or with proteinuria) developed in 15 unmonitored pregnancies (9%), and proteinuria alone developed in the third trimester in 2 pregnancies (1%). Hypertension was more common in the prospectively monitored pregnancies (6 pregnancies, 33%). In all, there were 174 births (95%), and all fetal deaths occurred in the first and second trimesters in the absence of maternal complications. However, all the mothers of the 4 small for gestational age babies had been hypertensive. In TBMN, maternal hypertension, prematurity, and small for gestational age rates did not exceed those in the normal population. Overall, pregnancy in women with TBMN does not appear to be attended by a significantly increased maternal or fetal risk.

40. Thin basement membrane nephropathy associated with other glomerular disease

Norby SM, Cosio FG.


Many reports confirm that thin basement membrane nephropathy (TBMN) commonly occurs together with other glomerular diseases such as minimal change glomerulonephritis, diabetes,
membranous nephropathy, immunoglobulin (Ig)A glomerulonephritis, and focal segmental glomerulosclerosis. We postulate 3 explanations for these observations. The association of minimal change glomerulonephritis with TBMN probably is artifactual whereas the association with diabetes and membranous glomerulonephritis probably coincidental. However, the link between TBMN and IgA disease and focal segmental glomerulosclerosis may be pathogenetic. Clinical evidence indicates that the presence of an associated glomerulopathy significantly worsens the prognosis of TBMN. Thus, patients with TBMN and another glomerular lesion usually have more marked proteinuria, and are more likely to have hypertension and renal insufficiency. The frequency of another glomerulopathy in patients with TBMN means that all patients in whom TBMN is suspected but who have heavy proteinuria or renal insufficiency should undergo a renal biopsy examination. However, there is no evidence that TBMN alters the prognosis of another glomerulopathy, and, in particular, patients with TBMN and IgA disease do not have different clinical features or a worse prognosis than those with IgA disease alone.

41. The risk of thin basement membrane nephropathy


Most individuals with thin basement membrane nephropathy (TBMN) have an excellent prognosis. For these patients, the only hazards are the anxiety related misconceptions about the diagnosis and the inconvenience, expense, and wastefulness of unnecessary investigations. However, there also are specific genetic implications for individuals with TBMN because, on average, half their offspring inherit the causative mutations and most of these have hematuria. In addition, despite the generally excellent outcome, some individuals with TBMN develop hypertension, proteinuria, or renal impairment. In some cases, renal failure is caused by apparently progressive but otherwise uncomplicated TBMN, and in others it results from a secondary or coincidental glomerular or tubulointerstitial renal lesion. In particular, TBMN appears to predispose to immunoglobulin (Ig)A glomerulonephritis, and the outcome for these patients is worse than for those with TBMN alone. The risk for patients with TBMN in relation to pregnancy and transplantation have not been well-studied but are described elsewhere in this issues.

42. Histopathological atlas of renal disease: minimal change disease and focal glomerulosclerosis

Ferrario F, Rastaldi MP.


Minimal change disease and focal segmental glomerulosclerosis are both clinically characterized by presence of nephrotic syndrome. The term minimal change disease describes a pathology appearance on light microscopy in which there are no definitive changes from normal glomeruli, although the degree of change that is considered significant remains the subject of some controversy. The focal
segmental solidification of the glomerular tuft, due to collapse of the capillary wall, affecting only some glomeruli (focal). It remains unresolved whether minimal change disease and focal segmental glomerulosclerosis are different diseases or whether they represent a spectrum of presentation of the same disease process.

43. Glomerulonephritis in a patient with chronic active Epstein-Barr virus infection


Summary: See Part 2/ET/3.

44. Elevated macrophage migration inhibitory factor (MIF) levels in the urine of patients with focal glomerular sclerosis


Summary: The pathogenesis of focal glomerular sclerosis (FGS) is poorly understood. Macrophage migration inhibitory factor (MIF) is a potent pro-inflammatory cytokine released from T cells and macrophages, and is a key molecule in inflammation. To examine further the possible role of MIF in FGS, we measured MIF levels in the urine. The purpose of the present study was to evaluate the involvement of MIF in FGS. Urine samples obtained from 20 FGS patients. The disease controls included 40 patients with minimal-change nephrotic syndrome (MCNS) and membranous nephropathy (MN). A group of healthy subjects also served as controls. Biopsies were performed in all patients prior to entry to the study. The samples were assayed for MIF protein by a sandwich enzyme-linked immunosorbent assay (ELISA). The levels of MIF in the urine of FGS patients were significantly higher than those of the normal controls and patients with MCNS and MN. In contrast, the levels of urinary MIF (uMIF) in patients with MCNS and MN did not differ significantly from normal values. In the present study, attention also focused on the relationship between uMIF levels and pathological features. Among the patients with FGS, uMIF levels were significantly correlated with grade of mesangial matrix increase and that of interstitial fibrosis. There was also a significant correlation between uMIF levels and the number of both intraglomerular and interstitial macrophages. Although the underlying mechanisms remain to be determined, our study presents evidence that urinary excretion of MIF is increased in FGS patients with active renal lesions.

45. Mitochondrial tRNA_{Leu(UUR)} mutation in a patient with steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis
Abstract. Background: The heterogeneity of mitochondrial cytopathies is characteristic for this group of disorders, which preferentially affect the muscle and nerve system. The A3243G transition in the tRNALeu(UUR) gene has been associated with slowly progressive forms of focal segmental glomerulosclerosis (FSGS). Here we present a patient who developed a severe nephrotic syndrome during her first pregnancy, which persisted after delivery, and proved resistant to immunosuppressive therapy. A sister of our patient had developed diabetes mellitus. We analysed the DNA for presence of mitochondrial DNA (mtDNA) A3243G transition. Methods: DNA was isolated from peripheral blood leukocytes and urine sediments. Polymerase chain reaction was used to amplify the mtDNA. Restriction enzyme analysis was used to detect the presence of the A3243G transition. Quantitative analysis of the A3243G mutation was done using the pyrosequencing technique. Results: Quantitative analysis revealed a proportion of mutated mtDNA of 30% in the leukocytes and 68% in the urine sediments of the proband. On further analysis, we also found the transition in the mother, the diabetic sister and the daughter of the proband. Conclusion: MtDNA abnormalities can cause a steroid-resistant nephrotic syndrome, histologically characterized by FSGS. Physicians should be especially mindful of mitochondrial abnormalities when hearing loss, diabetes mellitus, or neuromuscular disorders are present in the patient or family members.

46. Case of inflammatory vasculopathy and encephalopathy caused by treatment with tacrolimus


Nervenarzt 205; 76 (4): 475-8.

The case of inflammatory vasculopathy and encephalopathy caused by treatment with tacrolimus is reported. This 49-year-old woman developed progressive gait ataxia and right-sided hemiparesis after 7 years of tacrolimus therapy for focal sclerosing glomerulonephritis. MRI presented multifocal cerebral lesions with contrast enhancement. Oligoclonal banding was positive. When the treatment with tacrolimus was stopped, the clinical symptoms resolved completely and the MRI findings improved with corticoid monotherapy.

47. Characteristics and risk factors of intrarenal arterial lesions in patients with IgA nephropathy


Abstract. Background: Although the clinical importance of immunoglobulin-A nephropathy
**Methods:** To clarify these issues, we investigated the prevalence, underlying factors and significance of intrarenal arterial lesions in 1005 patients with IgAN. We distinguished different degrees of severity of small artery and arteriole lesions (mild, moderate and severe), using a semi-quantitative scoring system. We compared the arterial lesions of IgAN patients with those of 627 non-IgAN patients, who had mesangial proliferative glomerulonephritis without IgA deposits, and 221 patients with membranous nephropathy (MN). **Results:** The IgAN with arterial lesions were significantly younger than non-IgAN and MN patients (mean ages 34.6 vs 40.4, 47.7 years, respectively). The prevalence of intrarenal small artery and arteriolar lesions was 54.6% in IgAN patients, compared with 26.6 and 47.1% in non-IgAN and MN patients, respectively; the percentages of moderate/severe arterial lesions were 37.0 vs 21.6 and 23.1%, respectively; and the percentages of hyaline changes were 43.7 vs 16.8 and 21.2%, respectively. The differences in the prevalence of lesions between IgAN patients and the two other groups were statistically significant for all three parameters. Our search for lesions and various indirect outcome markers disclosed significant associations with hypertension, higher serum creatinine and uric acid, high urinary protein excretion, glomerulosclerosis, tubular atrophy and interstitial fibrosis. Furthermore, these parameters were changed more markedly in IgAN patients with moderate/severe arterial lesions and hyaline changes than in IgAN patients who had mild arterial lesions and wall thickening alone. **Conclusions:** The prevalence of small intrarenal arterial-arteriolar lesion was higher in IgAN patients than in non-IgAN and MN patients; moreover, the lesion in IgAN were associated with younger age, were more severe and exhibited a higher degree of hyaline changes. Finally, the severity of small arterial-arteriolar lesions was linked to several markers of adverse outcome.

48. Uric acid correlates with the severity of histopathological parameters in IgA nephropathy

Mylliymaki J, Honkanen T, Syrjanen J, et al.


**Abstract, Background:** Immunoglobulin-A nephropathy (IgAN) is the most common chronic glomerulonephritis worldwide. Many clinical and histopathological risk factors for progression have been found previously. Recently, metabolic risk factors, such as hyperuricaemia and hypertriglyceridaemia, also have been associated with progression of IgAN. **Methods:** In the present study we correlated clinical and metabolic risk factors with histopathological parameters in 202 patients with IgAN. Morphological changes in glomerular, tubulointerstitial and vascular tissue were semiquantitatively graded into three classes. Mesangial proliferation activity and the amount of inflammatory cells were also evaluated by immunohistochemical staining if Ki-67 (MIB-1), CD45 (LCA) and CD68 stainings. Serum uric acid, triglycerides and cholesterol, urine protein excretion (UPE), blood pressure and body mass index (BMI) were measured. Smoking habits and occurrence of diabetes mellitus also were evaluated. The independent role of serum uric acid in the development of renal morphological changes was evaluated in multivariate analysis. **Results:** Serum uric acid and UPE level correlated with several histological parameters. Uric acid level showed the strongest correlation with tubulointerstitial changes and UPE with glomerulosclerosis. The level of serum triglycerides correlated with interstitial fibrosis and hyaline arteriosclerosis. Blood pressure correlated with hyaline arteriosclerosis, glomerulosclerosis and tubulointerstitial changes. BMI and diabetes mellitus correlated with both tubulointerstitial and vascular damage. We
found no significant correlations between histopathological parameters and smoking habits or serum cholesterol level. Serum uric acid had independent associations with the presence of tubular atrophy and interstitial fibrosis and inflammation. **Conclusions:** We conclude that many metabolic factors are univariately associated with renal morphological findings in IgAN. These same factors are central in the metabolic or insulin resistance syndrome and may have a pathogenetic role in the progression of IgAN. Serum uric acid may have an independent role in development of tubulointerstitial lesions as well as being associated with inflammation in renal tissue of patients with IgAN.

49. Decreased synthesis of glomerular adrenomedullin in patients with IgA nephropathy

Kuo MC, Kuo HT, Chiu YW, et al.


Adrenomedullin (AM) immunostaining and gene expression have seldom been measured in human kidneys. Because previous studies have shown that AM exerts antiproliferative effects on rat mesangial cells in vitro and that urine AM levels are decreased in patients with chronic glomerulonephritis, we measured glomerular AM and its gene expression in patients with primary IgA nephropathy (IgAN). Glomerular AM was measured by immunohistochemical staining, and glomerular AM mRNA was measured by in situ hybridization. Plasma and urine AM were measured by radiimmunoassay. The results showed that both the intensity of immunostaining from glomerular AM and the glomerular expression of AM mRNA were significantly decreased in IgAN patients compared with normal controls (both *P*<0.05). Similar results were not observed in patients with non-IgAN MsPGN. Glomerular AM immunostaining and glomerular AM mRNA expression were significantly correlated (*P*<0.001), and were negatively correlated with the number of glomerular cells (*P*<0.05 and < 0.01, respectively). Both glomerular AM immunostaining and glomerular AM mRNA expression were correlated with urine AM levels (both *P*<0.001), but not with plasma AM levels. The urine AM level was significantly lower in IgAN patients than in normal controls (*P*<0.01), whereas the plasma level was not different between the 2 groups. Our findings indicate that glomerular production of MA was detected in patients with IgA nephropathy and that this lack of glomerular AM may be related to the pathogenesis of this mesangial disease.

50. Association of C-509T and T869C polymorphisms of transforming growth factor-β1 gene with susceptibility to and progression of IgA nephropathy

Lim CS, Kim YS, Chae DW, et al.


**Abstract.** **Aims:** Transforming growth factor (TGF)-β1 is a cytokine with both beneficial anti-inflammatory effects and detrimental profibrotic activity in the pathophysiology and progression of glomerulonephritides. The transcriptional activity of the gene for TGF-β1 and the plasma levels of
TGF-β1 protein are associated with C-509T polymorphism at the promoter region, and with T869C (Leu10Pro) polymorphism at codon 10, of the TGF-β1 gene. **Methods:** Using PCR-RFLP and the amplification refractory mutation system PCR, we investigated the C-509T and T869C polymorphism, respectively, to elucidate whether allele frequency differences exist between IgA nephropathy (IgAN) patients who were followed up for at least 3 years (n=108) and a normal population (n=55). We also determined the correlations between the TGF-β1 polymorphisms and the progression of IgAN. **Results:** In C-509T polymorphism, there were significant differences in genotype frequency between IgAN patients and normal control (CC:CT:TT, 20:29:33 vs 11:31:13, x²=6.299, p=0.043). In Kaplan-Meier survival analysis, the patients with TT genotype showed a poorer renal survival than those with CC+CT genotypes (p=0.042). In T869C polymorphism, there were also significant differences in genotype frequency between IgAN patients and normal controls (TT:Tc:CC, 4:79:25 vs 0:52:2, x²=12.552, p=0.002). The initial serum creatinine (Scr) level was higher in the patients with CC genotypes than in those with TT+TC genotypes. In Kaplan-Meier survival analyses, the patients with CC genotype showed a poorer renal survival than those with TT+TC genotypes, but not to a statistically significant extent (p=0.076). In the combined survival analyses, the high TGF-β1 producer group showed a poor renal survival rate (p=0.014). **Conclusion:** Compared to normal population, the frequencies of genotypes producing high TGF-β1 protein were higher in IgAN patients. Moreover, patients with genotypes producing high TGF-β1 plasma levels showed a poor renal survival rate.

51. Urinary glycosaminoglycan composition in chronic glomerulonephritis


**Abstract.** **Background:** Glycosaminoglycans (GAG) play an important role in regulating glomerular permeability, and a reduction in their plasmatic concentration or urinary loss has been implicated in the pathogenesis of disease associated with increased albumin permeability. The purpose of this study was to evaluate GAG excretion in renal pathology by analyzing the composition of urinary GAG in antibody mediated glomerular injury, such as mesangial glomerulonephritis (IgAN) and primitive membranous glomerulonephritis (GN), to verify the effects of glomerular capillary wall lesion with and without mesangial cell injury. **Methods:** Urinary GAG excretion was analyzed in 20 patients with IgAN, 18 patients with MGN, and in 18 healthy subjects (controls). GAG were isolated from 24hr urine using ion-exchange chromatography on DEAE-Sephacel, and the results are expressed as mg hexuronate/g creatinine (Cr). GAG composition was determined by cellulose acetate electrophoresis and expressed as relative percentages by densitometric scanning of Alcian Blue stained strips. **Results:** We found total GAG levels significantly higher in the urine of patients with MGN in comparison with controls and patients with IgAN. The electrophoretic pattern analysis demonstrated low sulfated chondroitin sulfate proteoglycan (LSC-PG) in all patients compared to 44% in controls (8/18), but also sulfated chondroitin sulfate (LSC) in 18% of patients (7/38) and slow migrating LSC (SM-LSC) in 8% of patients (3/38), only in the MGN group. Moreover, in patients with MGN, the LSC-PG relative content was significantly higher when compared to that observed in controls. Finally, in IgAN and MGN patients, a significant reduction in chondroitin sulfate (CS) relative content was observed. **Conclusions:** It seems likely that an increase in total GAG levels takes place when a reduction in renal function occurs, but the alteration of CS and heparan sulfate (HS) relative contents, and the presence of LSC_PG and free LSC also in the urine of IgAN patients, allows us to suggest that the
GAG distribution pattern becomes abnormal before an increase in total urine GAG excretion. In addition, the quali-quantitative determination of urinary GAG and GAG protein complex could constitute an additional non-invasive marker to appraise the metabolism of renal connective tissue in some renal diseases.

52. Tissue-specific expression of renin-angiotensin system components in IgA nephropathy


Abstract. Background: The renin-angiotensin II system (RAS) has been implicated in the development of glomerulonephritis. The aims of this study were to determine (1) the expression of RAS components, angiotensin (Ang II)-forming enzymes [angiotensin-I-converting enzyme (ACE) and chymase], and ANG II receptors, and (2) the correlation between RAS expression and severity of tissue injury in IgA nephropathy (IgAN). Methods: The expression levels of ACE, chymase, and Ang type 1 and type 2 receptor (AT1r and AT2R) mRNAs were determined by in situ hybridization in renal specimens from 18 patients with IgAN, 5 patients with non-IgA mesangial proliferative glomerulonephritis (minimal change nephrotic syndrome, n=5, and membranous nephropathy, n=5). Normal portions of surgically resected kidney served as control. Results: In normal kidney, a few mesangial cells and glomerular and tubular epithelial cells weakly expressed ACE, chymase and AT1R mRNAs. In IgAN and normal samples, ACE, chymase, AT1R and AT2R mRNAs were expressed in resident glomerular cells, including mesangial cells, glomerular epithelial cells and cell of Bowman’s capsule. The glomerular expression in IgAN were stronger than in minimal change nephrotic syndrome and membranous nephropathy. In IgAN, the expression in glomeruli correlated with the degree of mesangial hypercellularity, whereas the expression of ACE, chymase, AT1R and AT2R mRNAs in atrophic tubules and infiltrating cells and such expression correlated with the degree of tubulointerstitial damage. Conclusion: Our results suggest that renal cells can produce RAS components and that locally synthesized Ang II may be involved in tissue injury in IgAN through Ang II receptors in the kidney.

53. Inhibition of protein kinase CK2 prevents the progression of glomerulonephritis


Summary: See Part 2/PG/23.
54. Role of coagulation factor Xa and protease-activated receptor 2 in human mesangial cell proliferation


Background: Fibrin deposition and mesangial cell proliferation are frequently observed in the active type of mesangiproliferative glomerulonephritis. Coagulation factors, such as factor V and Factor Xa are colocalized with fibrin in the mesangial areas in active type of IgA nephropathy with mesangial cell proliferation. In this study, therefore, we studied the role of factor Xa an its receptor, protease-activated receptor 2 (PAR2) in mesangial cell proliferation and fibrin deposition, and examined anti-proliferative effects of a specific factor Xa inhibitor, DX-9065a, in cultured human mesangial cells. Methods: To examine the effect of DX-9065a on the factorXa-induced proliferation of cultured human mesangial cells, we measured thymidine incorporation and cell numbers. We also examined the effect of DX-9065a on extracellular regulated kinase (ERK) activation and fibrin production induced by factor Xa in human mesangial cells. Results: Factor Xa increased [(3)H]-thymidine incorporation and cell numbers in a dose-dependent manner in mesangial cells, which was inhibited by DX-9065a. DX-9065a also suppressed factor Xa-triggered fibrin deposition on mesangial cell surface. Factor Xa induced the activation of ERK in mesangial cells and this activation was also completely inhibited by DX-9065a, but not inhibited by PAR1 antagonist. Factor Xa-induced cell proliferation and ERK activation were inhibited by PD98059. Conclusion: There results suggest that factor Xa can induce mesangial cells and that PAR2 may play a crucial role in the cell proliferation induced induced by factor Xa. Our results implicate that DX-9065a may be a promising agent to regulate proliferation of mesangial cells and inhibit the coagulation process in mesangium.

55. The predictive value of peritubular capillaries C3d deposition in IgA glomerulonephritis

Gerghiceanu M, Penescu M, Mandache E.


The IgA glomerulonephritis (IgAN) is one of the most common primary glomerulonephritis and has a variable and difficult to predict evolution toward the end-stage nephrosclerosis. The deposition of C3d complement component in peritubular capillaries (PTCs) indicates a variant type of acute rejection while C3d deposition in primary glomerulonephritis (GN) is poorly documented. The aim of this study is to examine C3d expression in peritubular capillaries (PTCs) as a predictive marker and its correlation with the severity of renal injury in IgA glomerulonephritis. Polyclonal FITC conjugated rabbit anti-human C3c and C3d antibodies were use for direct immunofluorescent evaluation of the C3c and C3d deposits in 24 kidney biopsies with IgA glomerulonephritis. The study revealed that the C3d deposits in peritubular capillaries were associated with known predictors for rapid progression of IgAN: glomerular sclerosis (63,6%), atrophic tubules (90,9%) and interstitial sclerosis (81,8%). The intensity of the C3c glomerular immunofluorescent deposits was related with active lesions. Thus, the predictive value of C3d deposition on PTCs in IgAN is worth
to be taken into consideration as an unfavorable outcome of the disease and request further long run investigations.

56. Genetics of common progressive renal disease

Chow KM, Wong TY, Li PK.


Summary: See Part 2/PG/2.

57. Mechanisms of tubulointerstitial injury in IgA nephropathy

Lai K, Chan LY, Leung JC.


