

## Letters and Replies

### Cardiac troponin-I accurately predicts myocardial injury in renal failure

Sir,

The recent study by Martin *et al.* [1] contributes to the data on troponins in renal failure, but contains some inaccuracies due to developments in this area.

It has been previously claimed, a claim repeated in this paper, that there is non-specific elevation of cardiac troponin T (cTnT) in patients with renal dysfunction. This statement is incorrect and arises from a misinterpretation of the literature. Claims of non-specific elevation of cTnT are based on previous reports that cTnI is not found in patients with renal dysfunction. We (and others) have demonstrated unequivocally that there is elevation of both cTnT and cTnI in patients with renal dysfunction [2,3]. The authors present similar data for cTnI, as have other workers. The reason for these reports has been use of assay cut-offs for cardiac troponin I (cTnI) optimized for specificity at the expense of sensitivity. We have commented on this previously. Claims of non-specific elevation have also been based on the suggestion that there is re-expression of cTnT in skeletal muscle which is detected by the current assay. This has been comprehensively refuted by the recent studies by Apple and others [4,5].

That there should be elevation of cTnT and cTnI in patients with renal dysfunction is unsurprising given the high incidence of cardiac disease in this population. The reasons why more show elevation of cTnT than cTnI is currently unknown. There are a number of possible explanations. As cardiac troponin measurements are completely specific for myocardial damage, differences may be due to assay sensitivity. Direct comparison of the assay performance of the existing cTnT with cTnI assays shows markedly superior performance for the cTnT assay. Detection limits are lower and assay coefficient of variation around the diagnostic discriminant cut-off is better. Both troponins are present in equal amounts and should be equally detectable following myocardial injury. A survey of the literature shows that diagnostic cut-offs for cTnI in patients with definite myocardial damage differ by an order of magnitude. Hence failure to detect cTnI is more likely to be due to poor performance of the current generation of cTnI assays. In addition, it has been shown that cTnI levels are reduced by haemodialysis [3], probably due to adherence of the cTnI molecule to the dialysis membrane.

Finally, cTnT has been shown to be prognostic in patients with renal dysfunction [6,7]. Although the authors show that cTnI predicts an adverse outcome, adverse events were also seen in cTnI negative patients. Prospective studies where both cTnT and cTnI are measured are required but to date, it would seem that cTnT is a superior marker to cTnI for prognostic outcome assessment [8].

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### Reply

Sir,

We appreciate the insightful comments provided by Drs Collinson, Stubbs, and Morgan regarding the current status of laboratory assays for cardiac troponins. The body of literature evaluating troponin assays and their diagnostic use in myocardial injury is growing rapidly, making the interpretation of clinical studies more difficult as new information arises. Collinson and colleagues have provided an accurate description of the present state of the art regarding cardiac troponins as it has advanced since the time of our investigation.

The published literature has repeatedly confirmed the non-specific elevation of cardiac troponin-T (cTn-T) in the presence of renal insufficiency using assays commercially available at the time of our investigation [1–5]. In fact, practice guidelines published after the conclusion of our study espouse the benefits of cardiac troponin-I (cTn-I) as the rapid assay of choice over cTn-T because of spurious elevations in states of muscle injury or uraemia [6]. Even the most recent data by Collinson *et al.* demonstrates twice as many positive cTn-T samples compared to cTn-I, suggesting a lack of specificity for cTn-T despite a refined assay [7]. This may represent a dilemma opposite of that hypothesized by Collinson for cTn-I, with assay cut-offs for cTn-T optimized for sensitivity at the expense of specificity.