Background: IgA nephropathy (IgAN) runs a highly variable clinical course with frequent involvement of tubulointerstitial damage. A subgroup of IgAN with severe tubulointerstitial damage is often associated with the most rapid progression to end-stage renal failure. In IgAN, mesangial sclerosis and tubulointerstitial damage were found to be correlated with the increase in pore size of the glomerular barrier. Methods: The direct toxicity of proximal tubule epithelial cells (PTEC) by IgA in IgAN is still unresolved. Activation of PTEC by mediators released from infiltrating cells or resident kidney cells that induce tubular inflammation is the common final pathway in most chronic renal diseases. We hypothesize that mediators released from human mesangial cells (HMC) triggered by IgA deposition may lead to PTEC activation. Results: We found that IgA binding to PTE was less than one tenth that of HMC. The binding was nonspecific and exhibited no increased cell proliferation or enhanced synthesis of cytokines or adhesion molecules. However, when PTEC were cultured with IgA-HMC spent medium prepared from IgAN patients, there was enhanced proliferation of PTEC and increased synthesis of cytokines and adhesion molecules. Conclusion: These findings implicate a glomerulotubular cross-talk with mediators released from the mesangium, contributing to the pathogenesis of tubulointerstitial damage in IgAN. There are preliminary data to suggest that the expression of angiotensin II subtype-1 receptor and angiotensin II subtype-2 receptor in PTEC differs from that of HMC. These novel findings may provide clinicians new therapeutic approach for selective blockade of the tubulointerstitial injury in IgAN.

58. Characteristics and risk factors of intrarenal arterial lesions in patients with IgA nephropathy

59. Role of macromolecular IgA in IgA nephropathy


Primary IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis, leading to progressive renal failure in almost one third of the patients. The disease characterized by mesangial deposits of IgA. The pathogenesis of IgAN remains incompletely understood. The basic abnormality of this disorder lies within the IgA immune system rather than in kidney. Elevated levels of IgA and IgA-containing complexes are found in sera of most patients with IgAN, but increased levels alone are not sufficient to develop IgAN. Therefore abnormal physicochemical properties of circulating IgA such as presence of altered glycosylation of serum and mesangial IgA in patients with IgAN. Although the precise origin and nature of the mesangial IgA deposits are still uncertain, they contain at least in part macromolecular IgA, which may be derived from circulating IgA-containing complexes. Recently, novel insights have been obtained in the molecular composition of circulating high-molecular-weight IgA, which might include complexes with underglycosylated IgA1 and IgA-CD89 complexes. In this review various aspects of macromolecular IgA in relation to IgAN will be discussed.

60. Activation of tubular epithelial cells by mesangial-derived TNF-alpha: glomerular communication in IgA nephropathy


Background: IgA nephropathy (IgAN), characterized by mesangial IgA deposition, runs a variable clinical course with tubulointerstitial damage and renal failure in no less than 30% of patients. Histologically, IgA is rarely detected in renal tubules. The direct toxicity by IgA on renal tubules remains uncertain. We hypothesize that mediators released from human mesangial cells (HMC) triggered by IgA deposition may lead to activation of proximal tubular epithelial cells (PTEC). Methods: The binding of IgA to PTEC or HMC was assessed by flow cytometry. IgA-HMC medium was prepared by collecting the spent medium in which growth arrested HMC were incubated IgA isolated from patients with IgAN, healthy subjects, or other nephritic control patients. PTEC was cultured with the IgA-HMC medium in the presence or absence of neutralizing
antibodies to TNF-alpha, IL-1beta, TGF-beta, or PDGF. Gene expression and protein synthesis of TNF-alpha, MIF, or ICAM-1 by PTEC were determined by RT-PCR and ELISA, respectively.

Results: The binding of IGA isolated from patients with IgAN to PTEC was increased when compared to binding of IgA from healthy control subjects (P<0.005). However, the binding to PTEC was less than one tenth that of GMC in IgAN. The binding to PTEC was not mediated through known IgA receptors as shown by competitive binding assays and gene expression of the receptors. Despite the in vitro binding, PTEC cultured with isolated IgA exhibited no increased cell proliferation or enhanced synthesis of TNF-alpha, MIF, or sICAM-1. However, when PTEC were cultured with IgA-HMC medium prepared from IgAN patients, there was enhanced proliferation of PTEC (P<0.001) and increased synthesis of TNF-alpha, MIF, and sICAM when compared with PTEC cultured with IgA-HMC medium from control subjects (P<0.001). The synthesis of MIF and sICAM-1 by PTEC cultured with IgA-HMC medium was reduced by neutralizing antibodies to TNF-alpha (P<0.001) but not by neutralizing antibodies to IL-betea, TGF-beta, or PDGF.

Conclusion: Our finding implicates that TNF-alpha released from the mesangium after IgA deposition activates renal tubular cells. The glomerulotubular communication could play an important role in the pathogenesis of tubulointerstitial damage in IgAN.

61. IgA1-containing immune-complexes in IgA nephropathy differentially affect proliferation of mesangial cells.


Background: Sera of patients with IgA nephropathy (IgAN) contain circulating immune complexes (CIC) composed of galactose-deficient IgA1 complexed with antglycan antibodies. The role of these CIC in the pathogenesis of IgAN is not known. Methods: We studied how proliferation of cultured mesangial cells (MC) is affected by CIC prepared from sera of IgAN patients and healthy control subjects using size-exclusion chromatography. CIC-containing fraction were added to serum-starved MC in culture, and cell proliferation was measured using (3)H-thymidin incorporation. The results were confirmed by staining MC using an antibody against proliferating cell nuclear antigen. Results: The incubation of starved MC with serum fractions with M(r) 800 to 900kD, rich with galactose-deficient IgA1, stimulated proliferation, while fractions with smaller complexes were inhibitory. Furthermore, CIC-containing large molecular mass fractions isolated from serum of an IgAN patient collected during episode of macroscopic hematuria stimulated MC proliferation more than CIC obtained during a subsequent quiescent phase. To examine the role of IgA, we removed IgA1 from serum before fractionation. The resultant IgA1-depleted fractions were devoid of stimulatory IgA-CIC. Sera of IgAN patients were also fractionated after addition of desialylated galactose-deficient polymeric IgA1 to form additional immune complexes. Supplementation with a small quantity of this IgA1 increased cellular proliferation in assays using serum fractions of M(r) >/=800 to 900 kD; uncomplexed IgA1 did not affect MC proliferation significantly. In contrast, supplementation with a larger quantity of this IgA1 inhibited cellular proliferation in assays using serum faction of M(r) 700 to 800 kD. Conclusion: Overall, these findings suggest that CIC containing aberrantly glycolisated IgA1 affect proliferation of MC in vitro and, thus likely play a role in the pathogenesis of IgAN.
62. The chemokine receptor 5 Delta 32 mutation is associated with increased renal survival in patients with IgA nephropathy

Panzer U, Schneider A, Steinmetz OM, et al.


**Background:** Chemokine receptor 5 (CCR5) plays an important role in the recruitment of monocytes and T cells in inflammation and experimental studies suggest that CCR5 might be involved in the pathogenesis of IgA nephropathy. A mutation in the CCR5 gene (CCR5Delta32), leading to a nonfunctional receptor, was recently described. We therefore evaluated the potential role of this mutation on renal survival in patients with IgA nephropathy. **Methods:** The distribution of the CCR5 Delta32 genotype was determined by polymerase chain reaction (PCR) analysis in 228 patients with biopsy-proven IgA nephropathy. In vitro, the influence of the CCR5 Delta32 genotype on the chemotactic response of monocytes was assessed. **Results:** Of the 228 patients, 158 (83.2%) had a CCR5 wild-type genotype, 29 (15.3%) were heterozygous, and three patients had a homozygous CCR5 delta32 genotype (1.6%). Renal survival was significantly longer in patients with the CCR5 Delta32 genotype than in the wild-type group (Long-rank P<0.001). Using the multivariate Cox proportional hazard model, the CCR5 Delta32 genotype was identified as an independent factor associated with a lower risk to develop end-stage renal disease (ESRD) [hazard ratio (HR) 0.23, 95% CI 0.09 to 0.57, P=0.002]. In vitro analysis of monocytes from CCR5 Delta32 carriers showed a reduced chemotactic response to CCR5 ligands in vitro. **Conclusion:** Our study demonstrates an independent role of the CCR5 Delta32 genotype for the clinical outcome in IgA nephropathy. In vitro experiment revealed a reduced chemotactic response of monocytes from CCR5 Delta32 carriers, thus pointing out a possible pathophysiological explanation for the beneficial effect of the CCR5 Delta32 genotype.

63. Association of a single-nucleotide polymorphism in the immunoglobulin mu-binding protein 2 gene with immunoglobulin A nephropathy


Immunoglobulin A (IgA) nephropathy is the most common form of primary glomerulonephritis worldwide. The pathogenesis of IgA nephropathy is unknown, but it is certain that some genetic factors are involved in susceptibility to the disease. Employing a large-scale, case-control association study using gene-based single-nucleotide polymorphism (SNP) markers, we previously reported for candidate genes. We report here an additional significant association between IgA nephropathy and an SNP located in the gene encoding immunoglobulin micro-binding protein 2 (IGHMBP2) at chromosome 11q13.2-q13.4. The association (Chi2 = 17.1, p=0.00003; odds ratio of 1.85 with 95% confidence interval of 1.39-2.50 in a dominant association model) was found using DNA from 465 affected individuals and 634 controls. The SNP (G34448A) caused an amino acid substitution from glutamine to lysine (E928K). As the gene product is involved in immunoglobulin-
class switching and patients with A allele revealed higher serum levels of IgA \( p=0.048 \), the amino acid change might influence a class switch to increase serum IgA levels, resulting in a higher risk of IgA nephropathy.

64. Oxidative stress and damage induced by abnormal free radical reactions and IgA nephropathy

Chen JX, Zhou JF, Shen HC.


Objective: To estimate the oxidative stress and oxidative damage induced by abnormal free radical reactions in IgA nephropathy (IgAN) patients' bodies. Methods: Seventy-two IgAN patients (IgANP) and 72 healthy adult volunteers (HAV) were enrolled in a random control study design, in which the levels of nitric oxide (NO) in plasma, lipoperoxide (LPO) in plasma and in erythrocytes, and vitamin C (VC), vitamin E (VE) and beta-carotene (beta-CAR) in plasma as well as activities of superoxide dismutase (SOD), catalase (CAT) and glutathion peroxidase (GPX) in erythrocytes were determined with spectrophotometric methods. Results: Compared with the HAV group, the averages of NO in plasma, and LPO in plasma and in erythrocytes in the IgANP group were significantly increased \( p<0.0001 \), while those of VC, VE and beta-CAR in plasma as well as those SOD, Cat, and GPX in erythrocytes in the IgANP group were significantly decreased \( p<0.0001 \). Linear correlation analysis showed that with the increase of the values of NO, and LPO in plasma and in erythrocytes, and with the decrease of those of VC, VE, beta-CAR, SOD, Cat and GPX in the IgANP, the degree of histological damage of tubulointerstitial regions was increased gradually \( p<0.0001 \); and that the prolongation of the duration of disease the values of NO, and LPO in plasma and in erythrocytes were increased gradually, while those of VC, VE, beta-CAR, SOD, Cat and GPX were decreased gradually \( p<0.005 \). The discriminatory correct rates of the above biochemical parameters reflecting oxidative damage of the IgANP were 73.8%-92.5%, and the correct rates for the HAV were 70.0%-91.3% when independent discriminant analysis was used; and the correct rate for the IgANP was increased to 98.8%, the correct rate for the HAV was increased to 100% when stepwise discriminant analysis was used. The above biochemical parameters’ reliability coefficient (alpha) were used to estimate the oxidative damage of the IgAN patients as 0.8145, the standardized item alpha=0.9730, \( F=53273.5681 \), \( p=0.0001 \). Conclusions: A series of free radical chain reactions caused serious pathological aggravation in the IgANP bodies, thus resulting in oxidative damage in their bodies. In treating IgANP, therefore, it is necessary that suitable dose antioxidants should be supplemented to them so as to alleviate the oxidative damage in their bodies.

65. Distribution of IgG subclasses in a biopsy specimen showing membranous nephropathy with anti-glomerular basement membrane glomerulonephritis: An uncharacteristically good outcome with corticosteroid therapy


Few occurrences of anti-glomerular basement membrane glomerulonephritis superimposed on membranous nephropathy have been reported; most reported cases began as membranous nephropathy. Little is known about the etiology, pathogenesis, or immunoglobulin G subclasses in glomerular basement membrane deposits in these combined cases. The authors report the case of an elderly patient with apparently simultaneous onset of both membranous nephropathy and anti-glomerular basement membrane glomerulonephritis who had an excellent outcome with only pulse corticosteroid therapy. Successive renal biopsy specimens showed occurrence and disappearance of immunoglobulin G4 deposits in the glomerular basement membrane. Immunoglobulin G subclass analysis was important in recognizing membranous nephropathy underlying the anti-glomerular basement membrane disease.

66. Urinary glycosaminoglycan composition in chronic glomerulonephritis


Summary: See Part 2/PG/51.

67. Hypocomplementemia and membranoproliferative glomerulonephritis in children


68. Myeloid related protein 8 expression on macrophages is a useful prognostic marker for renal dysfunction in children with MPGN type I.


Background: To clarify the role of subclasses of macrophages in chronic glomerulonephritis, we evaluated the relationship between myeloid-related protein 8 (MRP8) and MRP14 expression on
macrophages and the progression of membranoproliferative glomerulonephritis (MPGN). **Methods:** We enrolled 35 patients with MPGN type 1 who had a normal creatinine clearance at the time of their first renal biopsy and divided them into 2 groups based on clinical status at the time of their most recent examination: 12 patients with normal urine test results and 12 patients with minor urinary abnormalities at the latest observation (group 1) and 7 patients with persistent nephropathy and 4 patients with renal insufficiency (group 2). The first and second renal biopsy findings and MRP8 and MRP14 expression on macrophages were investigated in both groups. **Results:** Mean scores for positive glomerular and interstitial MRP8 and CD68 staining at the time of the first and second biopsies were significantly higher in group 2 than group 1. At the time of the second biopsy, mean scores for interstitial CD68-positive (CD68+) staining were higher in group 2 than group 1. Mean scores for glomerular and interstitial MRP8+ and CD68+ staining at the time of the first biopsy correlated with chronicity index at the time of second biopsy in both groups. **Conclusion:** Results suggest that MRP8 expression on macrophages in glomeruli and interstitial lesions at first biopsy can be a useful prognostic marker for renal dysfunction in children with MPGN type I.

69. Pathogenetic mechanisms of diabetic nephropathy

Schena FP, Gesulado L.


Diabetes is the leading cause of ESRD because diabetic nephropathy develops in 30 to 40% of patients. Diabetic nephropathy does not develop in the absence of hyperglycemia, even in the presence of a genetic predisposition. Multigenic predisposition contributes to the development of diabetic nephropathy, thus supporting that many factors are involved in the pathogenesis of the disease. Hyperglycemia induces renal damage directly or through hemodynamic modifications. It induces activation of protein kinase C, increased production of advanced glycosylation end products, and diacylglycerol synthesis. In addition, it is responsible for hemodynamic alterations such as hyperfiltration, shear stress, and microalbuminuria. These alterations contribute to an abnormal stimulation of resident renal cells that produce more TGF-β1. This growth factor upregulates GLUT-1, which induces an increased intracellular glucose transport and D-glucose uptake. TGF-β1 causes augmented extracellular matrix protein deposition (collagen types I, IV, V, and VI; fibronectin, and laminin) at the glomerular level, thus inducing mesangial expansion and glomerular basement thickening. However, low enzymatic degradation of extracellular matrix contributes to an excessive accumulation. Because hyperglycemia is the principal factor responsible for structural alterations at the renal level, glycemic control remains the main target of the therapy, whereas pancreas transplantation is the best approach for reducing the renal lesions.

70. Genetics of common progressive renal disease

Chow KM, Wong TY, Li PK.

71. Adiponectin level is reduced and inversely correlated with the degree of proteinuria in type 2 diabetic nephropathy

Yenicesu M, Yimaz MI, Caglar K, et al.


Abstract. Aims: Adiponectin seems to be an important modulator for metabolic and vascular disease. We aimed to measure plasma adiponectin levels in type 2 diabetic patients and investigate any association with the severity of proteinuria. Methods: 80 patients (mean age 46.9±5.1 years; body mass index (BMI) 25.8±1.98 kg/m^2) and 47 healthy volunteers (mean age 46.1±5.5 years; BMI 26.74±2.23 kg/m^2) were included. Plasma adiponectin concentration, insulin levels, homeostasis model assessment (HOMA) indices, calculated glomerular filtration rate (GFR), high sensitive C reactive protein (hsCRP) and biochemistry panel were determined in all subjects. The association between adiponectin concentration and proteinuria was evaluated. Additionally, the relationship between adiponectin and hsCRP and calculated GFR were also investigated. Results: Adiponectin levels in patients were significantly lower than those of controls (n=80; 8.76±4.50 ug/ml for patients, n=47; 24.24±5.59 ug/ml for controls, p<0.001). Plasma adiponectin levels in patients with proteinuria were significantly lower than those without proteinuria (n=43, 6.81±2.82 ug/ml for proteinuria, n=37; 11.98±3.32 ug/ml for no proteinuria, p<0.001). There was significant negative correlation between plasma adiponectin concentration and the degree of proteinuria (r=-0.433, p<0.001). There were also significant negative correlations between adiponectin concentration and insulin levels as well as HOMA index in the patient group (r=-0.322, p=0.0004; r=0.301, p=0.032). Additionally there was a significant negative correlation between adiponectin and hsCRP levels in the patients group (r=-0.872, p<0.001). Conclusion: The results show that adiponectin is lower in patients with type 2 diabetes and the levels are negatively correlated with the severity of proteinuria.

72. Apolipoprotein E and progression of chronic kidney disease

Hsu CC, Kao WH, Pankow JS, et al.


Summary: See Part 2/PG/5.

73. Lower serum magnesium levels are associated with more rapid decline of renal function in
Abstract. Aims: Hypomagnesemia has been complicated in adversely affecting diabetic complications. This is a retrospective study designed to determine whether there is any association between serum magnesium concentration and the rate of renal function deterioration as determined by the slope of serum creatinine reciprocals versus time (l/SCr-vs-t), in patients with diabetes mellitus type 2 (DM2). Materials and Methods: DM2 patients without known kidney disease seen at Olive View-UCLA Medical Center for any reason during January – March 2001 were included. For each patient all available data from our electronic database for magnesium, hemoglobin A1c (HbA1c), serum creatinine (SCr), lipid profiles, routine urinary analysis, as well as history of hypertension and pharmacy profiles were retrieved. The average of all parameters obtained and linear regression analysis for the slope of l/SCr-vs-t plot were performed for each patient. Patients were stratified by gender and divided into four groups based on increasing magnesium. Correlation between each parameter including the slope of l/SCr-vs-t and the four magnesium group were analyzed. Results: 252 males and 298 females with a mean follow-up pf 62,6322.5 months were included. Patients belonging to lower magnesium groups for both genders had significantly worse slopes of l/Scr-vs-t plot independent of the presence of hypertension and use of ACEI/ARB, diuretics, HMG-CoA enzyme inhibitors or aspirin. In a multivariate regression analysis controlling for age, HbA1c and various components of the lipid profile. Magnesium remained an independent predictor for the slope of l/SCr-vs-t. A trend for worse proteinuria based on routine urinary analysis was observed among patients belonging to the lowest magnesium group. Conclusion: Lower magnesium is associated with a faster renal function deterioration in DM2 patients.

74. Acute renal failure

Lameire N, Van Biesen W, Vanholder R.


Summary: See Part 2/ET/22.

75. Acute renal failure in chronic kidney disease – clinical and pathological analysis of 104 cases

Zhang L, wang M, Wang H.

Abstract. Background: Acute renal failure in chronic kidney disease (A/C) constitutes an important part of acute renal failure (ARF), but until now there has been no research focusing on this entity. Patients and Methods: Clinical data were collected from all patients diagnosed as A/C by clinical materials and renal biopsy over a 12-year period (January 1990-December 2001) in the renal department of a teaching hospital, and the incidence, etiology, pathological and clinical features of A/C, and factors predicting prognosis were studied. Results: Altogether, 104 patients of A/C were identified, which accounted for 35.5% of biopsied acute renal failure cases during the same period. Drug-induced acute renal interstitial/tubular-interstitial disease, prerenal ARF and flare-up lupus nephritis were the most common causes of ARF in A/C patients. More than one third of A/C were associated with drugs, which occurred more commonly in older patients. After an average hospitalization of 28.5 days, about 39 patients required dialysis, 23 patients became dialysis-independent. The mortality was 1.9%. Furthermore, serum creatinine (scr) returned to normal level (<133 ummol/l) in 46.2% of all patients; Scr decreased by 15%, yet not normal in 26.0%. Multivariable logistic regression analysis indicated that hypertension, requirement of dialysis therapy and high Scr level were independent predictors of poor renal outcome. Conclusion: A/C constitutes an important part of ARF, and drug-induced ARF is prominent in China. Because early diagnosis and correct treatment may obviously affect prognosis, enough attention should be paid to this entity.

IV. CLINICAL PRESENTATION
1. Glomerulonephritis

Lau KK, Wyatt RJ.


Glomerulonephritis (GN) in the adolescent requires prompt diagnosis. When even mild degrees of renal insufficiency are documented, immediate referral to a nephrologist is necessary to ensure that serious conditions, such as rapidly progressive glomerulonephritis (RPGN), are correctly diagnosed and aggressively managed. In an adolescent with macroscopic hematuria, the demonstration of dysmorphic RBCs, RBC casts, and proteinuria indicates that the bleeding is of glomerular origin. Physicians caring for adolescents with chronic GN should have a basic understanding of the specific disorders. They may be involved in blood pressure monitoring and should be aware of the potential side effects of the antihypertensive and immunosuppressive medications used in patients with GN.

2. The investigation of hematuria

Kinkaid-Smith P, Fairley K.


3. The clinical significance of asymptomatic gross and microscopic hematuria in children

Bergstein J, Leiser J, Andreoli S.


Background: The development of asymptomatic gross or microscopic hematuria is relatively common in children. Objective: To evaluate the clinical importance of hematuria in children and the necessity for such an evaluation using a defined diagnostic protocol. Design: The protocol included a personal and family history, physical examination and blood pressure determination, and a set of comprehensive laboratory and radiological examinations. Results: Of 342 children with microscopic hematuria, no cause was uncovered in 274 patients. The most common cause discovered was hypercalcuria (16%), followed by post-streptococcal glomerulonephritis (1%). Of
228 with gross hematuria, no cause was uncovered in 86 patients. The most common cause discovered was hypercalcuria (22%). Ten patients had clinically important structural abnormalities. Fifty-three patients qualified for renal biopsy: 36 had IgA nephropathy. Conclusion: Our results suggest that diagnostic evaluation for potential causes of asymptomatic microscopic hematuria in children may not be necessary. Because of asymptomatic hematuria can, rarely, be the first sign of occult renal disease, long-term follow-up is mandatory. As clinically important abnormalities of the urinary tract are commonly discovered in children with asymptomatic gross hematuria, a thorough diagnostic evaluation is warranted.

4. Microscopic hematuria in pregnancy: relevance to pregnancy outcome


Background: The significance of dipstick or microscopic hematurie in pregnancy is uncertain, with some studies suggesting this is associated with a greater risk for preeclampsia. We sought to determine the prevalence and clinical significance of microscopic hematuria during pregnancy. Methods: This was a prospective case-control study in the antenatal Clinic of St George Hospital, Kogarah, Australia, a teaching hospital without tertiary referral antenatal care, with approximately 2,600 deliveries per year. One thousand pregnant women attending for routine antenatal care were invited to have a routine urinanalysis performed and be referred to a nephrology clinic for further investigation if dipstick microscopic hematuria was detected on more than 1 occasion before 32 weeks’ gestation. Main outcome measures were the prevalence of hematuria confirmed by urine microscopy, and the development of preeclampsia or gestational hypertension or delivery of a small-for-gestational-age baby. Results: One hundred seventy eight of 902 women (20%) who entered the study had dipstick hematuria on a least 2 occasions in pregnancy: 66 of 126 women (53%) who had hematuria before 32 weeks attended the nephrology clinic, where microscopic hematuria was confirmed in 40 women (61%). Renal imaging results were normal in all except 1 woman, and all woman had a serum creatinine level of 0.90mg/dL or less (< or =80 umol/L). the development of preeclampsia or gestational hypertension or delivery of a small-for-gestational-age baby were similar in women with and without dipstick hematuria. Microscopic hematuria persisted in half (15 women) of those who attended for follow-up after 3 months postpartum. Conclusion: Dipstick hematuria is very common during pregnancy, but rarely signifies a disorder likely to impact on the pregnancy outcome. Postpartum follow-up is recommended to detect women who have persistent hematuria and presumed underlying mild glomerulonephritis.

5. Biochemical risk markers: a novel area for better prediction of renal risk?

Stuveling EM, Bakker SJ, Hillege HL, et al.

Markers of progressive cardiovascular (CV) disease are close to becoming of value in clinical practice as an additive tool to the classical risk factors. These markers have been proposed from viewpoint of plausible pathophysiological concepts in vascular disease. Although these concepts have been investigated mainly in CV disease, there are accumulating data and evidence for an important role in renal disease progression as well. Indeed, in view of the overlap between CV and renal risk factors, it is tempting to speculate that novel risk markers will be able to predict accelerated decline of renal function in the population. In fact, some of these factors such as high-sensitive CRP and albuminuria are close to becoming valuable renal risk markers both for detecting the risk for disease progression and for the protective response to therapy.

6. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine


Abstract. Background: Detection of renal dysfunction is important in critically ill patients, and daily practice, serum creatinine is used most often. Other tools allowing the evaluation of renal function are the Cockcroft-Gault and MDRD (Modification of Diet in Renal Disease) equations. These parameters may, however, not be optimal for critically ill patients. The present study evaluated the value of a single serum creatinine measurement, within normal limits, and there commonly used prediction equations for assessment of glomerular function (Cockcroft-Gault, MDRD, and the simplified MDRD formula), compared with creatinine clearance (Ccr) measured on a 1 urine collection in an intensive care unit (ICU) population. Methods: This was a prospective observational study. A total of 28 adult patients with a serum creatinine <1,5mg/dl, within the first week of ICU admission, were included in the study. Renal function was assessed with serum creatinine, timed 1h urinary Ccr, and the Cockcroft-Gault, MDRD and simplified MDRD equations. Results: Serum creatinine was in the normal range in all patients. Despite this, measured urinary Ccr was <80ml/min/1,73m² in 13 patients (46,4%), and <60ml/min/1,73m² in seven patients (25%). Urinary creatinine levels were low, especially in patients with low Ccr, suggesting a depressed production of creatinine caused by pronounced muscle loss. regression analysis and Bland-Altman plots revealed neither the Cockcroft-Gault formula nor the MDRD equations were specific enough for assessment of renal function. Conclusion: In recently admitted critically ill with normal serum creatinine, serum creatinine had a low sensitivity for detection of renal dysfunction. Furthermore, the Cockcroft-Gault and MDRD equations were not adequate in assessing renal function.

7. Study of the biopsied nephrotic syndrome for 20 years in the Cadiz Bay Area: histological correspondence, renal prognosis and clinical prognostic factors

Quros PL, Ceballos M, Remon C, et al.

8. Renal manifestation of sexually transmitted diseases: sexually transmitted disease and the kidney

Abitbol CL, Friedman LB, Zilleruelo G.


9. HIV-associated immune complex glomerulonephritis with „lupus-like” features: a clinicopathologic study of 14 cases

Haas M, Kaul S, Eustace JA.


10. Glomerulonephritis in a patient with chronic active Epstein-Barr virus infection

Kano K, Yamada Y, Sato Y,


11. Five-year following-up of patients with epidemic glomerulonephritis due to Streptococcus zooepidemicus

Sesso R, Pinto SW.
12. Poststreptococal acute glomerulonephritis superimposed on bilateral renal hypoplasia


An 8-year-old girl with preexisting chronic renal failure (CRF) due to bilateral renal hypoplasia presented with edema, gross hematuria and acute deterioration of renal function. The diagnosis of poststreptococcal acute glomerulonephritis (PSAGN) was made based on clinical presentation, red blood cell casts, low level of C3 and elevated antistreptolysin O titer. Her course was prolonged, with serum creatinine increased from baseline level of 1.1 mg/dl to 2.2 mg/dl, returning toward the baseline level (1.2 mg/dl) after one month. Serum creatinine then started to increase again. The slope of creatinine clearance over time became steeper after the episode of PSAGN. A severe course of PSAGN and subsequent deterioration of renal function have previously been reported in patients with diabetic nephropathy or focal segmental glomerulosclerosis. The present case along with literature review suggest that individuals with fewer nephrons are at higher risk of severe course and outcome of PSAGN. Conversely, patients with severe PSAGN may be born with fewer nephrons due to low birth weight, unrecognized renal hypoplasia or other unknown causes.

13. Chronic renal disease in Kuwaiti nationals: a prospective study during the past 4 years.


Our study is a prospective one conducted at Al-Amiri Hospital and uncluding all new cases of chronic renal disease (CRD) seen at the capital area of Kuwait between 1 January 1999 and 30 December 2003. Diagnosis of CRD was based on clinical, laboratory, and radiological features. Kidney biopsies were done when indicated. A total of 271 cases of chronic renal failure (CRF) were diagnosed, of whom 143 were women. The median age was 40 years, (range, 5 to 80 years; mean 3/- SD: 40 +/- 14). The most common cause of CRF was glomerulonephritis (32%), of which systemic lupus erythematosus and vasculitis constituted 5% and 4%, respectively. Diabetic glomerulosclerosis was the second leading cause of CRD (24%), followed by tubulointerstitial disease (11%) and nephroangiosclerosis (10%). Less frequent causes included renovascular/ischemic disease (6%), obstructive nephropathy (3%), and adult polycystic kidney disease (3%). One hundred and seven patients had 121 incidents of acute deterioration of underlying renal disease. This was mostly due to drugs (22%), infection (21%), and volume depletion (13%). Antiinflammatory drugs were the most common drugs (63%) responsible for the acute decline in
renal function. By the end of study, 18 (7%) patients died. 55 (20%) required maintenance dialysis, and 40 (15%) had received a kidney allograft. Diabetic patients did not differ from nondiabetic with regard mortality, although had more renal replacement Therapy (p=0.002). Using the Cox regression model, analysis of the relative risk factors likely to contribute to mortality, age, gender, original kidney disease, fitness for transplantation, and mode of presentation, did not show significant factors except for less hazard to death in those diagnosed early with CRD (i.e., on routine testing, relative risk 0.06, p=0.01). In conclusion, our study indicates that early diagnosis and management of CRD can improve the patient’s quality of life and decrease the cost of frequent hospitalization, morbidity, and even mortality associated with end-stage renal disease.

14. Hypocomplementemia and membranoproliferative glomerulonephritis in children


15. C1q nephropathy: features at presentation and outcome

Lau KK, Gaber LW, Delos Santos NM, et al.


The study population comprised all 20 patients followed since 1990 through December 2004 at the Le Boheur Children’s Medical Center with diagnosis of C1q nephropathy (55% boys; 60% African Americans). All were aged under 18 years at biopsy (mean 11.2 years, 65% aged 11 or over); the youngest presented at age 18 months and progressed to end-stage renal disease at 14 months. None had clinical or laboratory features of systemic lupus erythematosus or membranoproliferative glomerulonephritis. Clinical features assessed at diagnosis were age, gender, blood pressure, history of macroscopic hematuria, urinary protein to creatinine ratio, serum creatinine, estimated glomerular filtration rate, renal histology, and pattern for immunofluorescent reactants. At the time of biopsy 40% had nephrotic syndrome and 30% nephrotic range proteinuria. Three patients with nephrotic syndrome also had chronic renal insufficiency at diagnosis. The most common histological feature was focal segmental glomerulosclerosis in 40%, but 30% had minimal change lesion. Four patients, all with nephrotic syndrome at diagnosis, progressed to end-stage renal disease. Of the 12 not presenting with nephrotic syndrome, none had chronic renal insufficiency at least follow-up. Kidney survival was 94% and 78% at 1 and 5 years, respectively, in all patients and 88% and 49% in those presenting with nephrotic syndrome.
Since isolated C3 mesangial proliferative glomerulonephritis in the absence of systemic disease (i-C3-GN) is an uncommon chronic glomerular disease, long-term prognosis and optimal therapeutic intervention for it are not yet fully defined, especially in children. We report clinical features, outcome, and interventions in 14 patients, ranging from 6 to 18 years old, with i-C3-GN. Microscopic or macroscopic hematuria with or without proteinuria was first noted between 3 and 8 years. When present, proteinuria ranged from 0.2 to 1.0g/24h. Persistent hypocomplementemia and circulating immune complexes were found in 1 patient. None of the patients had nephrotic syndrome or hypertension. Pecutaneous biopsy specimen showed varying degrees of mesangial proliferative glomerulonephritis; 2 patients showed mild mesangial proliferation, while others exhibited moderate histologic severity. In 1 patient with a mild mesangial increase tubulointerstitial changes were associated. Both patients exhibiting mild mesangial changes followed a benign clinical course with normal renal function over 10 years of follow-up. Patients with moderate severe mesangial alteration manifested slight renal function loss and moderate proteinuria at the time of biopsy, but these largely resolved after a six-month course of prednisolone combined with cyclophosphamide, warfarin, and an angiotensin-converting enzyme inhibitor. Thus, clinical manifestation and the need for aggressive treatment appear to vary among pediatric patients with i-C3-GN. Therapy combining prednisolone with immunosuppression seemed to reduce proteinuria and improve glomerular function in patients with moderately severe mesangial proliferation.

Henoch-Schonlein purpura (HSP) is an IgA-mediated systemic small vessel vasculitis of childhood. It is characterized by the symptoms including nonthrombocytopenic purpura, abdominal pain, hematuria/proteinuria, and arthralgia/arthritis. We conducted a retrospective study of 261 patients diagnosed with HSP from December 1991 to December 2001. Of the 261 patients, fifty-three (20.3%) developed renal manifestations after onset of the disease. Two patients developed nephrotic syndrome. Four patients had group A beta-hemolytic streptococcal pharyngitis and subsequent depressed serum C3 concentration typical of post-streptococcal glomerulonephritis. During the study period, the renal survival rate after disease onset was 100%. The prognosis of renal involvement was better than reports from other series. In this study we also found factors associated with HSP nephritis; these included older age at onset, GI bleeding, and central nervous system involvement. It is recommended that patients with HSP nephritis are followed for longer periods of time.
18. Henoch-Schonlein purpura with hypocomplementemia in children

Motoyama O, Iitaka K.


**Background:** The clinical course and prognosis of Henoch-Schonlein purpura (HSP) associated with hypocomplementemia are not clear. **Methods:** The clinical findings of 10 children with HSP and hypocomplementemia were studied. **Results:** Purpuric rash in all patients, abdominal pain in five, and arthralgia in nine were noted. The findings in HSP were not different from others with HSP. In eight patients, infection preceded hypocomplementemia. Serum levels of CH50, C3 or C4 were depressed variously. Complement levels returned to normal within 5 weeks in all patients. Antistreptolysin-O (ASO) titer was elevated in all patients and nephritis occurred in eight patients. Six patients had generalized edema and hypertension. Macroscopic hematuria occurred in two patients and heavy proteinuria in five patients. One patient was diagnosed as having poststreplococcal acute glomerulonephritis (PSAGN) combined with HSP nephritis to renal biopsy findings. In three of eight patients with nephritis, abnormal urinary findings continued for more than 1 year. **Conclusions:** Hypocomplementemia in children with HSP was transient and was not related to severity of HSP. Incidences of elevated ASO titer and nephritis were high. The nephritis resembled PSAGN during the acute stage and long-term clinical courses varied. These findings suggest PSAGN may be associated with HSP nephritis.

19. Immunotactoid glomerulopathy with microtubular deposit, with reference to the characteristics of Japanese cases


**Summary:** See Part 2/PG/19.

20. Fibrillary and immunotactoid glomerulonephritis: report of a case and review of the literature


21. Renal involvement in patients with polymyositis and dermatomyositis

Yen TH, Lai PC, Chen CC, et al.


22. Psoriatic nephropathy – does an entity?

Singh NP, Prakash A, Kubba S, et al.


23. Renal and thymic pathology in thymoma-associated nephropathy: report of 21 cases and review of the literature

Karras A, de Montpreville V, Fakhouri F, et al.


Background: Acquired thymic disease (malignant thymoma or thymic hyperplasia) is associated with various autoimmune diseases, such as myasthenia gravis (MG), pure red-cell aplasia (PRCA), pemphigus vulgaris or systemic lupus erythematosus (SLE). Renal disease has rarely been observed in association with thymoma. Methods: This retrospective, multicentric study collected data on patients with thymic disease and biopsy-proven renal involvement. Results: Twenty one patients were studied (age: 49 +/- 14 years; male/female ratio: 8/13). Thymic pathology revealed mostly high-grade malignant thymoma (B2 and AB type): two cases were associated with non-malignant thymic hyperplasia. MG was found in nine out of 21 cases, SLE in three, PCRA in three and pemphigus in two. In 47% of these cases, nephropathy occurred after curative treatment of thymoma (108 +/-83 months; range: 8-180 months), mainly based on surgical thymectomy associated with radiotherapy. Clinical and laboratory findings included nephrotic syndrome (75%), renal failure (50%), frequent presence of antinuclear antibodies and hypogammaglobulinemia. Renal pathology showed minimal change disease in 14 patients and focal segmental glomerulosclerosis (FSGS) in
one. Membranous nephropathy was observed in four cases, ANCA-associated glomerulonephritis in two and thrombotic microangiopathy in one. Most patients with minimal change disease or FSGS (11/13) were steroid-sensitive. Despite good response to steroids, 38% of patients died from thymoma and 17% developed end-stage renal failure. **Conclusions:** Glomerulopathy can be associated with thymoma or thymic hyperplasia. The present series shows that minimal change disease is the most frequent thymoma-associated glomerular lesion and that it may occur several years after thymectomy.

**24. The increase of antiglomerular basement membrane antibody following pauci-immune-type crescentic glomerulonephritis**


A 50-year-old woman was admitted because of high fever and fatigue. Proteinuria, hematuria, and elevated BUN (47.8 mg/dl) and creatinine (3.4 mg/dl) suggested rapidly progressive glomerulonephritis. The serological study revealed all negative results for rheumatoid factor, antinuclear antibody, serum cryoglobulins, MPO-ANCA, PR3-ANCA, and anti-streptolysin O. Antiglomerular basement membrane (GBM) antibody, as assessed by ELISA, was 11 EU/ml (normal, <10). Kidney biopsy on the eight hospital day demonstrated pauci-immune-type crescentic glomerulonephritis without ANCA. Methylprednisolone pulse therapy (500mg/day), 3 days) and 45 mg/day prednisolone orally were started. Atz 3 weeks after kidney biopsy, the anti-GBM antibody value increased from 11 EU/ml to 116 EU/ml, and MPO- and PR3-ANCA were still negative. HLA type was DR8 and DR 15(2), with a genotype of HLA-DRB1*08021 and HLA-DRB1*15011. The present case suggests that HLA-DR15 plays an important role on antibody production against alpha 3(IV) NC1 autoantigen after severe nephritis or tissue damage.

**25. Characteristics and prognosis of Chinese patients with anti-glomerular basement membrane disease**


**Background:** Patients with anti-glomerular basement membrane (GBM) disease were predominantly reported in Caucasian population and report from Chinese were lacking. The general picture of Chinese patients with anti-GBM disease was still unclear. This study is to investigate the characteristics and prognosis of Chinese patients with anti-GBM disease. **Methods:** Data from 105 patients with anti-GBM disease diagnosed in our hospital, between 1997 and 2002, were analyzed retrospectively. All the 105 sera were screened by enzyme-linked immunosorbent assay (ELISA) using highly purified bovine alpha(IV)NC1 as solid phase ligands. Clinical and pathological data of 69 patients with complete clinical remission (n=5), partial remission (n=10), and treatment failure
were compared and the prognostic factors were evaluated. **Results:** Patients increased chronologically and three quarters of the 105 patients were diagnosed in the least 3 years. Most of the patients were between 20 and 29 years (n=31) and a smaller second peak was found in patients over 60 years. 25/105 (24%) were also ANCA-positive. Patients with both anti-GBM antibodies and ANCA positive were elder (50 +/- 19 vs. 34 +/- years, p<0,01) and female predominant (15/25 vs 16/80, p < 0.05), 56/97 (58%) patients presented as Goodpasture syndrome, 40/97 (41%) patients presented as rapidly progressive glomerulonephritis and one patient had pulmonary hemorrhage only. The following factors predict poor prognosis: (1) serum creatinine more than 600 umol/l on diagnosis (p<0,01); (2) oliguria or anuria on diagnosis (p<0.001); (3) a high percentage (>85%) of glomeruli had crescents (p<0,01), and (4) renal involvement before pulmonary hemorrhage (p<0,05). Patients with serum creatinine over 600 umol/l on diagnosis had higher levels of anti-GBM antibodies (106 +/- 48% vs 73 +/- 40%, p<0,01). Intensive plasma exchange therapy predicts a better prognosis in the patients with serum creatinine less than 600 umol/l (p<0,05). **Conclusion:** Anti-GBM disease is not rare in China and behaves similarly to elsewhere. Early diagnosis and intensive plasmapheresis might be the most promising approaches to improve the outcomes.

26. Two unusual cases of Anderson-Fabry disease in a Japanese family

Chinen S, Tana T, Kohagura K, et al.


**Abstract.** A 16-year-old Japanese girl was admitted to our hospital on February 27, 2001, for acute renal failure. She had not shown proteinuria or hematuria in any school examination through 2000. The first renal biopsy specimen showed focal segmental glomerulosclerosis and tubulointerstitial change. Electron microscopy showed numerous myeloid bodies in the glomerular epithelium suggesting the diagnosis of Anderson-Fabry disease. After electron microscopy, we measured WBC alpha-galactosidase A, which was slightly decreased to 36,1 nmol//mgP/h (normal: 49,8 – 116,4). WBC alpha-galactosidase A levels for other family members were 74,3 for the mother, 4,8 for the father, 45,6 for the elder sister and 16,3 for the younger sister. During the follow-up, she had two episodes of nephrotic syndrome, which responded well to steroid therapy. Both second and third renal biopsy showed numerous myeloid bodies by electron microscopy. A 52-year-old man, the father of the case one patient, was admitted for renal biopsy because of proteinuria and low levels of WBC alpha-galactosidase. Biopsy specimen showed typical changes under light microscopy and typical myeloid bodies by electron microscopy. Our cases underscore the importance of electron microscopy when examining the biopsy specimen and suggest that undiagnosed Anderson-Fabry disease may present, in particular on chronic dialysis

27. Clinical presentation and monitoring of lupus nephritis

Balow JE.

The diversity of clinical presentation of lupus nephritis parallel the diversity of pathologic lesion seen in the kidneys of patients with SLE. Renal manifestation range from asymptomatic hematuria or proteinuria to overt nephritic and nephrotic syndromes, rapidly progressive glomerulonephritis, and chronic renal failure. Subclinical nephropathy both during presentation and during monitoring of disease activity is frequently missed because of the notorious unreliability of routine screening urinalyses performed in high-throughput clinical pathology laboratories. Requisitions for urine microscopy should be flagged for special attention in patients at risk for lupus nephritis. Depression of classic complement pathway components and high titers of anti-DNA, anti-nucleosome, or antiC1q antibodies identify patients are increased risk of renal involvement or flares of nephritis. Several disease activity and damage indexes are available, but they are mostly used in clinical research setting and none achieved wide use for standard clinical practice.