Unarguably there is a high degree of cardiac disease in the chronic renal failure population, particularly in the United States where diabetes mellitus and hypertension are prevalent. This makes the notable elevation of cardiac troponins less surprising, yet more important to decipher. Both assays are, indeed, highly specific for cardiac damage compared to conventional creatine kinase-MB (CK-MB) assays. In addition, a number of studies have demonstrated the exaggerated mortality curve associated with elevations of cTn-I or cTn-T in patients with unstable coronary syndromes [8,9]. This has been replicated by Apple and co-workers in a population of patients with renal disease, incidentally noting that newer generation cTn-T assays performed no better in discriminating true myocardial damage in the setting of uremia than the first generation assays [10]. Finally, the statistically significant mortality difference in our patient population with elevated cTn-I is consistent with the above published data and furthers the knowledge of cardiac troponins as tools for coronary risk stratification.

The evidence for skeletal muscle expression of troponins in certain disease states is conflicting, with recent cited data utilizing a novel troponin-T assay unavailable for review [11]. In addition, corroborating evidence of hypothesized dialytic clearance of cTn-I does not exist.

It is important to recognize the limits of studies evaluating myocardial ischaemia and serodiagnostic markers for these events. Ultimately, there is no 'gold standard' against which to perform these analyses. However, it is equally important to recognize the ongoing evolution of serodiagnostic markers in myocardial ischemia. Our investigation is the only prospective evaluation of cardiac troponin assays in patients with renal failure which utilized diagnostic cardiac studies to determine the performance characteristics of the assay. These data demonstrate the clinical benefits associated with this assay and support the implementation into current clinical practice patterns. As reported, this could result in a substantial improvement in diagnostic efficiency and a corresponding reduction in health care costs. Though cTn-T may be equally sensitive for the detection of myocardial injury and recently available assays may improve the specificity in renal failure, cTn-I remains a viable and clinically proven standard against which to judge uremic patients with myocardium at risk.

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### Home haemodialysis—beware the psychological impact on the helper and/or family

Sir,

We have read with great interest the recently published personal opinion by Mackenzie and Mactier detailing the past, present and future aspects of home haemodialysis [1]. As the authors point out, after an initial boom period during the 1970s and early 1980s, the number of patients being maintained on this mode of dialysis has progressively decreased in the last decade. Among the reasons put forward for this worldwide trend are the advent of CAPD; an increase in the number of regional dialysis units; the perceived complexity of the technique and doubts about its cost effectiveness. None of these have, however, been able to fully explain the decline in acceptance, among both staff and patients, of this mode of renal replacement therapy.

Patients deemed suitable for home haemodialysis have always been considered to be those with the lowest risk of developing complications. This entailed minor or absent co-morbidity, a well functioning, easily accessible vascular access and last, but not least, a positive psychological profile of both patient and helper. As Mackenzie and Mactier report, the helper in most situations is the patient's spouse or life long partner. Initial psychiatric assessment of home haemodialysis patients and helpers has invariably been complimentary stressing the strong family bond.

We would, however, like to sound a word of caution. Based on our experience, admittedly modest, we have encountered, not infrequently, psychological disturbances of varying severity affecting mainly the helper and/or other family members. Disturbances have ranged from mild insomnia, nightmares in which the recurring theme revolved around the dialysis procedure, extreme anxiety leading to functional disability (decreased school performance), to frank psychotic depression. These manifestations were insidious in onset, usually appearing 2–4 years after the commencement of treatment. Importantly, transfer of the patient to hospital haemodialysis did not ameliorate the psychological damage sustained which, in some cases, continued for a long time to come, even after the patient's eventual death. It is surprising to us that this aspect of home haemodialysis has not received the full attention it so richly deserves. It, undoubtedly, has been one of the major factors which has led us to cease offering home haemodialysis as a treatment option. We would be eager to hear the authors' comments on this issue.