28. Lupus erythematosus proliferative glomerulonephritis in fetus


Summary: See Part 2/PG/24.

29. Infantile systemic lupus erythematosus presenting with pulmonary hemorrhage


Systemic lupus erythematosus in infants born to healthy mothers is a rare entity. We describe a male infant who presented at 1 month of age with pulmonary hemorrhage and glomerulonephritis due to systemic lupus erythematosus, confirmed serologically and histologically. He was managed with a combination of prednisone and intermittent cyclophosphamide, but also received mycophenolate mofetil, with a complete serological and clinical remission at 30-month follow-up. This case underscores the importance of a broad approach to the evaluation of pulmonary hemorrhage and glomerulonephritis in the very young and the need for aggressive immunosuppressive therapy to achieve sustained serological and clinical remission.

30. Lupus nephritis in children in Malaysia

Khoo JJ, Thevarajah B, Yap YC, et al.
31. Association of systemic lupus erythematosus and dermatopolymyositis


Systemic lupus erythematosus (SLE) associated with dermatopolymyositis (DM). This association is rare. Diagnosis may be difficult because of their common clinical findings. We report here a case. A 22-year-old man was admitted for arthritis with fever, diffuse myalgia and periorbital skin heliotrope rash. Electromyogram and muscular biopsy were suggestive of DM. The patient was treated with oral prednisone. Two months and half later, he was admitted for impure nephrotic syndrome in relation with diffuse proliferative glomerulonephritis. Antibodies against native double-stranded-DNA were positive, and normal skin biopsy showed complex deposits on dermo-epidermic junction, suggestive of SLE. The patient was treated with high doses of prednisone and 6 monthly intravenous pulses of cyclophosphamide. Skin lesions and nephrotic syndrome improved. Presently, the patient remains asymptomatic. While being of different pathogenesis, SLE and DM may coexist in the same patients.

32. Relationship between anti-double-stranded DNA antibodies and exacerbation of renal disease in patients with systemic lupus erythematosus


Objective: To examine the relationship between changes in anti-double-stranded DNA (anti-dsDNA) antibody levels and the risk of renal flare in patients with systemic lupus erythematosus (SLE), using data from 2 randomized, controlled, trials. Methods: Analyses were based on 487 patients with SLE and a history of lupus nephritis who had an anti-dsDNA antibody titer \( \geq 15 \) IU/ml at baseline, as measured by Farr assay. Results are presented for the combined population of patients, the placebo arms, and the drug treatment arms in which a dsDNA-based bioconjugate (abetimus sodium; LJP 394) was used. Results: Changes in anti-dsDNA antibody levels were inversely correlated with changes in the C3 level \( (P<0.0001 \text{ in both trials}) \). Cox proportional hazards regression models showed that changes in anti-dsDNA antibody levels correlated with the risk of renal flare. The models predicted that a point estimate of a 50\% reduction in anti-dsDNA antibody levels is associated with a 52\% reduction (95\% confidence interval [95\% CI] 26-68\%,}
nominal P= 0.0007) and 53% reduction (95% CI 33-69%, nominal P< 0.0001) in the risk of renal flare in the 2 trials, respectively. In the 2 trials, the incidence of renal flare was lower in patients with sustained reductions in anti-dsDNA antibodies (3.0% and 4.1%, respectively) than in patients with stable or increasing antibody levels (21.3% and 20.3%, respectively). Conclusion: Changes in anti-dsDNA antibody levels were directly correlated with the risk of renal flare and inversely correlated with changes in the C3 level. Reducing anti-dsDNA antibody levels may represent a therapeutic objective in SLE patients with lupus nephritis, because it is associated with a reduced risk of renal flare.

33. Long-term outcome of type V lupus membranous glomerulonephritis

Pasten VR, Massardo VL, Rosenberg GH, et al.


Background: The long-term outcome of the pure form of WHO type V lupus membranous glomerulonephritis is apparently more benign than that of other forms of lupus glomerulonephritis. However 12% of such patients progress to terminal renal failure. The presence of proteinuria may be an indication of cytotoxic agents. Aims: To study the clinical long-term outcome of WHO type V lupus membranous glomerulonephritis. Materials and Methods: A retrospective analysis of all kidney biopsies of a University Pathology Department, with the diagnosis of WHO type V lupus membranous glomerulonephritis. Review of medical records of patients with the disease and one clinical assessment of all living patients. Results: Between 1973 and 2000, 703 kidney biopsies were done to patients with systemic lupus erythematosus. Of these, 40 were membranous glomerulonephritis and in 33 patients (28 women, age range 6-71 years), data on the evolution and survival was obtained. Nineteen had type Va and the rest type Vb nephritis. Two presented with renal failure and 11 with proteinuria over 3.5 g/24h. The median follow-up since the renal biopsy was 63 months (range 1-316). At the end of follow-up, four had a creatinine clearance of less then 15 ml/h and four a clearance between 15 and 29 ml/h (one of these received a renal allograft). Eleven (33%) patients had died, mostly due to infections. Life expectancy at five years with a creatinine clearance over 15 ml/h was 75%. Bad prognostic factors were an elevated creatinine and high blood pressure at the moment of biopsy. Conclusions: The clinical outcome of these patients was bad. Twelve percent reached a stage of terminal renal failure. This is in contrast with the 3% progression to a similar stage of proliferative glomerulonephritis treated with i.v. cyclophosphamide. New therapies for this condition must be sought.

34. Serum neopterin, tumor necrosis factor-alpha and soluble tumor necrosis factor receptor II (p75) levels and disease activity in Egyptian female patients with systemic lupus erythematosus

Mahmoud RA, el-gendi HI, Ahmed HH.

**Objective:** To determine the clinical value of assaying serum levels of neopterin, tumor necrosis factor-alpha (TNF-alpha) and soluble tumor necrosis factor receptor II (p75) (sTNFRII) in patients with systemic lupus erythematosus (SLE), manifested with lupus nephritis (LN), neuropsychiatric lupus erythematosus (NPLE), and/or vasculitis compared with established parameters (complement C3 and C4). **Patients and Methods:** Serum concentration of neopterin, TNF-alpha, sTNFRII were studied in 40 female patients with SLE at various degrees of disease activity and in 10 healthy controls, matched for age and sex, using an ELISA kit. Disease activity was assessed by the SLE disease activity index (SLEDAI) score. Thirty-five, 30 and 28 of our patients presented with LN, NPLE and/or vasculitis, respectively, as the main clinical manifestation. **Results:** Serum levels of neopterin, TNF-alpha and sTNFRII were significantly increased, while the TNF-alpha/sTNFRII ratio, C3 and C4 levels of SLE patients were significantly lower than those of healthy controls. Neopterin and sTNFRII were the only parameter that showed significantly higher levels in SLE patients with mild activity compared to normal subjects and were only parameters that showed a significant elevation in membranous nephritis an in mild NPLE compared to patients without nephritis and NPLE. Patients with vasculitis had significant elevation of serum neopterin, TNF-alpha and sTNFRII levels compared to patients without vasculitis. We found significant correlations between all measured variables and the SLEDAI score. Also, serum neopterin levels showed significant positive correlation with serum TNF-alpha, sTNFRII and TNF-alpha/sTNFRII levels. Serum neopterin and sTNFRII could be used to identify SLE patients from normals with a sensitivity and specificity of 100%. Multivariate linear regression analysis showed that serum sTNFRII was the only significant independent variable among parameters for prediction of SLE disease activity. **Conclusion:** We suggest that serum sTNFRII and neopterin are more sensitive markers of disease activity than TNF-alpha, C3 or C4. However, sTNFRII may be a clinically useful independent marker for prediction of SLE disease activity and to differentiate normal subjects from those having mild SLE.

35. Urine chemokines as biomarkers of human systemic lupus erythematosus activity

Rovin BH, Song H, Birmingham DJ, et al.


The purpose of this study was to evaluate urine monocyte chemoattractant protein-1 (MCP-1) and IL-8 as biomarkers of SLE flare. Urine was collected every month from patients who were followed prospectively in the Ohio SLE Study. Renal and nonrenal flares were identified and MCP-1 and IL-8 were measured by specific ELISA in samples that were collected at flare. When available, MCP-1 and IL-8 were also measured in urine samples before and after flare. For comparison, MCP-1 and IL-8 were measured in the urine of healthy individuals and in renal and nonrenal SLE patients with stable disease activity (disease controls). Most patients were receiving maintenance immunosuppressive therapy before flare. At renal flare, mean urine MCP-1 (uMCP-1) was significantly greater the uMCP-1 at nonrenal flare and from healthy volunteers and renal disease controls. The level of uMCP-1 correlated with the increase in proteinuria at flare and was higher in patients with proliferative glomerulonephritis and in patients with impaired renal function. Urine MCP-1 was increased beginning 2 to 4 mo before flare. Patients who responded to therapy showed a slow decline in uMCP-1 over several months, whereas nonresponders had persistently high uMCP-1. In contrast uIL-8 did not change with disease activity and was not elevated at renal or nonrenal flare compared with disease controls. In conclusion, uMCP-1 but no uIL-8 is a sensitive and specific biomarker of renal SLE flare and its severity, even in patients who receive significant
immunosuppressive therapy. Persistently elevated uMCP-1 after treatment may indicate ongoing kidney injury that may adversely affect renal prognosis.

36. Urinary excretion of beta2-microglobulin and IgG predict prognosis in idiopathic membranous nephropathy


An accurate prediction of the prognosis of patients with idiopathic membranous nephropathy (iMN) should allow restriction of immunosuppressive treatment to patients who are at highest risk for ESRD. On the basis of retrospective studies, it has previously been suggested that the urinary excretion of beta2-microglobulin (Ubeta2m) and IgG (UigG) are useful predictors of renal insufficiency in patients with iMN. The threshold values of 0,5 micro/min (Ubeta2m) and 250mg/24h (UigG) have been validated in a new and larger patient cohort. From 1995 onward, 57 patients with iMN (38 men, 19 women; age 48 +/- 16yr), a nephrotic syndrome, and a serum creatinine level </=1,5 mg/dl were studied prospectively. At baseline, a standardized measurement was carried out to determine renal function and protein excretion. The end point renal death was defined as a serum creatinine exceeding 1,5mg/dl or a rise of serum creatinine of >50%. Mean (+/-SD) follow-up was 53 +/-23mo. Thus far, 25 (44%) of the patients have reached the end point renal death. Multivariate analysis confirmed Ubeta2m as the strongest predictor for development of renal insufficiency. Sensitivity and specificity were 88 and 91%, respectively, for Ubeta2m, and both were 88% for UigG. When the excretions of both proteins were combined, specificity improved to 97%. It is concluded that the present data validate the accuracy of Ubeta2m and of UigG in predicting renal outcome in patients with iMN. These markers can be used to guide decisions on the start of immunosuppressiv treatment.

37. Antineutrophil cytoplasmic antibodies (ANCA)

Radice A, Sinico RA.


Abstract. Antineutrophil cytoplasmic antibodies (ANCA) area sensitive and specific marker for ANCA associated systemic vasculitis. Using indirect immunofluorecence on ethanol-fixed neutrophils, two major fluoroscopic patterns can be recognised: a diffuse cytoplasmic staining (C-ANCA), and a perinuclear/nuclear staining )P-ANCA). In patients with vasculitis, more of 90% of C-ANCA are directed against proteinase 3 (PR3-ANCA) whereas approximately 80-90% of P-ANCA recognise myeloperoxidase (MPO-ANCA). Although C-ANCA (PR3-ANCA) is preferentially associated with Wegener’s granulomatosis (WG), and P-ANCA (MPO-ANCA) with microscopic polyangiitis (MPA), idiopathic necrotising crescenting glomerulonephritis (iNCGN)
and Churg-Strauss syndrome (CSS), there is not absolute specificity. Between 10-20% of patients with clinical WG show P-ANCA (MPO-ANCA), and even a larger percentage of patients with MPA or CSS have C-ANCA (PR3-ANCA). Furthermore, it should be stressed that approximately 10-20% with WG or MPA (and 40-50% of cases of CSS) have negative assay for ANCA. The best diagnostic performance is obatinaed when indirect immunofluorescence is combined with PR3 and MP-specific ELISAs. ANCA with different and unknown antigen specificity are found in a variety of conditions other than AASV, including inflammatory bowel diseases, other autoimmune diseases, and infections where their clinical significance is unclear.

38. Antineutrophil cytoplasmic antibodies (ANCA) in Chinese patients with anti-GBM crescentic glomerulonephritis


Summary: See Part 2/PG/31.

39. How can relapses be detected and prevented in primary systemic small-vessel vasculitidies?

Langford CA.


Relapse is an important outcome measure in patients with Wegener’s granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome. Although relapse are common in these diseases, it remains unclear why these occur and whether they are influenced by exogenous or endogenous factors. A key to minimizing the consequences of relapse is early recognition through monitoring. This is particularly essential to detect glomerulonephritis that is often asymptomatic and can be rapidly progressive. While the presence of relapse is currently based on objective evidence of active disease, investigations seek to identify factors that may distinguish patients at risk of relapse or markers that reliably predict the occurrence of relapse prior to organ injury. With the ability to successfully induce remission and the toxicities of available therapies, the relapse rate has become a critical issue in assessing the efficacy of new treatment. Recent clinical trials have sought to investigate safer therapeutic options that decrease disease relapse.

40. ANCA associated pauci-immune retinal vasculitis

Background: Antineutrophil cytoplasmic antibodies (ANCA) are useful diagnostic serological markers for the most common forms of necrotising vasculitis. ANCA associated represent distinctive clinicopathological categories – for example, Wegener’s granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, and idiopathic necrotising crescentic glomerulonephritis, collectively known as the small vessel pauci-immune glomerulonephritides. Methods: Three cases of ANCA associated pauci-immune retinal vasculitis are described. Their systemic features are described and the clinical significance of ANCA as a diagnostic test in relation to retinal vasculitis discussed. Results: These three cases represent a spectrum of clinical features associated with retinal vasculitis. Two cases have evolved into clinical recognisable entities as microscopic polyangiitis. Adherence to the international consensus statement on testing and reporting of ANCA is recommended and the authors speculate that the incidence of microscopic polyangiitis may be underestimated because of the under-recognition of systemic involvement in patients with retinal vasculitis. Conclusion: The receipt of a positive ANCA result should always raise the suspicion of a pauci-immune systemic vasculitis and prompt appropriate investigation. The authors emphasise the importance of the evaluation of systemic features in these patients with retinal vasculitis, enabling earlier recognition and thereby preventing significant morbidity and mortality.

41. Neutrophilic dermatosis associated with propylthiouracil-induced p-ANCA (p-antineutrophil cytoplasmic antibodies)


Summary: See Part 2/ET/9.

42. Histological and clinical predictors of early and late renal outcome in ANCA-associated vasculitis


Background: Renal involvement remains a major determinant in antineutrophil cytoplasmic autoantibody-associated small vessel vasculitis (AASV). While some patients may develop persistent renal damage, other have a favourable outcome. Methods: To identify patients at risk for poor renal outcome, we evaluated 95 renal biopsies (67 initial biopsies and 28 repeat biopsies) of 67 patients with AASV for the presence and extent of active (Al) and chronic (C1) lesions,
Retrospectively, AI, Ci, levels of proteinuria and dose of cyclophosphamide (CYC) were related to renal outcome. Results: Recovery of renal function in patients initially dialysis dependent was associated with a lower CI compared with patients who remained on dialysis (P<0.001), while AI did not differ significantly. In these patients, age <65 years revealed a positive predictive value of 85% for renal function recovery. Patients initially requiring dialysis exhibit a higher AI and CI compared with those who did not. Renal function in long-term follow-up correlated with CI and the amount of proteinuria. This relationship increased with time, exhibiting at 4 years a correlation coefficient of 0.607 for CI (P<0.01) and 0.775 for proteinuria (P<0.001). Follow-up biopsies showed a more pronounced CI with initial biopsies (P<0.001). None of the investigated initial parameters was predictive for renal relapse. However, there was a relationship between dose and duration of CYC and time relapse. Compared with the initial biopsy, repeat biopsies of eight patients with a creeping serum creatinine in clinical remission showed a decrease Al (P<0.001) while CI increased rapidly. These patients also had less initial CYC (NS). Conclusion: These data suggest that in AASV, evaluation of renal histopathology is helpful predicting early and late renal outcome. Chronicity and proteinuria were the best determinants of poor renal prognosis. Activity may regress under therapy, while chronicity may progress despite treatment. The amount of CYC seems to influence the occurrence of early relapses and renal survival.

43. Kidney disease associated with primary antiphospholipid syndrome: clinical signs and histopathological features in an experience of five cases


Summary: See Part 2/PG/29.

44. Thin glomerular basement membrane disease: clinical significance of a morphological diagnosis – a collaborative study of the Italian Renal Immunopathology Group

Frasca GM, Onetti-Muda A, Mari F, et al.


Abstract. Background: Thin glomerular basement membrane disease (TBMD) is a nephropathy defined by diffuse thinning of glomerular basement membrane (GBM) at electron microscopy examination, without the alterations of Alport’s syndrome (ATS). It is known that many patients with TBMD have a type IV collagen disorder and that the disease occasionally may be progressive. This study investigated 51 patients with the morphological diagnosis of TBMD lacking any sign of ATS, with the aim of defining the prevalence of type IV collagen mutation and the course of the disease. Methods: Patients were investigated as follows: (a) clinical picture and family investigation; (b) renal biopsy findings; (c) immunohistochemical study of renal tissue for collagen IV alpha-chains; (d) pedigree reconstruction and molecular investigations in genes encoding type IV
collagen chains, when DNA samples were available; and (e) follo-up data. Results: Renal biopsy analysis revealed no light microscopy changes in 27 patients and minimal abnormalities in the remainder. Global glomerular sclerosis was found in seven cases and superimposed mesangial immunoglobulin-A deposits in four. Normal staining of GBM for alpha(IV) chains was observed in all but one patients, where alpha5(IV) was absent and molecular investigation revealed a COL4A5 mutation. Five out of 25 cases had a mutation in the COL4A3/COL4A4 genes. Eight out of 38 patients followed up for 12-240 months (21%) showed signs of disease progression or hypertension. Conclusions: This study confirms that a considerable proportion of patients with TBMD have a type IV collagen disorder and that this lesion is not always benign. Thus, families should be investigated carefully whenever possible and patients and affected relatives should be examined periodically for signs of disease progression.

45. Thin basement membrane nephropathy in pregnancy

Packham D.


Summary: See Part 2/PG/39.

46. Thin basement membrane nephropathy associated with other glomerular diseases

Norby SM, Cosio FG.


Summary: See Part 2/PG/40.

47. The risks of thin basement membrane nephropathy


Summary: See Part 2/PG/41.
48. Focal segmental glomerulosclerosis: definition and relevance of a partial remission.


Focal segmental glomerulosclerosis (FSGS) is one of the most common primary glomerular disease to terminate in ESRD. A complete remission (CR) confers an excellent long-term prognosis, but the quantitative benefits of partial remission (PR) have not been defined. This study evaluated the rate of renal function decline (slope of creatinine clearance) and renal survival in nephrotic FSGS patients with CR, PR, or no remission. It also examined relapse rate from remission and its impact on outcome. Multivariate analysis included clinical and laboratory data at presentation and follow-up, BP control, the agents used, and immunosuppressive therapy. The study cohort was 281 nephrotic FSGS patients who has a minimum of 12 mo of observation and were identified from the Toronto Glomerulonephritis registry. Over a median follow-up of 65 mo, 55 experienced a CR, 117 had a PR, and 109 had no remission. A PR was independently predictive of slope and survival from renal failure by multivariate analysis (adjusted time-dependent hazard ratio, 0.48; 95% confidence interval, 0.24 to 0.96; P = 0.04). Immunosuppression with high-dose prednisone was associated with a higher rate of PR and CR. Relapse from PR was frequent (56%) and associated with a more rapid rate of renal function decline and worse renal survival compared with relapse-free partial remitters. Only female gender and nadir of proteinuria during remission were associated with a sustained remission. A PR in proteinuria and its maintenance are important therapeutic targets in FSGS, with implications for both slowing progression rate and improving renal survival.

49. Focal and segmental glomerular sclerosis (FSGS) in a man and woman with Fabry’s disease

Svarstad E, Bostad L, Kaarboe O, et al.

Abstract. We describe a man and women with Fabry’s disease. Renal biopsies showed late and early stages respectively of focal and segmental glomerulosclerosis (FSGS) and vascular changes. Clinically the hemizygous patients had advanced renal disease with nephrotic range proteinuria and serum creatinine 122 umol/l. The female carrier had minimal albuminuria, boderline GFR with a normal serum creatinine, acroparesthesias, moderate fatigue, tinnitus and headache accompanied by ischemic cerebral lesions. Enzyme replacement therapy (ERT) was initiated according to our Fabry protocol, partly due to the renal morphologic findings. We conclude that FSGS and vascular changes may be an early morphologic finding in Fabry’s disease, even in patients with subtle albuminuria. The potential role of FSGS as a marker of progressive renal disease in some Fabry patients is discussed. As FSGS and vascular changes obviously may exist across a wide range of clinical presentation and have potential prognostic indicator implications, we suggest that a renal biopsy should be performed prior to enzyme replacement therapy in all adult Fabry patients with proteinuria of various levels. Efforts should be made to develop a scoring system to evaluate potential histologic markers. Protocol biopsises may have therapeutic implications and may provide valuable information in the evaluation of start and dosing of ERT.
50. HCV associated glomerulopathy in Egyptian patients: clinicopathological analysis


51. Focal segmental glomerulosclerosis associating Kimura disease

Dede F, Ayli D, Atilgan KG, et al.


Kimura disease presents as a benign subcutaneous mass. Although it principally affects the skin and soft tissues, there is a high prevalence of related renal disease. We report a case of Kimura disease from western Asia, presenting itself as nephrotic syndrome, and this case was seen at a nontransplant kidney, presenting with focal segmental glomerulosclerosis.

52. Membranous nephropathy associated with familial chronic ulcerative colitis in a 12-year-old girl

Ridder RM, Kreth HW, Kiss E, et al.

Pediatr Nephrol 2005 Jun 22 [Epub ahead of print]

Summary: See Page 2/ET/14.

53. IgA deficiency and membranous glomerulonephritis presenting as nephrotic syndrome


Selective IgA deficiency associated with glomerulonephritis is rare and no previous reports in childhood have been made of the association of IgA deficiency and membranous glomerulonephritis (MGN). We report a 5-year-old boy with selective IgA deficiency and MGN. He presented with nephrotic syndrome. Percutaneous renal needle biopsy showed diffuse global thickening on light microscopy and heavy IgG and moderate C3 deposits were found on immunofluorescence. Electron microscopy detected extensive global subepithelial deposition of electron-dense material with frequent intramembranous extension and spike formation. The pathological diagnosis was diffuse MGN stage 1. Oral prednisolone (1mg kg\(^{-1}\)), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blocker (ARB) were given resulting in reduction of proteinuria. The prednisolone dose was gradually tapered and discontinued after 2 months. At present the patients has been in complete remission for 10 months despite the discontinuance of prednisolone. In conclusion, our treatment with corticosteroid, ACEI and ARB reduced proteinuria and was effective for our case with selective IgA deficiency and MGN.

54. Urinary excretion of beta2-microglobulin and IgG predict prognosis in idiopathic membranous nephropathy: a validation study


Summary: See Part 2/CP/36.

55. Changes in the clinical features of MPGN type-I in childhood over three decades

Hasegawa O, Honda M, Ikeda M.


This retrospective study was conducted to evaluate changes in the clinical features of MPGN type-I in childhood a 30-year period from 1970 through 1999. Renal biopsies were performed on 2,260 children with glomerulonephritidies, among whom were 71 patients with MPGN type-I. Changes in the mode of onset were investigated in patients separated according to the period of onset into two groups by 1974 in which school urinary screening had been widespread. The difference in symptoms after onset was examined between patients with the onset in the 1980s and 1990s under the same circumstances of school urinary screening and of our steroid regimen. Finally, the incidence of this disease in each of the three decades were analyzed. Chance proteinuria and/or hematuria increased (p=0,0107) and acute nephritic syndrome decrease (p=0,0237) in the ratio of the initial symptom on and after 1974. regarding the clinical presentation after onset, non-nephrotic range proteinuria increased (p=0,0415) and nephrotic syndrome decreased (p=0,0415) in the 1990s, in comparison with the respective rates in the 1980s. The incidence of this disease decreased (p<0,01) in chronological order. Conclusion: The clinical features of this disease definitely changed over three decades suggesting that the clinical presentation has ameliorated in the recent
years, regardless of effective palliation of severe symptoms afforded by our steroid regimen.

56. Myeloid-related protein 8 expression on macrophages is a useful prognostic marker for renal dysfunction in children with MPGN type I


Summary: See Part 2/PG/68.

57. Membranoproliferative glomerulonephritis type II in a 10-year-old girl

Tibbs ME, Andreoli SP, Phillips CL.


The clinical course of a 10-year-old female patient who presented with hematuria, proteinuria, and hypertension is described. Four months after being diagnosed with acute glomerulonephritis, the child was referred to a pediatric nephrologist due to persistent hematuria and unresolved proteinuria. A renal biopsy was performed due to the persistent urinary abnormalities and a family history of renal failure. The renal biopsy demonstrated pathological findings characteristic of membranoproliferative glomerulonephritis type II. The child was treated with an antihypertensive agent and steroids. Despite poor prognostic clinical and pathological features, she has minimal urinary abnormalities, normal renal function, and normal blood pressure on antihypertensive medication six years after the diagnosis of membranoproliferative glomerulonephritis type II.


Background: Pharmacological blockade of the renin-angiotensin-aldosterone system ameliorates glomerular and tubulointerstitial damage. For optimal renoprotection, high doses of angiotensin II converting enzyme inhibitors and angiotensin II subtype I receptor antagonists are commonly recommended, but cannot always be administered. The aim of this study was to evaluate the effects of low-dose (25mg) losartan on proteinuria and tubular injury extent. Material and Methods: This
was an open, randomized, 12-month study on the effects of 25mg losartan (n=19) vs. 10mg of enalapril (n=14) as a control on proteinuria, urinary excretion of N-acetyl-beta-D-glucosaminidase (NAG), and blood pressure in patients with primary glomerulonephritis. The second part of the study was an uncontrolled assessment of the renal effects of 50mg administration of losartan.

**Results:** There were no significant differences between the groups in the effects on proteinuria and NAG excretion. Losartan and enalapril reduced proteinuria by 32.8% (p<0.021), respectively, but did not affect NAG excretion. The antiproteinuric effect of losartan, achieved without changes in blood pressure, was particularly evident in subjects with proteinuria >1.2 g/24h and normal blood pressure. 50mg of losartan caused a significant decrease in NAG excretion vs. The baseline (p<0.027).

**Conclusions:** 25mg of losartan and 10mg of enalapril equally reduce proteinuria. The significant antiproteinuric effect of losartan was achieved despite no changes in blood pressure. There were no difference between the drugs regarding their influence on tubular injury exten. 50mg of losartan seems to be the minimal dose to improve tubular status. [See Part 2/TR/5.]

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59. Histological grading of IgA nephropathy predictor renal outcome: revisiting H.S. Lee’s grading system

HS Lee, MS Lee, SM Lee, et al.


**Abstract.** **Background:** The glomerular grading system is useful to compare biopsy specimens and to predict the natural course of disease in IgA nephropathy (IgAN), although no grading system can be perfect. **Methods:** H. S. Lee’s grading system for IgAN was refined as follows: grade I, normal or focal mesangial cell proliferation; grade II, diffuse mesangial cell proliferation, or <28% of glomeruli with crescent (Cr)/segmental sclerosis (SS)/global sclerosis (GS); grade III, 25-49% of glomeruli with Cr/SS/GS; grade IV, 50-75% of glomeruli with Cr/SS/GS; grade V, >75% of glomeruli with Cr/SS/GS. This refined H. S. Lee grading system was then tested for clinical relevance on 187 patients with IgAN followed up for an average of 6.5 years (minimum, 3 years). In the survival analysis, a modified primary end-point (progressive renal disease) was used. **Results:** The glomerular grades were significantly related to hypertension, serum creatinine levels and the amounts of proteinuria at time of biopsy. By univariate analysis, glomerular grades, hypertension, renal insufficiency and significant proteinuria (>1g/day) were significantly associated with progressive renal disease. By multivariate analysis using the Cox regression model, glomerular grades, hypertension, renal insufficiency and significant proteinuria were independent prognostic factors for progressive renal disease. At the end of follow up, glomerular grades were significantly related to serum creatinine level, amounts of proteinuria, hypertension and progressive renal disease. **Conclusions:** These findings indicate that the refined H. S. Lee grading system for IgAN is useful in assessing the patient’s clinical outcome and is sufficiently simple and easy to reproduce as to be universally applicable in prognostic work.

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60. IgA nephropathy what you have need to known in 2005

Although considered as a benign glomerulopathy, IgA nephropathy (IgAN) is now a well-known cause of end-stage renal disease (ESRD). Fifty percent of people suffering from IgAN develop renal insufficiency and 20 to 30% may reach ESRD after 20 to 25 years of evolution. ACEI is indicated to obtain a tight control of blood pressure and to reduce proteinuria. Corticosteroids alone or in association with immunosuppressants are indicated for aggressive, proliferative form of the disease or when there is an unfavorable outcome despite symptomatic treatment.


In Hodgkin’s disease, the most common paraneoplastic glomerular abnormality is minimal change nephropathy, although other glomerular disease occasionally have been described. We report a case of extracapillary immunoglobulin A glomerulonephritis presenting as acute renal failure in a women with newly diagnosed Hodgkin’s disease. Treatment with the bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone regimen resulted in complete hematologic and renal remission for more than 1 year after diagnosis.

62. IgA nephropathy in a young man with primary hyperparathyroidism

Brandenburg JE, Brodersen HP, Janssen U.


Summary: See Part 2/ET/12.

63. Renal manifestations of the metabolic syndrome

Tuttle KR.

Conclusions: Unhealthy lifestyles, with overeating as a dominant feature, have a number of adverse consequences. Metabolic syndrome has emerged as one of the most important because of its role in damage to vascular target organs, including the kidney. Many unanswered questions remain and should be a research priority, considering the epidemic of obesity in the developed world. The natural history, risk factors and mechanisms of chronic kidney disease (CKD) in metabolic syndrome should be elucidated further. Rigorous clinical trials of weight loss and nutritional strategies that include renal endpoints should be a priority. Given what is known about the renal haemodynamic disturbances in persons with diabetes and/or obesity, the safety of 'high protein-low carbohydrate' diets, in particular, should be scrutinized carefully. Furthermore, treatment of risk factors (control of hypertension, renin-angiotensin system inhibition, lipid lowering, reduction of glycaemia and insulin resistance) in metabolic syndrome should be elevated to determine their impact on clinical outcomes. While genetics undoubtedly predispose to metabolic syndrome, the environment is the only aspect that can be controlled at present. Therefore, prevention of obesity and promotion of healthy lifestyles, emphasizing physical activity and prudent eating habits, are likely to be the most effective approaches and should be a public health priority.

64. Acute renal failure

Lameire N, Van Biessen W, Vanholder R.


Summary: See Part 2/ET/22.

65. The structure of causes of acute renal failure and the efficacy of its treatment according to the materials of an intensive nephrological care unit

No authors listed


The study was undertaken to study the frequency, causes, and efficacy of treatment for acute renal failure (ARF) at the intensive nephrological care unit. The data on 117 patients with ARF of various etiology were studied. In them, ARF was caused by acute interstitial nephritis in 18.8%, by urosepsis in 18.8%, by non-urological sepsis in 19%, by destructive pancreatitis in 18%, in 13% rapidly progressive glomerulonephritis was present in systemic vasculitis. In 8.5% of the patients, ARF developed as a complication severe pneumonias along with respiratory failure. Only single case were presented with ARF of other intoxication etiology, crush syndrome, or acute vascular diseases. Renal replacement therapy was used in all cases. Its mode (intermittent or low-flow continous) was determined by the severity of renal failure and the general condition of patients. The overall mortality was 38% in the whole group. It was 55% in sepsis, 33% in destructive pancreatitis, 8,3% in urosepsis, 8% in acute interstitial nephritis,
64.7% in rapidly progressive glomerulonephritis. According to the type of therapy, there were no significant differences in mortality rates. There was also a correlation of the mortality rates and the APACHE scores.

66. Acute renal failure due to mesangial proliferative glomerulonephritis in a pregnant women with primary Sjogren’s syndrome

Adam FU, Torun D, Bolat F, et al.

Clin Rheumatol 2005 May 26 [Epub ahead of print]

Summary: See Part 2/ET/13.
V. TREATMENT

1. Glomerulonephritis

Chadban SJ, Atkins RC.


Summary: See Part 2/EP/3.

2. Glomerulonephritis

Lau KK, Wyatt RJ.

Summary: See Part 2/CP/1.

3. Angiotensin-converting-enzyme inhibitors slow renal decline in IgA nephropathy, independent of tubulointerstitial fibrosis at present.


Summary. Background: Tubulointerstitial fibrosis (TIF) is a marker of progression of diabetic and non-diabetic nephropathy, correlating with creatinine clearance (CCr), and functional outcome. Angiotensin-converting-enzyme inhibitors (ACEIs) slow the rate of decline of renal function in proteinuric patients. Aim: The examine whether ACEis affect TIF, directly or indirectly. Design: Prospective 3-year follow-up study. Methods: We enrolled 49 patients with IgA nephropathy (IgAN), treating some with ACE inhibitors (n=26, 1-2mg/day temocapril or trandolapril) and some with calcium-channel blockers (CCB, n=13, 2,2-5mg/day amlodipine). Blood pressure, serum creatinine, and urinanalysis were measured monthly, and 24-h endogenous creatinine clearance (CCr) at least once a year. Results: In the CCB group, TIF was positively correlated with rate of decline in CCr (dCCr), consistent with previous observations. In the ACEI group, dCCr was lower (0,02+0,02 vs. O,06+0,03), and the TIF-dCCr correlation was absent. Discussion: In the absence of post-treatment histological data, it is not possible to say whether ACEIs have an effect on TIF. However, ACEIs appear to show the progression of renal failure in IgAN, regardless of the degree of TIF at presentation.

4. Telmisartan in patients with mild/moderate hypertension and chronic kidney disease


Abstract. Aims: This study assessed the clinical efficacy and safety of telmisartan, an angiotensin II receptor blocker with a long terminal elimination half-life and almost exclusively excreted in bile, in patients with varying severity of chronic kidney disease (CKD). Patients and Methods: Adults with diastolic pressure (DBP) 90-109 mmHg and stable CKD were enrolled: mild/moderate (creatinine clearance (CrCL) 30-74 ml/min/1,43m^2), severe (CrCL <30 ml/min/1,73m^2) or requiring maintenance hemodialysis. A two- to four-week single-blind, placebo run-in period preceded once-daily telmisartan 40mg administration for four weeks. Telmisartan 80mg was given after four- or eight-week treatment if DBP >85 mmHg. After 12-week treatment trough DBP/systolic blood pressure (SDP), DBP and SDP control rates, renal function and tolerability were recorded. Results: Mean changes in DBP/SDP were -10,3/-10,7 mmHg for mild/moderate CKD (n=27), -11,2/-14,9
mmHg for severe CKD (n=24) and –15.0/-21.1 mmHg for hemodialysis patients (n=28). DPB control rates (<90 mmHg)/SBP response (<140 mmHg or ≥ 10 mmHg reduction) occurred in 59.3%/66.7%, 63.0%/70.4% and 71.4%/92.9% of mild/moderate CKD, severe CKD and hemodialysis patients, respectively. Incidences of drug-related adverse events were low, and all were known adverse events of telmisartan and common to other angiotensin II receptor blockers. At the end of treatment, a decrease in 24-h urine creatinine occurred in 5/53 (9.4%) patients: Two patients discontinued treatment prematurely due to the worsening of CKD and one due to aggravated proteinuria. **Conclusion:** Once-daily telmisartan provided effective and well-tolerated treatment of mild/moderate hypertension in CKD patients, with no worsening of renal function.

5. Randomized, controlled study of the effects of losartan versus enalapril in small doses on proteinuria and tubular injury in primary glomerulonephritis.


**Background:** Pharmacological blockade of the renin-angiotensin-aldosterone system ameliorates glomerular and tubulointerstitial damage. For optimal renoprotection, high dose angiotensin II converting enzyme inhibitors and angiotensin II subtype 1 receptor antagonists are commonly recommended, but cannot always be administered. The aim of this study was to evaluate the effects of low-dose (25mg) losartan on proteinuria and tubular injury extent. **Material/Methods:** This was an open, randomized, 12-month study on the effects of 25mg of losartan (n=19) vs. 10mg of enalapril (n=15) as a control on proteinuria, urinary excretion of N-acetyl-beta-D-glycosaminidase (NAG), and blood pressure in patients with primary glomerulonephritis. The second part of the study was an uncontrolled assessment of the renal effects of 50mg administration of losartan.

**Results:** There were no significant differences between the groups in the effects on proteinuria and NAG excretion. Losartan and enalapril reduced proteinuria by 32.8% (p<0.029) and 40.9% (p<0.021), respectively, but did not affect NAG excretion. The antiproteinuric effect of losartan, achieved without changes in blood pressure, was particularly evident in subjects with proteinuria >1.5 g/24 h and normal blood pressure. 50mg mg of losartan caused a significant decrease in NAG excretion vs. the baseline (p<0.027). **Conclusions:** 25mg of losartan and 10 mg of enalapril equally reduce proteinuria. The significant antiproteinuric effect of losartan was achieved despite no changes in blood pressure. There were no differences between the drugs regarding their influence on tubular injury extent. 50 mg of losartan seems to be the minimal dose to improve tubular status. [See Part 2/CP/58.]

6. Influence of angiotensin-converting enzyme gene polymorphism on the anti-proteinuria efficacy of angiotensin-converting enzyme inhibitor in Han nationality of southern Sichuan province in China

Objective: To investigate the association between angiotensin-converting enzyme (ACE) gene polymorphism and reducing urinary protein efficacy of angiotensin-converting enzyme inhibitor (ACEI) in patients with primary chronic glomerulonephritis in Han nationality of southern Sichuan province.

Methods: Ninety-nine primary glomerulonephritis patients with urinary protein were enrolled in this study. They were treated with benazepril for at least 3 months. The ACE gene insertion/deletion (I/D) polymorphisms in intron 16 were determined by PCR. A comparison of the reducing urinary protein efficacy of benazepril was made between the patients with different ACE genotypes.

Results: Urinary protein excretion was significantly higher in patients with ACE DD genotype than that in patients with ID genotype. After benazepril treatment for 3 months, the rates of urinary protein decline were observed. The rates of reduction of proteinuria in patients with DD genotype and ID genotype were obviously higher than in patients with II genotypes (<p<0.05).

Conclusion: Benazepril could decline the rate of urinary protein excretion in patients with primary chronic kidney glomerulonephritis, and significant relationship was observed between ACE gene polymorphism and the reducing urinary protein efficacy of ACEI.

7. Renoprotection with and without blood pressure reduction


Background: AT1-receptor blockade dose dependently lowers blood pressure (BP) and albuminuria. Reduction of BP and albuminuria are independent treatment targets for renoprotection, but whether this requires dose similar dose titration is unknown. Methods: We tested this in two studies designed to find the optimal antialbuminuric dose of losartan in type 1 diabetic (DM, N = 50) and nondiabetic renal patients (ND, N = 12). After baseline, treatment followed with losartan 50, 100, and 150mg/day, each dose for eight (DM) or six weeks (ND). At the end of each period, albuminuria (24-hour samples) and mean arterial pressure (MAP) were measured. Patients were divided into „good” and „poor” BP responders (BP+, BP-) according to BP response above or below group median. Results: Baseline MAP in the BP- groups was 102 (97,104) mm Hg in DM (median, 95%) and 91 (80, 100) mm Hg in ND. The top of the dose response for BP (obtained at losartan 100 mg) in the BP- groups was –2 (-4, 3) mm Hg in DM and –1 (-6, 2) mm Hg in ND, versus –15 (-18,-12) mm Hg and –16 (-26, -18) mm Hg in BP+ groups (both P<0,05). Albuminuria was reduced dose dependently both in BP- and BP+; with 100mg the reduction in albuminuria in DM BP- was –32% (-49, 13) versus –45% (-60, -38) in DM BP+ and –45% (-70, -7) versus –25% (-58, -6) in ND BP- and BP+ (all P>0,05): Moreover, in patients in whom BP fell below the recommended treatment target of 130/80 mm Hg (13 in DM and 10in ND), albuminuria was progressively reduced, with further increasing the dose of losartan most patients. Conclusion: Absence of BP response to losartan does not preclude a reduction in albuminuria, and optimal reduction of albuminuria may require titration beyond the predefined BP target.
8. Optimizing therapeutic strategies to achieve renal and cardiovascular risk reduction in diabetic patients with angiotensin receptor blockers

Schmieder RE.


The major challenge for the treatment of hypertensive patients with type 2 diabetes is to achieve the uniformly recommended blood pressure goal of 130/80 mmHg, and 120/75 mmHg in proteinuric patients. Such low target blood pressure levels require the administration of multiple drugs. Angiotensin receptor blockers and combination of angiotensin receptor blockers with diuretics fulfil the criteria to lower blood pressure effectively with a placebo-like side effect profile. Beyond pressure control, clinical prospective trials have documented that it does matter what kind of antihypertensive agent is used to control blood pressure. Large-scale follow-up trials have documented blood pressure independent effects of angiotensin receptor blocker on cardiac [left-ventricular hypertrophy (LVH), congestive heart failure] and renal protection (proteinuria, chronic renal failure). Of note, in these trials, angiotensin receptor blockers have been combined with diuretics, and most of the included patients have been on combination therapy comparing two to four antihypertensive agents. In addition to the combination of an angiotensin receptor blocker with a diuretics, the combination of an angiotensin receptor blocker with an angiotensin-converting enzyme inhibitor appeared to be most effective in reducing proteinuria, attenuating chronic renal failure and treating congestive heart failure.

9. The acute effect of atorvastatin on proteinuria in patients with chronic glomerulonephritis

Özsoly RC, Koopman MG, Kastelein JJ, et al.


Abstract. Background: Hyperlipidemia may develop early in the course of renal disease, and statin treatment to lower lipid levels in these patients is effective. In addition, it has been suggested that proteinuria may decrease after prolonged periods of statin treatment. In the present study, we set out to evaluate the short-term effect of atorvastatin after only six weeks of therapy. Material and Methods: Plasma albumin, creatinine, creatinine clearance, proteinuria and lipid profiles were assessed in 31 consecutive patients with glomerulonephritis and proteinuria >0.3 g/24h. All patients were treated with ACE inhibition for more than three months. Twenty patients consented to additional treatment with atorvastatin 10mg daily in conjunction with a cholesterol-reducing diet, while 11 patients received standard care. Analysis were performed at baseline and after six weeks. Results: After six weeks of treatment with atorvastatin urinary protein excretion was reduced from 1.80g/24h to 1.42g/24h (22%, p=0.005), while no change was observed in this parameter in the untreated patients over the same period. Plasma albumin did not change in treated or untreated patients. Lipid and lipoprotein parameters improved in all treated patients (all p<0.001). No correlation was observed between the percentual changes in lipids and proteinuria. Plasma creatinine and creatinine clearance did not change (p>0.05). Conclusion: Six weeks of therapy
with low-dose atorvastatin, added to ACEI inhibition, resulted in a 22% decrease of proteinuria compared to untreated patients.