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1. Mackenzie P, Mactier RA. Home haemodialysis in the 1990s. *Nephrol Dial Transplant* 1998; 13: 1944–1948

## Reply

Sir,

We agree with Drs Bernheim and Korzets that the psychosocial status of the patient and helper is an extremely important factor in determining suitability for home haemodialysis. We routinely interview all patients and their helpers to assess their suitability for home haemodialysis training and, if either are considered unable to cope with the rigours and demands of home haemodialysis, we advise that they do not train for haemodialysis at home. In our paper [1] we highlighted that very few patients or their helpers developed psychological problems leading to technique failure with home haemodialysis. Of the 90 patients trained to perform home haemodialysis between 1 January 1990 and 31 December 1995 only two patients discontinued home haemodialysis because of anxiety and stress. We have tried to limit 'burn-out' associated with home haemodialysis by encouraging patients and their helpers to go on holiday and by providing respite haemodialysis at the hospital if the patient's helper has other commitments. In contrast to the experience of Drs Bernheim and Korzets we have not encountered any long-term psychological sequelae in our home haemodialysis patients or their families.

It is well established that a small proportion of patients on all modalities of dialysis are at risk of depression or other psychological illnesses [2]. Therefore, whilst individual patients and/or their helper may develop psychological problems we do not agree that this is an adequate reason to discontinue offering home haemodialysis as an option for treatment of suitable patients with end-stage chronic renal failure. We would rather express the psychological problems of dialysis highlighted by the authors as 'chronic dialysis—beware the psychological impact on the patient and their family'.

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## Anti-glomerular basement membrane antibody-mediated nephritis: when not to treat

Sir,

Sánchez Fructuoso and colleagues report two cases of anti-glomerular basement membrane antibody-mediated nephritis (anti-GBM nephritis) in association with diabetes mellitus, and caution that co-incident disease can be missed [1]. Having published in a similar vein [2], I agree that it is important to maintain a high index of suspicion for

co-incident or unusual pathology and that an aggressive biopsy policy is often appropriate. This is particularly true when the clinical course is atypical, potential alternative diagnoses are significant, or there is the potential for therapeutic intervention.

I was, however, concerned that both the reported cases of anti-GBM nephritis were treated with immunosuppression. I note that the doses of immunosuppression were low, reflecting the patients' age and co-morbidity. However, both patients presented in dialysis-dependent renal failure with no extra-renal manifestations. Treatment under these circumstances is contrary to usual practice, and may have exposed the patients to significant risk despite little prospect of renal recovery.

There are well-recognized markers thought to be predictive of poor response to therapy, several of which were present in the patients described. These include: oligo-anuria, creatinine >600 µmol/l; requirement for dialysis; high titre of anti-GBM antibody (>65%); and histological findings such as high crescent counts and glomerular or interstitial fibrosis [2–4]. Speculative immunosuppression in the face of such factors is probably not warranted. Indeed, in two large series from the UK [2,5], only two of 96 patients presenting with anti-GBM disease and serum creatinine >500 µmol/l regained independent renal function. (One was a young man with an acute presentation and an unusually favourable renal histology, while details on the other were not provided.)

We all recognize that medicine is an inexact science. However, it is important to balance therapeutic enthusiasm with prognostic realism. On the published evidence, it would seem prudent to reserve aggressive intervention in anti-GBM disease for patients with extra-renal involvement (principally alveolar haemorrhage), serum creatinine <600 µmol/l, co-existent anti-neutrophil cytoplasmic antibodies, or (very rarely) acute presentation with preserved glomerular architecture.

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## Reply

Sir,

Dr Andrews expresses his concern about the immunosuppressive treatment used on our patients. Indeed, the response to treatment is extremely poor in patients with anti-glomerular basement membrane antibody-mediated nephritis (anti-GBM nephritis) presenting oligoanuria, the need for dialysis or a high proportion of crescentic glomeruli. This has led highly

experienced teams such as that of Dr Andrews to adopt the policy of not treating this group of patients. This attitude, however, has been criticized by other groups [1] since presentation of anti-GBM nephritis with oliguria or severe renal insufficiency may not always be accompanied by advanced histological lesions. In some cases, acute tubular necrosis lesions have been observed which are probably associated with the haematuria of glomerular origin and these could be responsible for the oliguria-renal insufficiency rather than the glomerular lesions themselves. On the other hand, there are reports of patients with marked oliguria or anuria who have recovered sufficient renal function to avoid long-term dialysis or transplantation [1–4]. We have the same experience in an unpublished case. We feel that the determining factor may be the nature of the crescent, i.e., cellular crescents as shown by our patients are more likely to be reversible.