10. No effect of fluvastatin on the bone mineral density of children with minimal change glomerulonephritis and some focal mesangial cell proliferation, other than an ameliorating effect on their proteinuria


Aim: There are conflicting data regarding the clinical benefit of the effect of HMG-CoA reductase inhibitors (statins) in osteoporosis. We have reported that fluvastatin (a statin) is effective in improving proteinuria and renal function in childhood IgA nephropathy with mild histological findings and moderate proteinuria. The aim of the present study was to clarify the effect of fluvastatin on the bone mineral density, bone metabolic markers, proteinuria, and renal function of children minimal change glomerulonephritis with some focal mesangial cell proliferation whose glomeruli did not stain positive for IgA and on moderate proteinuria. Patients and Methods: We conducted a prospective controlled study of 36 children who recently been diagnosed with normcholesterolemic minimal change glomerulonephritis with some focal mesangial cell proliferation and moderate proteinuria, and in whom strenuous exercise was restricted. The 36 patients were randomly assigned to receive 20 mg of fluvastatin (group 1) or 5 mg/kg dipyridamole (group 2) for two years. Results: by the end of trial, there was no difference in BMD between the groups, and there were no changes in the four bone metabolic parameters. However, the urinary protein, hematuria and BUN levels had significantly decreased in group 1 compared to baseline, and the serum total protein and albumin levels and creatinine clearance had significantly increased in group 1 compared to baseline and group 2. Conclusion: The results of this study suggest that fluvastatin therapy has an antiproteinuric effect and improves renal function in moderately proteinuric patients with mild histological glomerulonephritis, but not increase BMD.

11. Statins’ dosage in patients with renal failure and cyclosporine drug-drug interactions in transplant recipient patients

Launay-Vacher V, Izzedine H, Deray G.

Int J Cardiol  2005;  101: 9-17.

Abstract. Dyslipidemia is frequent in patients with renal failure and in transplant recipient patients. This to a wide use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) in patients impaired renal function or in patients treated with cyclosporine as post-transplantation immunosuppressive therapy. As a result, it is crucial for those patients’ physicians to be aware of how to handle these when renal function is impaired and/or when cyclosporine is co-administered. Most statins have an extensive hepatic elimination and the renal route is usually a
minor elimination pathway. However, pharmacokinetic alterations have been described for some drugs in patients with renal insufficiency. Cyclosporine is a widely used immunosuppressive therapy in solid organ transplant patients and drug-drug interactions are likely to occur when statins and cyclosporine are administered together. Those interactions may theoretically results in increased statins and/or cyclosporine serum levels with potential muscle and/or renal toxicity. As a result, caution is warranted if concurrent administration is performed. In this review, we synthesize the data from the literature on (1) the pharmacokinetics and dosage adjustment of atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin in patients with renal failure and (2) the potential drug-drug interactions between these drugs and cyclosporine in transplant recipient patients.

12. Effect of folic acid on methionine and homocysteine metabolism in end-stage renal disease


**Background:** The pathogenesis of hyperhomocysteinemia in end-stage renal disease (ESDR) is unclear. Folic acid lowers, but not normalize, the plasma homocysteine level in patients with ESRD, but its effect on whole body metabolism of homocysteine is unknown. **Methods:** We studied the effect of 3 weeks of oral treatment with 5 mg folic acid per day on homocysteine metabolism in six chronic hemodialysis patients and six healthy controls. Primed, continuous infusions with $[^{2}H_{3}\text{-methyl-1-C}^{13}]$ methionin were used to determine flux rates of methionine transmethylation, homocysteine remethylation, and homocysteine transsulfuration. Metabolic homocysteine clearance was defined as the ratio of transsulfuration and plasma homocysteine levels. **Results:** Folic acid treatment lowered plasma homocysteine significantly by 39% (95% CI 5 to 73) in the ESRD group, but plasma homocysteine remained higher than baseline values in the control group. In ESRD patients, homocysteine remethylation and methionin transmethylation rate increased by 34% (95% CI 5 to 62) and 22% (95% CI 5 to 39), respectively (i.e., levels that were similar to the baseline values of the control group). Transsulfuration rate and metabolism homocysteine clearance were not significantly altered by folic acid treatment in both the ESRD and the control group. **Conclusion:** In ESRD patients, folic acid treatment lowers, but not normalize plasma homocysteine, whereas homocysteine remethylation and methionon transmethylation increase to levels found in untreated healthy controls. These findings indicate a persistent folate-independent, defect in metabolic homocysteine clearance in ESRD.

13. Treatment of glomerulonephritis: will we ever have options other than steroids and cytotoxics?

Avaid B, Quigg RJ.


Glomerulonephritis refers to a collection of primary renal disorders and those secondary to a
systemic disease, all characterized by inflammation within the glomerulus. Given the underlying immunologic nature of these disorders, they are routinely treated with corticosteroids and various cytotoxic agents. Although in many instances such therapies are successful, they are associated with significantly morbidity; as such, alternatives are clearly necessary. Our understanding of the pathogenesis of immunologic glomerular disease was grown remarkably, in large part from the study of rodent disease models. Fundamental to each disorders is the development of an antigen-specific immune response, followed by the effector stage of inflammation. To block the immune response, antigen-specific therapy can be used to induce tolerance, such as throught the use of double-stranded DNA molecules in lupus nephritis. Since other antigen system are less well characterized, inducing a more generalized impairment in the immune response by blocking costimulatory molecules CD40-CD154 and CD28-CD80/86 is a growing approach to treat various immunologic disorders and transplantation. To reduce glomerular inflammation, a variety of effector system have been targeted, including complement, cytokines/chemokines, adhesion molecules, and mediators of cellular proliferation. Of these, antibodies targeting C5 in the complement system, and antibody and receptor antagonists of tumor necrosis factor-alpha (TNF-alpha) have already been used in glomerular disorders with some promise. Less specific blockade of receptor-mediated events stimulated by platelet-derived growth factors and cell cycle proteins may soon be applied to glomerulonephritis. Finally, interruption of fibrosing pathways, which lead to glomerulosclerosis and interstitial fibrosis common to the end-stage of all glomerulonephritis, is the subject of intense effort which may yield effective biologic therapies. In spite of all these advances, we still are dependent on steroids and cytotoxics to treat glomerulonephritis. To get past this, we must devote significant resources to take observations made in basic research laboratories to develop therapeutics and prove their utility in human disease.

14. Inhibition of protein kinase CK2 prevents the progression of glomerulonephritis


Summary: See Part 2/PG/23.

15. CXCR3-binding chemokines: novel multifunctional therapeutic targets

Lazzeri E, Romagnani P.


The goal to attenuate inflammation without inducing generalized immunosuppression has focused the attention on chemokines, a family of chemotactic peptides that regulate the leukocyte traffic into tissues. However, the development of drugs that block chemokine activity may be hampered by the observation that some chemokines display pleiotropic biologic functions. For example, the chemokines CXCL9/Mig, CXCL10/IP-10, and CXCL11/I-TAC exhibit the ability to recruit
different leukocytes subsets, the capacity to induce the proliferation of vascular pericytes as well as a powerful anti-tumor effects, which are mediated by a common receptor, named CXCR3. Because of their pleitropic biologic effects, these chemokines have been proposed as possible therapeutic targets in cancer, allograft rejection, glomerulonephritis, diabetes, multiple sclerosis, and autoimmune disorders of thyroid. The chemokine CXCL4/PF4 shares several activities with CHCL9, CXCL10, and CXCL11, including angiostatic effects, although its specific receptor has remained unknown for a long time. Recently, we provided evidence that the different functions of CXCL9, CXCL10, and CXCL11 on distinct cell types can be at least partly explained by the interaction of these chemokines with two distinct receptors. Indeed, in addition to the classic form of CXCR3 receptor, which we have renamed as CXCR3-A, a novel CXCR3 receptor variant (CXCR-B) was identified, that not only mediates the angiostatic activity of CXCR3 ligands, but also acts as functional receptor for CXCL4. In this review, we focus on the accumulating evidence demonstrating the pivotal role of CXCR3-binding chemokines in several human diseases. Studies based on CXCR targeting have shown its importance in different pathologic conditions and orally active small molecules capable of inhibiting this receptor are now being developed in order to be tested for their activity in humans.

16. Pharmacological therapy of lupus nephritis

Fine DM.

JAMA 2005; 293: 3053-3060.

Kidney involvement is common in systemic lupus erythematosus, occurring in up to 60% affected adults during the course of their disease. Diffuse proliferative lupus nephritis (World Health Organization clas IV), the most ominous variant, has traditionally been treated with cyclophosphamide and glucocorticoids. With cyclophosphamide, women of childbearing potential must weight the risk of sustained amenorrhea, infertility, increased susceptibility to infection, bone marrow suppression, hemorrhagic cystitis and malignancy against the benefits of better disease control compared with glucocorticoids alone. Because of the host of adverse effects associated with cyclophosphamide, alternative approaches to the treatment of lupus nephritis are desirable. A 31-year-old woman developed class IV lupus nephritis in the postpartum period. Seeking to preserve fertility and avoid other known toxicities of cyclophosphamide, she chose to undergo therapy with mycophenolate mofetil. In the treatment of severe lupus nephritis, mycophenolate mofetil has emerged as an alternative to cyclophosphamide, offering a major advance in the therapy of lupus nephritis.

17. Effects of long-term treatment with mizoribine in patients with proliferative lupus nephritis

Abstract. **Aim:** Mizoribine (MZR) is a purine antimetabolic immunosuppressant agents that has few little severe adverse effects. We studied whether maintenance therapy with MZR and prednisolone (PSL) in severe proliferative lupus nephritis patients could improve immunity, reduce proteinuria, prevent renal relapse, and reduce steroid dose. **Methods:** Long-term maintenance therapy with MZR and PSL was evaluated in ten patients with biopsy-proven proliferative lupus nephritis. Patients with severe lupus nephritis, who had proteinuria of 0.5 g or more even after treatments with plasma exchange and/or pulse methylprednisolone, were recruited. MZR at an average dose of 140±10 (100-200) mg was administered two to three times/day in combination with PSL. The average period for the MZR maintenance therapy was 89.7±5.5 (70-126) months. Urine protein excretion, serum hemolytic complement activity (CH50), C3, serum creatinine, general and biochemical blood examinations, anti-ds-DNA antibody were collected at each monthly medical examination. **Results:** All patients were females, mean age 43.0±3.3 years. A significant decrease in proteinuria was noted two years after the combination therapy (p=0.0016). Five patients experienced lupus nephritis relapse. Patients who did not experience relapses had their MZR combination therapy initiated earlier (p=0.037) when compared with the patients who experienced relapses. Serum creatinine levels remained unchanged in all patients throughout treatment and follow-up, even during renal relapses. Levels of C3 and CH50 normalized as proteinuria decreased. None of the patients developed serious side effects during MZR treatment. A significant steroid-sparing effect was observed three years after initiating MZR (p=0.0025). **Conclusion:** From our long-term observation, maintenance therapy with low-dose PSL combined with MZR can eliminate proteinuria and have steroid-sparing effect. Early initiation of the therapy can protect against renal relapses among severe proliferative lupus nephritis patients without serious side effects.

18. Implication of the peak serum level of mizoribine for control of the serum anti-dsDNA antibody titer in patients with lupus nephritis


Abstract. **Aim:** Mizoribine (MZR) is a novel selective inhibitor of inosine monophosphatase dehydrogenase that was developed in Japan. We previously reported the efficacy and safety of oral MZR pulse therapy, which is associated with elevated peak serum MZR levels, in selected patients with lupus nephritis. However, only limited information is available as yet on the optimal peak serum level of MZR that would yield an enhanced clinical efficacy without serious toxicity in patients with lupus nephritis. **Methods:** A total of 11 patients with clinically stable lupus nephritis treated with oral MZR pulse therapy combined with low-dose prednisolone were enrolled in the cross-sectional study. The peak serum concentration of MZR (as determined by HPLC) and serum anti-ds-DNA antibody titers (as determined by ELISA) were examined in the patients in order to evaluate the correlation between these two parameters. The correlation between the dose of MZR (mg/kg) administered orally as a single daily dose and the peak serum level of the drug was also examined. In two of the participants, serial measurements of the changes in the peak serum levels of MZR and anti-dsDNA titers could be conducted over 10 months. **Results:** A significant inverse correlation (r=0.596, p=0.0116) was observed between the peak serum levels of MZR and the serum anti-dsDNA antibody titers in the study participants, while the dose of prednisolone remained
inchanged. The peak level of MZR in the serum was significantly correlated with the single dose of MZR ($r=0.509$, $P=0.0371$). In the two patients in whom serial measurements were conducted, the first patient who showed a peak serum MZR level of less than 2.5 – 3.0 ug/ml eventually developed an increase of the serum anti-dsDNA titer with hypocomplementemia and proteinuria. On the other hand, in the second patient who showed a peak serum MZR level in excess of 40 ug/ml, persistently low serum anti-dsDNA titers with normocomplementemia were observed. **Conclusion:** Although this study conducted on a small sample, we speculate from the results that a peak serum level of MZR of at least more than 2.5 – 3.0 ug/ml is necessary to achieve satisfactory clinical efficacy of the drug for the treatment of lupus nephritis. Further study is needed to confirm these preliminary findings.

19. **Rituximab in childhood systemic lupus erythematosus refractory to conventional immunosuppression: case report.**

Edelbauer M, Jungraitmayr T, Zimmerhackl LB.


Rituximab, a chimeric monoclonal antibody specific for human CD20, has recently been used for the treatment of autoimmune diseases. A 14-year-old patient with severe systemic lupus erythematosus (SLE) and class IV glomerulonephritis presented with immunologic and clinical resistance to conventional immunosuppressive therapy for 10 months after diagnosis. To induce remission of active SLE, treatment with 6 onthly rituximab at 375 m/m$^2$, oral mycophenolate and prednisone was initiated followed by maintenance rituximab every 3 months. The SLEDAI decreased significantly from 31 at diagnosis to 14 after nine application of rituximab. Extrarenal symptoms of SLE improved significantly. However, after induction therapy with rituximab the patient presented a reversible intrinsic acute renal insufficiency for a period of 3 weeks. The discontinuation of the daily medication (oral prednisone and mycophenolate) by the patient herself may explain the progression of active SLE associated with the reversible acute renal failure. Under intensive immunosuppressive therapy improvement of active renal disease manifestations and stabilization of plasma creatinine concentrations to normal values was observed. However, proteinuria remain elevated and improved only after a protracted period (median protein-to-creatinine ratio 5.2 g/g, range 0.8-11.2 g/g). hematuria and urinary cell casts persisted. In conclusion, the extrarenal symptoms of the patients responded particularly well to rituximab. However, despite complete B-cell elimination, renal remission of SLE was not achieved. Thus, it may be possible that humoral and cellular immune mechanisms have a fundamental involvement in the pathogenesis of SLE nephritis.

20. **Failure of rituximab to treat a lupus flare-up with nephritis**


Abstract. The autoantibodies secreted by B lymphocytes have recently been shown to play an important role in the autoimmune disease. B lymphocyte depletion by rituximab, a monoclonal anti-CD20 antibody, has been introduced for the treatment of several autoimmune disorders. Few reports have underlined its potential use for the treatment of systemic lupus erythematosus (SLE). We report here the occurrence of extracapillary glomerulonephritis associated with a thrombotic event shortly after rituximab treatment for a lupus flare-up in a patient with anticardiolipin antibodies. This observation suggests that rituximab alone may be insufficient to control severe SLE with glomerulonephritis and should therefore be used with caution in patients with this condition.

21. Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the T cell costimulatory molecule CD40 ligand: an open-label trial

Sfikakis PP, Boletis JN, Lionaki S, et al.


Objective: Autoreactive B cells play a key role in tissue injury in systemic autoimmune disease, and therefore a treatment resulting in B cell depletion could have benefit. This open-label study was undertaken to evaluate the efficacy of the anti-CD20 monoclonal antibody rituximab in the treatment of lupus nephritis. Methods: Lupus patients with active proliferative nephritis (4 with focal disease and 6 with diffuse disease) received rituximab (4 weekly infusion of 375 mg/m²) combined with oral prednisolone. Clinical, laboratory, and immunologic responses, including peripheral lymphocyte subsets measured by flow cytometry, were prospectively assessed at monthly intervals for 12 months. Complete remission of nephritis was defined as normal serum creatinine and albumin levels, inactive urine sediment, and 24-hour protein <500mg. Partial remission was defined as >50% improvement in all renal parameters that were abnormal at baseline. Results: B cell depletion lasted from 1 month to 7 months and was tolerated. Partial remission was achieved in 8 of 10 patients within a median of 2 months (range 1-4 months); in 5 of them, complete remission was subsequently established (at a median of 3 months from baseline), and it was sustained at 12 months in 4. As early as 1 month from baseline, the expression of the costimulatory molecule CD40 ligand on CD4+ T cells was decreased by 4-fold, and it was almost blocked when partial remission was clinically evident. The expression of T cell activation markers CD69 and HLA-DR was significantly decreased at time points when partial remission was observed, and was further decreased during complete remission. In contrast, in patients who did not exhibit a response or when relapse was detected in patients in whom an initial remission had been achieved, such decreases were not prominent. Serum concentrations of double-stranded DNA autoantibodies were decreased in all patients, regardless of clinical outcome. Conclusion: Following B cell depletion, clinical remission of lupus nephritis is associated with a decrease in T helper cell activation, suggesting an additional role for B cells, independent of autoantibody production, in promoting disease. A controlled trial to confirm these promising clinical results is warranted.

22. Preventing renal failure in patients with severe lupus nephritis
Background and Methods: Advances in immunosuppressive treatment regimens, with increased efficacy, while minimizing the treatment-related toxicities, and better prevention and treatment of complications, have resulted in improved patient and renal survival in subjects with severe proliferative lupus nephritis over the past few decades. This review discusses the issues that are pertinent to the preservation of renal function in these patients. Results and Conclusion: Treatment of severe proliferative lupus nephritis can be divided into an initial phase of induction followed by a prolonged maintenance phase, both of which impact upon the long-term renal and patient survival. The immunosuppressive potency of the treatment required for disease control varies according to the disease activity during the different phases. Despite variations in the choice, duration, and route of administration of antiproliferative agents, data to date suggest that immunosuppressive treatments combining cyclophosphamide or mycophenolate mofetil with corticosteroid appear to have similar efficacy in terms of inducing immunologic remission. In this regard, the immunologic efficacy of treatment is prerequisite to the prevention of irreversible loss of nephrons, but long-term renal outcome is also dependent other than treatment efficacy, such as preexisting renal parenchymal damage and blood pressure control. Prompt diagnosis, early effective therapy, and reducing the risk of relapses are the disease specific measures that are essential to long-term renal preservation and the prevention of renal failure in subjects with severe proliferative lupus nephritis.

23. Mycophenolate mofetil in lupus nephritis

Ginzler EM, Aranow C.


There is increasing body of literature suggesting the efficacy and tolerability od mycophenolate mofetil (MMF) for the treatment of lupus nephritis. The rationale for its use is based upon its successful profile as an immunosuppressive agent for prevention of allograft rejection, as well as studies in murine models of lupus which have reported improved renal function and animal survival compared placebo. This report review the data regarding MMF therapy in murine lupus models, and describes the initial anecdotal experience with MMF in human lupus, especially in patients with glomerulonephritis who were unresponsive to corticosteroids and cyclophosphamide, or who had unacceptable toxicity on this standard of care regimen. The results of several nonblinded, controlled clinical trials are also described, in which MMF was compared to intravenous or oral cyclophosphamide in patients with lupus nephritis. MMF was found to be well tolerated, with most studies showing fewer infections than that associated with cyclophosphamide. Efficacy of MMF was at least equivalent to cyclophosphamide, and therefore appears to provides an alternative as a standard of care for induction and maintenance treatment of lupus nephritis.

24. Infantile systemic lupus erythematosus presenting with pulmonary hemorrhage
Systemic lupus erythematosus in infants born to healthy mothers is a rare entity. We describe a male infant who presented at 1 month of age with pulmonary hemorrhage and glomerulonephritis due to systemic lupus erythematosus, confirmed serologically and histologically. He was managed with a combination of prednisone and intermittent cyclophosphamide, but also received mycophenolate mofetil, with a complete serological and clinical remission at 30-month follow-up. This case the importance of a broad approach to the evaluation of pulmonary hemorrhage and glomerulonephritis in the very young and the need for aggressive immunosuppressive therapy to achieve sustained serological and clinical remission.

25. Mycophenolate mofetil induced myopathy in a patient with lupus nephritis


We describe a case of mycophenolate mofetil (MMF) induced myopathy in a patient with lupus nephritis. Two months after starting MMF treatment she developed asthenia, lower limb weakness, and abnormal increase of muscle enzymes. An electromyogram showed a myogenic pattern with small polyphasic discharges without neurogenic signs involving proximal muscles of lower limbs. Muscle biopsy revealed the presence of fibers of variable size with irregular sarcoplasmic basophilic areas. Using oxidative enzyme techniques, many type fibers showed a moth-eaten appearance resembling minicores. The ultrastructural findings consisted of myofibrillary lesions with multiple small foci of Z-band streaming. MMF withdrawal was followed by complete clinical and enzymatic recovery.

26. Mycophenolate mofetil in nonlupus glomerulonephropathy

Karim MY, Abbs IC.

Lupus 2005; 14: s39-s41.

Mycophenolate mofetil (MMF) initially found widespread use in the immunoprophylaxis of rejection in organ transplantation. It has subsequently been used in lupus glomerulonephritis, where early studies have shown it to be effective in induction and maintenance therapy. The randomised studies have mostly studied small groups of patients and their conclusions do need to be confirmed in larger studies. MMF has also been used in small numbers of patients in a variety of nonlupus
glomerulopathies, which have different underlying immunopathology as well as clinical course, including IgA nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, hepatitis-C-associated glomerulonephritis and even Goodpasture’s syndrome. In this article, we discuss its use in such nonlupus glomerular disease.

27. Clinicopathologic features, outcome, and therapeutic interventions in four children with isolated C3 mesangial proliferative glomerulonephritis


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Since isolated C3 mesangial proliferative glomerulonephritis in the absence of systemic disease (i-C3-GN) is an uncommon chronic glomerular disease, long-term prognosis and optimal therapeutic intervention for it are not yet fully defined, especially in children. We report clinical features, outcome, and interventions in 4 patients, ranging from 6 to 18 years old, with i-C3-GN. Microscopic or macroscopic hematuria with or without proteinuria was first noted between 3 and 8 years. When present, proteinuria ranged from 0.2 to 1.0 g/24 h. Persistent hypocomplementemia and circulating immune complexes were found in 1 patient. None of the patients had nephrotic syndrome or hypertension. Percutaneous renal biopsy specimens showed varying degrees of mesangial proliferative glomerulonephritis; 2 patients showed mild mesangial proliferation, while others exhibited moderate histologic severity. In 1 patient with a mild mesangial increase, tubulointerstitial changes were associated. Both patients exhibiting mild mesangial changes followed a benign clinical course with normal renal function over 10 years of follow-up. Patients with moderately severe mesangial alteration manifested slight renal function loss and moderate proteinuria at the time of biopsy, but these largely resolved after a six-month course of prednisolone combined with cyclophosphamide, warfarin, and an angiotensin-converting enzyme inhibitor. Thus, clinical manifestation and the need aggressive treatment appear to vary among pediatric patients with i-C3-GN. Therapy combining prednisolone with immunosuppression seemed to reduce proteinuria and improve glomerular function in patients with moderately severe mesangial proliferation.

28. Crescentic post-streptococcal glomerulonephritis with nephrotic syndrome in the adult: is aggressive therapy warranted?


The prognosis for adults with acute post-streptococcal glomerulonephritis (PSGN) who present with crescentic glomerulonephritis and nephrotic proteinuria is not known. We report a patient with rapidly progressive glomerulonephritis and nephrotic-range proteinuria following acute pharyngitis, in whom serologic and kidney biopsy findings led to a diagnosis of PSGN. The patient was treated
with corticosteroids and anti-hypertensive medications resulting in improvement in renal function and decrease in proteinuria. These results suggest that aggressive treatment of crescentic PSGN with nephrotic syndrome can result in a favorable outcome.

29. Development of glomerulonephritis during anti-TNF—(alpha) therapy for rheumatoid arthritis

Stokes MB, Foster K, Markowitz GS, et al.


Summary: See Page 2/ET/17.

30. Steroid resistance in prolonged type I membranoproliferative glomerulonephritis and accelerated disease remission after steroid withdrawal


Two cases of severe proteinuria and hypocomplementemia were referred to our out patient clinic for continous follow-up. Initial onset of clinical symptoms was at the age of 15 years in both caese. They had already been diagnosed as type I membranoproliferative glomerulonephritis (type I MPGN) by renal biopsy when oral prednisolone administration had been initiated. Several courses of steroid pulse therapy were performed for the flares of the disease, resulting in only temporary amelioration of renal symptoms. Percutanous renal biopsy was performed during admission on both cases, showing severe glomerular and tubulointerstitial damages, in addition to type I MPGN findings such as mesangial cell and matrix interposition and subendothelial deposits. Because the continous administration of steroid for more than 10 years did not ameliorate the clinical symptoms, steroid was markedly reduced or stopped in these cases. Such withdrawal from steroid therapy accelerated the amelioration of renal symptoms, including decrease in proteinuria, elevation of plasma protein and complement levels, and disappearance of generalized edema. The clinical courses of these cases indicate clinical choice of withdrawal from steroid therapy as one of the treatments in prolonged type I MPGN, which present in childhood and shows steroid resistance.

31. Long-term follow-up of diffuse membranoproliferative glomerulonephritis type I.


In Japan, the school urinary screening system facilitates early detection and treatment of membranoproliferative glomerulonephritis (MPGN) in childhood. The present study investigated the long-term prognosis in 19 children with diffuse MPGN type I who received steroid therapy. Before signs of glomerulonephritis were confirmed, all patients displayed abnormal urinanalysis results, predominantly through school urinary screening. Treatment comprised a regimen of alternate-day prednisolone after steroid pulse or cyclophosphamide therapy, and follow-up was continued for 12-24 years. Excluding 1 patient on short-term therapy, 18 patients received long-term alternate-day prednisolone therapy for 4-12 years. Treatment was discontinued when amelioration was confirmed on renal biopsy. As of the last observation, urinary abnormalities and hypocomplementemia had disappeared in 15 patients, while mild proteinuria without hypocomplementemia remained in 14 patients. No patients required hemodialysis. Moreover, no severe adverse effects attributable to treatment were identified other than mild short stature. Early detection and therapy using pulse methylprednisolone followed by alternate-day prednisolone was thus confirmed as safe and useful for treating diffuse MPGN type I.

32. Apheresis for MPO-ANCA-associated RPGN—indications and efficacy: Lessons learned from Japan nationwide survey of RPGN

Yamagata K, Hirayama K, Mase K, et al.

J Clin Apheresis  2005 May 5  [Epub ahead of print]

A national survey concerning rapidly progressive glomerulonephritis (RPGN) was conducted in Japan between 1989 and 2000 and resulted in the registration of 715 patients with RPGN. Among the documented patients, the most frequent primary disease was primary pauci-immune crescentic glomerulonephritis (n = 283), and the second most frequent was microscopic polyangitis (n = 127). Overall, 370 patients had MPO-ANCA, and 23 patients PR3-ANCA. We found that both renal and patient survivals were significantly worse in patients with MPO-ANCA-associated RPGN than patients with PR3-ANCA. Fifty-three patients received apheresis therapy with various combinations of immunosuppressive regimens. They had higher serum creatinine, higher CRP, and a higher frequency of complicated pulmonary involvements as compared to the controls without apheresis therapy. In dialysis-dependent patients, no additional benefit from apheresis therapy was observed. Only pulmonary renal syndrome patients with CRP > 6 mg/dl at presentation showed a slightly better prognosis (patient survival with apheresis; 66.7%, without apheresis; 56.7%). Furthermore, a rapid MPO-ANCA titer reduction was observed in patients treated with apheresis. Patients with MPO-ANCA-associated RPGN were older, and had more chronic and sclerotic lesions than patients with PR3-ANCA-associated RPGN. Base on these findings, we suggest that a lower dose of immunosuppressant should be considered in order to avoid opportunistic infection. In this situation, cytapheresis is the treatment of choice. Nevertheless, in patients with an aggressive form of RPGN with rapid deterioration of renal function like the PR3-ANCA-associated RPGN, or pulmonary renal syndrome complicated severe inflammation, or relapse with high MPO-ANCA titer, we conclude that apheresis therapy should be considered.

33. Case of inflammatory vasculopathy and encephalopathy caused by treatment with tacrolimus
34. Resolution of primary amyloidosis by melphalan and prednisolone: a case report


Abstract. We here report a case of a 50-year-old man who showed histologically evident resolution of primary amyloidosis by melphalan and prednisolone. The patient was admitted to our hospital for further evaluation of nephrotic syndrome and remarkable hepatomegaly with refractory ascites, on September 11, 1998. Laboratory tests at presentation showed nephrotic syndrome with slight renal impairment and elevation of the enzymes of the biliary system. Monoclonal light chains were not detected in the serum or urine by immunoelectrophoresis. A renal biopsy revealed global deposition of amyloid in all glomeruli, interstitium and blood vessels. Immunofluorescence staining was positive for kappa light chains. Liver biopsy specimen showed extensive deposition of amyloid along sinusoid walls. Bone marrow aspiration contained 7% plasma cells but no clusters or abnormal cells. Based on these findings, systemic AL-(amyloid light chain) amyloidosis was diagnosed, and the treatment with combinations of melphalan and prednisolone was started from October 1998 at intervals of 4 – 6 weeks. Renal impairment progressed, resulting in the initiation of maintenance hemodialysis in February 1999. Reinfusion of ascites into the hemodialysis circuit had been performed from March 1999 for refractory ascites, and ascites disappeared in July 1999. Furthermore, urinary output increased after 14 courses of chemotherapy. Renal function gradually ameliorated with a concomitant reduction in the enzymes of biliary system, and finally hemodialysis was discontinued in April 2001. Sixteen courses of chemotherapy were administered by April 2001. Proteinuria was negative in August 2001. A second renal biopsy was performed on November 20, 2001, which showed markedly decreased amyloid deposition and a proliferation of mesangial cells and increase in matrix in various degrees. We report a case of a patient with primary amyloidosis who was successfully treated by melphalan and prednisolone, resulting in marked resolution of renal amyloidosis.

35. Initial functional status predicts infections during steroid therapy for renal disease


Abstract. Background and aim: Corticosteroid therapy is an effective way of treatment for many renal diseases, however, it is sometimes associated with infections. Our aim is to identify useful predictive markers of infection during steroid therapy. Methods: We examined 121 patients (M/F = 71/50, mean age 43.8, range 15-82 years) who were treated with corticosteroids (IgA nephropathy in 51, minimal-change disease in 17, membranous nephropathy in 16, rapidly progressive glomerulonephritis (RPGN) in 13, lupus nephritis in 12, and other disorders in 12). Karnofsky’s performance score (KPS) was employed to assess the physical functional status at the time of diagnosis. Infections were defined as conditions that required more than 1-week care, and those that caused the patient’s death. Results: Nineteen patients (15.7%) had infections during treatment. A logistic multivariate analysis showed significant correlations between infection and the use of immunosuppressive agents (relative risk RR = 7.7, p=0.0265), ages of 52.9 years or more (RR=7.7, p=0.0026), initial number of lymphocytes (Lym) less than 1,250/ul (RR = 14.2, p=0.0011), and KPS less than 77.4 (RR=12.1, p=0.0020). All correlations with infection were independent of all the other variables, listed above. Conclusion: KPS, along with age, Lym and the use of immunosuppressive agents, are useful for the prediction of infectious complications during steroid therapy.

36. Ribavirin monotherapy for hepatitis C virus-associated membranous nephropathy

Hu SL, Jaber BL.


Abstract: Glomerular diseases associated with hepatitis C virus (HCV) infection are increasingly being recognized. Antiviral therapy with interferon-alpha (IFN-alpha) and ribavirin eradicate viral activity in a significant proportion of patients with chronic active hepatitis, often with amelioration of extrahepatic manifestations, including glomerular pathology. Unfortunately, adverse effects often preclude the use of INF-alpha. We describe a patient with refractory nephrotic syndrome secondary to HCV-associated membranous nephropathy who sustained a complete remission following the initiation of ribavirin monotherapy. The existing literature on the association between these two disorders and therapy with ribavirin is reviewed.

37. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naive HIV-1-infected patients. Data from a double-blind randomized active-controlled multicentre study

Izzedine H, Hulot JS, Vittecoq D, et al.


Abstract. Background: Tenofovir disoproxil fumarate (TDF) was developed for the treatment of human immunodeficiency virus (HIV) infection. However, controlled data are sparse on the long-term renal tolerability of TDF at the currently approved daily dose of 300mg in treatment-naive HIV-infected patients. Methods: Over 144 weeks, this 600 patients, multicentre randomized,
placebo-controlled, double-blind trial compared stavudine (301 patients) and TDF (199 patients), both administered combination with lamivudine and efavirenz, in antiretroviral-naive patients. TDF or placebo and stavudine or placebo were administered in an open-label fashion. All medications were taken orally. At screening, all patients had serum creatinines <1.5mg/dl, calculated creatinine clearances >60 ml/min and serum phosphorous >2.2mg/dl. Results: The incidences of grades 1 (>0.5mg/dl increase from baseline), 2 (2.1-3.0mg/dl) and 3 (3.1-6.0mg/dl) serum creatinine elevation at week 144 were 4, <1 and 0%, respectively, in the TDF group and 2.0 and <1 in the stavudine control group (P=NS). There were no grade 4 (>6mg/dl) serum creatinine elevations. At week 144, there was no change from baseline in the mean (0.83mg/dl) serum creatinine in the TDF group compared with a 0.1 mg/dl decrease from baseline (0.83mg/dl) in the stavudine control group. The incidences of grades 1 (20.0-2.2 mg/dl), 2 (1.5-1.9mg/dl) and 3 (1.0-1.4mg/dl) hypophosphataemia at week 144 were 4.3 and <1% respectively, in the TDF group and 4.2 and <1% in the control group (P=NS). No patient experienced grade 4 (<1.0mg/dl) hypophosphataemia. At week 144, the decrease of mean serum phosphorus levels from baseline in both group was similar (0.2 from 3.6mg/dl for the TDF group, and 0.1 from 3.5mg/dl for the stavudine control group). No patient developed Fanconi’s syndrome or proximal rena tubular dysfunction during the study. Conclusion: Through 144 weeks, TDF and stavudine, and lamivudine, had similar renal safety profiles in treatment-naive HIV-infected patients with normal renal function at baseline.

38. Treatment of chronic hepatitis with interferon in children with kidney disease


The study aimed at evaluation of chronic hepatitis treatment results in children previously treated from nephrological indications in 1994-2002 years. Material and Methods: Examination was performed in 42 children in the age 10.2 +/- 4.8 years at the onset time of interferon (INF) treatment application. In 30 children (71.4%) chronic HBV infection, in 8 (19.1%) – HCV infection, in 4 (9.5%) – mixed HBV and HCV infection in phase of replication was revealed. Among examined children in 26 (61.9%) symptoms of glomerulonephritis were previously reported, in 17 (40.5%) – symptoms of nephrotic syndrome; in 9 (21.4%) – chronic renal failure was observed. 22 children received prednisone treatment. Concentration of albumin, gammaglobulin, bilirubin, hemoglobin, creatinine, haematocrit, leukocytosis, activity of alanine aminotransferase (ALT), chronic hepatitis markers, before, during and 6 and 12 months after treatment termination were evaluated. IFN alpha2, alpha2b and human recombined IFN-alpha were applied. Results: In 22 (524%) children ALT values before treatment not exceeded 100IU/l. Liver biopsy was performed in 39 children. In 18 (46.2%) – high activity of inflammatory process was revealed; only in 5 of them with ALT activity above 100 IU/l. Higher leukocytosis at the beginning of treatment was acomained by diminished activity of inflammatory process, In 14/34 children seroconversion was obtained in HBe markers, before, during and 6 and 12 months after treatment termination were evaluated. IFN alpha2, alpha2b and human recombined IFN-alpha were applied. Results: In 22 (524%) children ALT values before treatment not exceeded 100IU/l. Liver biopsy was performed in 39 children. In 18 (46.2%) – high activity of inflammatory process was revealed; only in 5 of them with ALT activity above 100 IU/l. Higher leukocytosis at the beginning of treatment was acomained by diminished activity of inflammatory process, In 14/34 children seroconversion was obtained in HBe markers, in 4/12 HCV-RNA elimination occured after the 1st course of IFN. Only in 5 (11.9%) children treatment was stopped because of side effects (not connected with urinary tract), in 1 – because of relapse of main disease. 2nd course was applied in 13 children. In 2 – seroconversion in HBe was obtained. Conclusions: Considering the small number of examined children full evaluation of chronic hepatitis treatment efficacy is not possible. It seems comparable as observed in population of children without the risk of nephropathies. IFN treatment in children on previous medication of kidney disease, in most cases does not create complications leading to earlier drug cessation. In the case of glomerulonephritis also does not bear an increased risk of relapse of main
39. Darbepoetin alfa administered once monthly maintains hemoglobin concentrations in patients with chronic kidney disease


Abstract. Background: Darbepoetin alfa is an erythropoiesis-stimulating glycoprotein that functions by the same mechanism as recombinant human erythropoietin (rHuEPO), but has a threefold longer serum half-life. Reduction in the frequency of darbepoetin alfa administration would be beneficial to patients with renal disease and their healthcare providers. This study evaluated the effect of extending the darbepoetin alfa dosing interval to once monthly in patients with chronic kidney disease (CKD) not receiving dialysis. Methods: This study was a multicenter, open-label study of 97 patients with CKD not on dialysis. Patients receiving stable subcutaneous doses of darbepoetin alfa once every two weeks were converted to darbepoetin alfa once monthly for 29 weeks. The proportion of patients who successfully maintained hemoglobin concentrations between 10.0 and 12.0 g/dl and the mean darbepoetin alfa dose were evaluated. Safety measurements (e.g. adverse events, laboratory parameters, blood pressure) and seroreactivity were assessed. Results: Hemoglobin concentration was maintained within the target range in 79% (95% confidence interval (CI)=71% to 87%) of all patients receiving darbepoetin alfa and in 85% (95% CI=78%-93%) of patients who completed the study period. The mean ± standard deviation monthly darbepoetin alfa dose was similar between baseline (88.7±49.9 ug) and the evaluation period (86.6±78.8 ug). The safety profile for monthly darbepoetin alfa administration was comparable with that previously observed with more-frequent administration. Conclusion: Patients with CKD who are clinically stable on darbepoetin alfa administered once every two weeks can be safely and effectively converted to darbepoetin alfa administered once monthly.

40. Pleiotropic renal actions of erythropoietin

Chatterjee PK.


Context Erythropoietin (EPO) which is used clinically as recombinant human EPO (rHuEPO) for anaemia associated with end-stage renal failure and cancer chemotherapy, also has pleiotropic properties. Although EPO and its receptor are primary mediators of the normal physiological response to hypoxia. RHuEPO can provide impressive protection against acute ischaemic injury in several organs and tissues. The longer-acting hyperglycosylated derivative of EPO, darbepoetin alfa, is also used for anaemia and has pleiotropic properties. However, the ability of EPO or its analogues to act directly to reduce the severity of renal injury associated with chronic renal failure is not known.
Starting point Ferdinand Bahlmann and colleagues (Circulation 2004; 110: 1006-1.) investigated whether low-dose subcutaneous darbepoietin alfa could protect against renal dysfunction and injury in rats with induced chronic renal failure. Given once weekly, the drug improved renal function and reduced histological evidence of renal injury. Treated rats also had greater weight gain than controls, with no change systemic blood pressure. The drug did not increase packed-cell volume and it improved survival.

Where next? Although the pleiotropic action of rHuEPO can ameliorate ischaemic and nephrotoxic acute renal failure, Bahlmann’s work is the first evidence that darbepoetin alfa reduces the renal dysfunction and injury of chronic renal failure. Thus rHuEPO and its analogues might have a use in patients with different types of renal failure. These pleiotropic actions seen at lower doses, must be separated from haemopoietic properties that occur at clinical doses and which, at time highest doses, might lead to unwanted effects. Novel analogues of EPO are devoid of haemopoietic activity but still possess protective properties. Their ability to reduce renal injury and dysfunction awaits investigation.

41. Effect of soy protein-rich diet on renal function in young adults with insulin-dependent diabetes mellitus

Stephenson TJ, Stechell KD, Kendall CW, et al.


Abstract. Background: Diabetic nephropathy is the most frequent cause of end-stage renal disease in the Western world. Dietary intake, including protein amount and type, seems to affect the progression of renal disease. This pilot study tested the hypothesis that substituting soy protein for animal protein in the diets of diabetics would help correct glomerular hyperfiltration. Methods: Twelve young adults (aged 29.9±2.4 years) with type 1 diabetes mellitus (duration of diabetes 15.1±2.3 years) and hyperfiltration (glomerular filtration rate, GFR>120ml/min/1.73m^2) completed a crossover, dietary intervention trial. After a four-week assessment of baseline characteristics and dietary habits, subjects were assigned to either a control or soy diet for eight weeks after which each subject was crossed over to the alternative diet for another eight-week period. Results: Mean GFR was significantly reduced (p<0.02) after eight weeks on the soy diet ((143±7.4ml/min/1.73m^2) compared with baseline (159±7.7ml/min/1.73m^2) and control diets (161±10,0ml/min/1.73m^2). Urinary excretion of the soy isoflavones was significantly higher (p<0.01) at the end of the soy diet (genistein 1,014,6±274,1 nmol/h, daidzem 2,645,1±989,6 nmol/h) compared with baseline (geninstein 53,7±31,1 nmol/h, daidzen 151,1±74,1 nmol/h) and control diets (geinstein 41,1±13,3 nmol/h, daidzein 127,5±54,0 nmol/h). The soy diet significantly reduced total and LDL cholesterol by 7% and 9%, respectively. Conclusions: Implementation of a soy-based diet appears to reduce the GFR and total and LDL cholesterol of young adults with type 1 diabetes and glomerular hyperfiltration, thus affecting positively their clinical profile.

42. A pregnant patient with renal vein thrombosis succesfully treated with low-dose thrombolytic
Objective: An 18-year-old woman with membranous glomerulonephritis was seen at 26 weeks of gestation with a right vein thrombosis with 95% occlusion. Results: Both thrombolytic and anticoagulation therapy were administered with success. Conclusion: Thrombolytic therapy, when used cautiously under intensive care settings, may prolong gestation to enhance the chances of favorable outcome.

43. Low-molecular-weight heparin successfully treating a nephrotic patient complicated by renal and ovarian vein thrombosis and pulmonary embolism

Wang IK, Lee CH, Yang BY, et al.


Thromboembolic complications, frequently associated with idiopathic membranous glomerulonephritis, are frequent and serious problems associated with nephrotic syndrome. However, ovarian vein thrombosis associated with nephrotic syndrome has never been reported. This study describes the case of a 35-year-old woman with idiopathic membranous glomerulonephritis who developed left renal vein thrombosis with ovarian vein thrombosis and pulmonary embolism. The thromboembolic complications were successfully treated with low-molecular-weight heparin. Low-molecular-weight heparin thus appears safe and effective for treating thromboembolism in nephrotic patients.

44. Acute renal failure

Lameire N, Van Biesen W, Vanholder R.


Summary: See Part 2/ET/22.
45. The structure of causes of acute renal failure and the efficacy of its treatment according to the materials of an intensive nephrological care unit

[No author listed]


Summary: See Part 2/CP/65.
VI. TRANSPLANTATION

1. Are autoimmune diseases or glomerulonephritis affecting the development of panel-reactive antibodies in candidates for renal transplantation?


Panel reactive antibodies (PRA) are a major obstacle to kidney transplantation (KTx). It is not completely clear why only some patients develop PRA, whereas others do not. We hypothesized that other factors, such as autoimmune diseases involving the kidney, might be a trigger for PRA development. We reviewed the original diseases that led to renal failure and their possible role in PRA development. Charts of 270 patients on the active waiting list for KTx were reviewed for complete demographics, presence of PRA, peak PRA level, first KTx or retransplantation, original disease, blood transfusions, pregnancy and rejection. Patients were divided into group 1 (PRA>10%) and group 2 (PRA<10%). There was a significantly higher proportion of patients in group 1 with autoimmune diseases than in group 2. The same proportion was found significant for all of the patients as well as for the patients listed for the first KTx (new patients). Previous KTx has significant impact on both class I and II peak PRA levels when compared with new patients who are already sensitized. A subanalysis of retransplantation showed patients with autoimmune disease (54%) have more graft loss due to rejection compared with nonautoimmune disease (43%). There is an association between high PRA level and autoimmune disease causing renal failure regardless of the previous KTx status. Besides the risk of recurrence, autoimmune disease seems to affect the risk of graft loss due to rejection.

2. Analysis of allograft biopsy specimens in renal transplants with proteinuria: is proteinuria a culprit of graft loss?
It has been proposed that proteinuria occurring after renal transplantation may be not only a marker but also a culprit of allograft dysfunction. We retrospectively analyzed the data from 55 patients who underwent transplant renal biopsy for proteinuria and/or azotemia occurring beyond 1 year after transplantation. Proteinuria was considered as significant when \( \geq 30 \text{mg/dL} \), and results of transplant biopsy were categorized according to the Banff 97 classification. Logistic regression was used to estimate odds ratios (OR) for graft loss associated with proteinuria and transplant pathology. The patients were followed for 86.0 +/- 32.8 months after transplantation, and transplant biopsy was performed at 54.1 +/- 31.0 months. Proteinuria at 1 year after transplantation noted in 29.1% of patients was not significantly associated with graft loss (OR = 1.94, 95% CI from 0.59 to 6.41). In addition, proteinuria at the time of transplant biopsy was not significantly associated with graft loss. Chronic allograft nephropathy was the most frequent transplant pathology. Only glomerulonephritis was significantly associated with proteinuria at the time of the transplant biopsy. On the other hand, graft loss was significantly associated with the presence of proteinuria both at 1 year after transplant biopsy and at the final follow-up. These results suggest that posttransplantation proteinuria is an important marker of graft dysfunction, but is not predictive of graft loss in biopsy-proven cases. Appropriate management guided by the results of a transplant biopsy may improve the outcome.

### 3. Cytokines and chemokine gene expression in human kidney transplantation


Despite advances in immunosuppression in past decades, allograft rejection remains the main reason for kidney graft failure. Recently, despite great improvements in understanding of molecular basis of allograft rejections, renal histology remains the primary method to monitor the onset of graft rejection. The aim of the present study was to ascertain whether cytokine and chemokine expression profiles in kidney allografts contributed to the diagnosis of graft dysfunction. We analyzed mRNA expression in 174 kidney graft biopsies for the following cytokines: TGF-beta1, TNF-alpha, IL-10, and chemokine RANTES. Based on the expression levels obtained by real-time RT-PCR, we correlated data with the results of morphologic examinations. All tested cytokines and chemokines were upregulated (\( P < 0.001 \)) during acute rejection compared to nonrejecting controls. Upregulation was also found in chronic allograft nephropathy (CAN9 group for TGF-beta1, IL-10 (\( P < 0.001 \)), TNF-alpha, and RANTES (\( P < 0.01 \)). Upregulated expression of IL-10 (\( P < 0.001 \)), TGF-beta1, (\( P < 0.01 \)) and RANTES (\( P < 0.01 \)) showed borderline changes. Higher expression levels (\( P < 0.001 \)) of TGF-beta1 and IL-10 were also found during ATN. IL-10 was upregulated (\( P < 0.01 \)) in specimens with recurrent glomerulonephritis. Weakly increased (\( P < 0.05 \)) expression of TGF-beta1 were found during CsA toxicity. Distinctive expression levels between acute rejection and CAN were only found for IL-10 (\( P < 0.01 \)). TNF-alpha showed a different expression profile in acute rejection versus ATN (\( P < 0.001 \)). These findings suggest that distinct cytokine and chemokine expression profiles in grafts may contribute to the diagnosis for and elucidation of the immunopathologic process during graft dysfunction.
4. Review article: hepatitis C virus infection and type-2 diabetes mellitus in renal disease and transplantation


A link between hepatitis C virus infection and development of diabetes mellitus has been suggested by many investigators; however, this remains controversial. The mechanisms underlying the association between hepatitis C virus and diabetes mellitus are unclear but a great majority of clinical surveys have found a significant and independent relationship between hepatitis C virus and diabetes mellitus after transplantation and orthotopic liver transplantation. We have systematically reviewed the scientific literature to explore the association between hepatitis C virus and diabetes mellitus in end-stage renal disease; in addition, data on patients undergoing orthotopic liver transplantation were also analyzed. The unadjusted odds ratio for developing post-transplant diabetes mellitus in hepatitis C virus-infected renal transplant recipients ranged between 1.58 and 16.5 across the published studies. The rate of anti-hepatitis C virus antibody in serum was higher among dialysis patients having diabetes mellitus (odds ratio 9.9; confidence interval 2.663-32.924). Patients with type-2 diabetes-related glomerulonephrits had the highest anti-hepatitis C virus prevalence [19.5% (24/123) vs. (73/2247); P < 0.001] in a large cohort of Japanese patients who underwent renal biopsy. The link between hepatitis C virus and diabetes mellitus may explain, in part, the detrimental role of hepatitis C virus on patient and graft survival after orthotopic liver transplantation and/or renal transplantation. Preliminary evidence suggest that anti-viral therapies prior to renal transplantation and novel immunosuppressive regimens may lower to occurrence of diabetes mellitus in hepatitis C virus-infected patients after renal transplantation. Clinical trials are under way to assess if the hepatitis C virus-linked predisposition to new onset diabetes mellitus after renal transplantation may be reduced by newer immunosuppressive medications.

5. Prevalence of HIV-1-infection in dialysis unit in Spain and potential candidates for renal transplantation: Results of a Spanish Survey

Barrill G, Trullas JC, Gonzalez-Parra E, et al.


Introduction: Patients with HIV infection end-stage renal disease (ESRD) have improved their survival in the few years. HIV infection is not considered a contraindication for renal transplantation, but little experience exists in renal transplantation in HIV infected individuals. There is no information about the prevalence of HIV infection in Spanish patients under renal replacement therapies (RRT). Methods: A survey was performed in Spanish dialysis unit during 2004. The objective was to study the prevalence and characteristics of HIV infection in patients under RRT in Spain. We also aimed to know how many of them met the Spanish criteria to be
included on the renal transplantation waiting list. **Results:** HIV prevalence was 1.15% (95%CI 0.85-1.45) of 4,962 patients who were under RRT, mostly under hemodialysis and, less commonly peritoneal dialysis. The most frequent risk factor for HIV infection was parenteral drug use (58%). The most common causes of ESRD were glomerulonephritis (44%). The median time under RRT was 46 months. Coinfections with hepatitis C (60%) and B (7%) were found. Thirty-four percent of patients had a history of aids-defining events. Eighty-six percent were under HAART. The median CD4 cell count was 333 cells/l and the viral load was undetectable in 68%. Of 40 patients with a completed clinical questionnaire, 9 (22.5%) met the Spanish criteria for renal transplantation. **Conclusion:** HIV prevalence in patients under RRT in Spain is 1.15% (0.85%-1.45%) and 22.5% of these patients met the Spanis criteria to be included on a renal transplantation waiting list.

6. Pediatric renal transplantation: 13 years of experience – report from the Chilean Cooperative Multicenter Group


Between 1989 and 2002, 178 renal transplant were performed in 168 pediatric patients in Chile. The mean age was 10.9 +/- 3.7 years (range 1 to 17.9). End-stage renal disease etiologies were: congenital renal hypoplasia/dysplasia, chronic glomerulonephritis, and reflux nephropathy. Seventy received a graft from living donor (LD), and 108 from a cadaveric donor (CD). Only 9% received antibody induction. Acute rejection episodes were reported in 76 patients: 38% in LD recipients and 48% in CD recipients (P=NS). One-, 3-, and 5-year graft survival were 88%, 84%, and 76%, respectively, for LD and 86%, 79% and 68% for CD recipients. Actuarial graft survival was significantly better among those patients with serum creatinine < 1 mg/dL at year post transplant compared with those with creatinine > 1 mg/dL, (P < 0.05). The graft survival rate has improved from the first period (1989 to 1996) to the second period (1997 to 2002); (P = 0.05). Patient survival rates at 1, 3, and 5 years were 98%, 98%, and 98%, respectively, for LD, and 95%, 94%, and 94% for CD. Global height/age Z-score decreased from –0.7 at birth to –1.5 when dialysis started, and to -2.24 at the time of transplantation. The Z-score height/age at 1, 3, and 5 years posttransplantation was -2.25, -2.24, and -2.5. No significant differences were observed in transplant outcomes comparing patients younger than 7 years with those older ones. In conclusion, pediatric renal transplant has been performed in Chile with acceptable morbidity. The patient and graft survival are similar to the reported international experience. In the last period there was a significant improvement in graft survival.

7. Unusual post-transplantation recurrence of focal segmental glomerulosclerosis which resolved with cyclosporine but not with sirolimus

Skhiri H, Morelon E, Noel LH, et al.

Recurrence of idiopathic focal segmental glomerulosclerosis (FSGS) is frequent after the first kidney transplantation (KT), but a recurrence that only occurred after the second KT has never been reported. Although cyclosporine reduces proteinuria and prolongs graft survival in patients with recurrent glomerulosclerosis, the effectiveness of sirolimus for this condition is still not known. We report, for the first time as far as we know, the case of a 35-year-old black male patient who experienced a recurrence of FSGS, 10 days after a second KT, although no recurrence had occurred after the first. Cyclosporine treatment led to a decrease in proteinuria, whereas mycophenolate mofetil and angiotensin-converting enzyme inhibitor had no effect. Cyclosporine was replaced by sirolimus as treatment for chronic allograft nephropathy 24 months after KT. Nephrotic syndrome, which reappeared 3 weeks after the switch, was cured by cyclosporine re-introduction. The absence of FSGS recurrence after the first graft does not totally preclude its recurrence after the second. This observation points to the effectiveness of cyclosporine for the recurrence of FSGS and indicates that sirolimus should be given in such cases.

8. Recurrent nephrotic syndrome after living-related renal transplantation resistant to plasma exchange: report two cases


Abstract: We encountered two patients of recurrent nephrotic syndrome (NS) after renal transplantation that was resistant to plasma exchange (PEX). Case 1 was 34-year-old man with a living-related renal transplant for type-I membranoproliferative glomerulonephritis (MPGN) related end-stage renal disease (ESRD). He developed overt proteinuria 7 months post-transplant and presented with NS 5 months later. Biopsy of the transplant kidney revealed recurrent type I MPGN, but no features of acute rejection (AR) or chronic allograft nephropathy (CAN). he was treated with cyclophosphamide (CP), oral prednisolone (40mg/d), an anti-platelet agent, heparin sulfate, and PEX, but the nephrotic state persisted and renal function was deteriorated. He recommenced hemodialysis 3 yr and 9 months after renal transplant. Case 2 was a 47-year-old male who underwent living-related renal transplant for ESRD due to focal segmental glomerulosclerosis (FSGS). He presented with proteinuria shortly after renal transplantation. He also had frequent episodes of AR. Graft biopsy revealed recurrent FSGS. Treatment of pulse methylprednisolone and PEX was transiently effective, but NS relapsed shortly after PEX. Graft biopsy at our hospital showed features of CAN with moderate interstitial fibrosis and tubular atrophy, presence of intraglomerular foam cells but no segmental scleosis. Treatment with 12 courses of low-density lipoprotein aperesis (LDL-A) reduced proteinuria from 9.6 to 2.0 g/d, and incomplete remission has been maintained for more than 1 yr after LDL-A with slowly progressive renal dysfunction. Despite recent therapeutic advances, including the use of immunosuppressants and PEX, treatment of recurrent disease remains difficult. The LDL-A might be useful in cases with recurrent FSGS resistant to PEX.

9. Recurrence of membranoproliferative glomerulonephritis type II in renal allografts: The North American Pediatric Renal Transplant Cooperative Study Experience
Membranoproliferative glomerulonephritis type II (MPGN II) is an uncommon form of complement-dependent acquired renal disease. Although it has been recognized since the 1970s that MPGN II recurs almost universally in renal transplants, data regarding the long-term consequences of disease recurrence are limited. Therefore, a retrospective comparative analysis of 75 patients with MPGN II contained in the North American Pediatric Renal Transplant Cooperative Study transplantation database was performed. Five-year graft survival for patients with MPGN II was significantly worse (50.0 +/- 7.5%) compared with the database as a whole (74.0 +/- 0.6%). Living related donor organs had a significantly better 5-year survival (65.9 +/- 10.7%) compared cadaveric donor organs (34.1 +/- 9.8%). The primary cause of graft failure in 11 (14.78%) patients was recurrent disease. Supplemental surveys were obtained on 29 (38%) of 75 patients. Analysis of these data indicated that recurrent disease occurred in 12 (67%) of the 18 patients with posttransplantation biopsies. Although there was no correlation between pretransplantation presentation, pre- or posttransplantation C3 levels, and either disease recurrence or graft failure, there was a strong association between heavy proteinuria and disease recurrence. The presence of glomerular crescents in allograft biopsies had a significant negative correlation with graft survival. At last follow-up, patients with recurrent disease had significantly higher serum creatinine and qualitatively more proteinuria than patients without biopsy-proven disease. These data indicate that recurrent MPGN II has a significant negative impact on renal allograft function and survival.

10. IgA nephropathy with crescents in kidney transplant recipients


Background: Crescentic glomerulonephritis is an uncommon finding in renal allografts. Recurrence or de novo mesangial deposition of immunoglobulin A (IgA) in renal allografts most often is clinically benign, but some case reports have shown that IgA nephropathy in renal allografts can present as crescentic glomerulonephritis and may lead to rapid deterioration of graft function and/or graft loss. Methods: We reviewed diagnoses of all allograft biopsies at University of Washington Medical Center (Seattle, WA) from 1989 to 2003 and found 33 cases of glomerulonephritis with crescents. Eight of these cases were the result of recurrent or de novo IgA nephropathy. Clinical and pathological features of these patients were reviewed. Results: Six of 8 cases with crescents were the results of recurrent IgA nephropathy, and 2 cases were presumptive de novo IgA nephropathy. Of the 8 patients with IgA nephropathy with crescents, 6 patients presented clinically with increasing serum creatinine levels; 4 patients with proteinuria; and 4 patients with hematuria. In 6 patients, there was 10% to 30% involvement of glomeruli, with crescents partially or completely filling urinary spaces. The other patients showed lesser (approximately 7% of sampled glomeruli) involvement. Four patients with IgA nephropathy with crescents developed renal failure and returned to hemodialysis therapy. Three patients had a benign clinical course, with stabilization of renal function. One patient was lost to follow-up. Conclusion: We identified a
cohort of patients with glomerulonephritis with crescents in renal allografts with IgA nephropathy as the cause. In half the affected patients, this led to early progressive renal insufficiency and return to hemodialysis therapy.

11. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection

Dragun D, Müller DN, Brasen JH, et al.


Abstract. Background: Antibodies against HLA-antigens cause refractory allograft rejection with vasculopathy in some, but not all, patients. Methods: We studied 33 kidney-transplant recipients who had refractory vascular rejection. Thirteen had donor-specific-anti-HLA antibodies, whereas 20 did not. Malignant hypertension was present in 16 of the patients without anti-HLA antibodies, 4 of whom had seizures. The remaining 17 patients had no malignant hypertension. We hypothesized that activating antibodies targeting the angiotensin II type 1 (AT1) receptor might be involved. Results: Activating IgG antibodies targeting the AT1 receptor were detected in serum from all 16 patients with malignant hypertension and without anti-HLA antibodies, but in no other patients. These receptor-activating antibodies are subclass IgG1 and IgG3 antibodies that bind to two different epitopes on the second extracellular loop of the AT1 receptor. Tissue factor expression was increased in renal-biopsy specimens from patients with these antibodies. In vitro stimulation of vascular cells with an AT1-receptor-activating antibody induced phosphorylation of ERK½ kinase and increased the DNA binding activity of the transcription factors activator protein 1 (AP-1) and nuclear factor-kappaB. The AT1 antagonist losartan blocked agonistic AT1-receptor antibody-mediated effects, and passive antibody transfer induced vasculopathy and hypertension in a rat kidney-transplantation model. Conclusions: A non-HLA, AT1-receptor-mediated pathway may contribute to refractory vascular rejection, and affected patients might benefit from removal of AT-receptor antibodies or from pharmacologic blockade of AT1 receptors.

12. Statins’ dosage in patients with renal failure and cyclosporine drug-drug interactions in transplant recipient patients

Launay-Vacher V, Izzedine H, Deray G.

Int J Cardiol 2005; 101: 9-17.

Summary: See Part 2/TR/11.

13. Does pretransplant obesity affect the outcome in kidney transplant recipients?
The effect of obesity on renal transplant outcome remains unclear due to conflicting published studies. The purpose of this study was assess whether obesity affects the outcome in renal transplant patients. **Methods:** We retrospectively analyzed 33 obese (BMI >30; mean = 34.1 +/- 3.68; group I) and 35 nonobese (BMI < or == 30; mean = 23.6 +/- 3.18; group II) renal transplants performed at our center between March 1999 to december 2002. These two groups were well matched with respect to age, sex, donor, source, hypertension, diabetes, ischemic heart disease, hyperlipidemia, nativ kidney disease (PCKD, 6 vs 4; diabetic, 5 vs 4; glomerulonephritis, 6 vs 7; FSGS, 2 vs 2; and IgA, 2 vs 7), HLA mismatch and immunosuppressants medications (Neoral, 21 vs 25; tacrolimus, 11 vs 10; Cellcept, 28 vs 31; Prednisone, 33 vs 35; ATG, 7 vs 8; Basiliximab, 14 vs 13; and Rapamycin, 5 vs 2, group I and II, respectively). Follow-up was from 7 months to 4,4 years. **Results:** Significant differences were moted in operating time, wound infection, perinephric hematoma, lymphocele, and number of hospital days. There were no significant differences between the two groups in the incidence of wound dehiscence, deep vein thrombosis, pulmonary embolism, atelectasis, urine leak, delayed graft function, acute rejection rate, and the following posttransplant variables: diabetes mellitus, myocardial infarction, hyperlipidemia, hypertension, and incisional hernia. We conclude that obesity significantly increases operating time, wound complications, and hospitalizations.

14. Living-unrelated (paid) renal transplantation – ten years later


Due to the increase of organ shortage and still inadequate development of cadaver transplantation, many end-stage patients from the Balkan region travel mostly to India to buy a kidney. Despite all the ethical dilemmas and discussions, organ sales is present nowadays in Third-World countries. Sixten patients (13 from Macedonia and 3 from Kosovo, SCG) were observed clinically during a period of 10 years. Recipients of mean age 36,5 years (range 10 to 58) displayed the following underlying disease: chronic glomerulonephritis (n = 5), urethral valves with feflux (n = 2), ADPKD (n = 1), hypertensive nephropathy (n = 4), lithiasis (n = 1), and unknown cause of ESRD (n = 3). The donor population was young (22 to 26 years). Most patients records did not include data on HLA, cross-match, MLC, kind of surgery, or usual pretransplant workup. The immunosuppressive protocol included CyA, PRED, and AZA of MMF. All transplanted patients were followed on an outpatient basis in our department; patients with complications were hospitalized. The 1, 3, 5, and 10 year Kaplan Meier graft survival rates were 78,6%, 33,8%, and 18,8%, respectively. Seven patients were lost (43,7%), two during the first month after transplantation, two at the end of the first year, and three at 5, 6, and 8 years thereafter. The main reasons for death were severe pulmonary infections with sepsisi, hepatitis B with liver cirrhosis, Kala Azar, CMV, and cancer of the colon. Five grafts were lost due to repeated rejection episodes and chronic graft nephropathy. The last three cases remained with good renal function and actual serum creatinine values of 135 +/- 9. In view of this experience, the authors cannot recommend this type of transplantation, not only from ethical point of view, but also from frequent medical and surgical complications which are
sometimes life threatening.

15. Pregnancy after kidney transplantation. Case load of the Transplantation Center of Vicenza


**Background:** Pregnancy after kidney transplant has become possible thanks to recent surgical and pharmacological breakthroughs. **Materials and Methods:** We performed a retrospective study including all pregnant women transplanted in our center after 1997. The following variables were analyzed. The type of nephropathy, patient age when dialysis began, patient age at transplantation, the time between dialysis and transplantation and the time between transplantation and childbirth. Immunosuppressive therapy, type of delivery, baby’s weight and Apgar score were also considered. **Results:** We followed four pregnancies in three patients who were, respectively, diagnosed with chronic pyelonephritis, post-partum cortical necrosis and immunoglobulin A (IgA) glomerulonephritis (GN). We observed complications in three cases and two pre-term births. In one case, the baby’s weight at birth was lower when compared to the gestation age. We did not observe any significant disease in the baby’s follow-up. **Conclusions:** We concluded that our data were in agreement with those in the literature confirming that pregnancy after kidney transplant, although possible, carries an elevated risk; and therefore, patients have to be referred to highly specialized centers.