Additionally, when a patient presents at the hospital with acute renal failure it is very difficult to make the decision not to do anything or offer any type of therapy. This may lead to irreversible renal failure with no hope for the patient. We prefer to administer low dose immunosuppression and wait. Not only did our patients lack complications due to therapy, but 2 months later one underwent an episode of pulmonary

haemorrhage, probably because of the insufficient intensity of the treatment.

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## Letters

### Sjögren's syndrome complicated by MPO-ANCA positive crescentic glomerulonephritis

Sir,

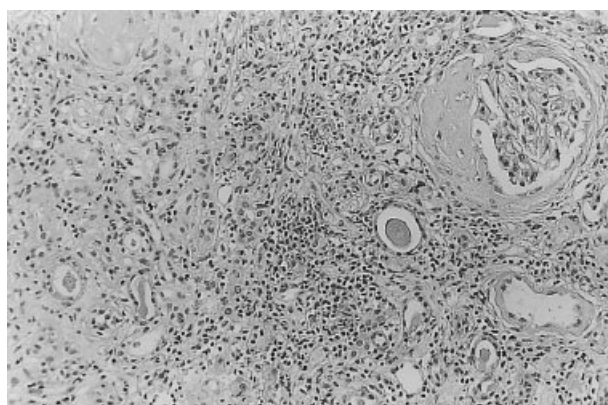
Although Sjögren's syndrome (SS) is occasionally complicated with tubulointerstitial nephritis as one of the extraglandular manifestations, the association of crescentic glomerulonephritis is not common [1,2]. We report here a female patient with SS associated with rapidly progressive glomerulonephritis and myeloperoxidase-specific anti-neutrophil cytoplasmic antibodies (MPO-ANCA). Renal biopsy revealed crescentic glomerulonephritis with scant immune-deposit, in addition to tubulointerstitial nephritis. She developed progressive renal failure, but this was reversed by steroid therapy and plasma exchange.

**Case.** A 67-year-old woman was admitted to our department on October 7, 1997 for nasal bleeding and progressive renal dysfunction. One year prior to admission, she noted the numbness and livedo of lower extremities. On March, 1997, she was found to have proteinuria and renal dysfunction (BUN 24.9 mg/dl, creatinine 1.7 mg/dl). One month prior to admission, she had noted recurrent nasal bleeding. The patient was admitted for further examination. On admission, her temperature was 36.6°C, pulse, 80 beats/min; blood pressure; 160/90 mmHg. Examination of chest revealed fine crackles present at the lower back of chest. There was livedo on the limbs. Findings included, marked anaemia (Hb 5.2 g/dl), elevated serum BUN (33 mg/dl) and Cr (2.8 mg/dl), positive nuclear antibody (X320, speckled pattern), antibody for SS-A 32.5 U/ml (normal range: 7–20 U/ml), positive rheumatoid factor (RF) and cryoglobulins.

Immunoelectrophoresis of serum protein demonstrated no monoclonal band and cryoglobulins were classified as

type III. High concentrations of serum MPO-ANCA was noted (603 ELISA U/ml) serum proteinase 3 specific anti-neutrophil cytoplasmic autoantibodies (PR-3-ANCA) were not detected. Urinalysis showed proteinuria (0.43 g/day) and microhaematuria.

Chest computed tomography (CT) scan showed irregular opacities, interstitial fibrosis, and mild pericardial effusion. Schirmer's test demonstrated 5 mm (right eye) and 5 mm (left) tearflow at 5 min. Minor salivary gland biopsy showed chronic inflammation with lymphocyte infiltration and acinar atrophy consistent with SS. A renal biopsy specimen contained 24 glomeruli, 11 of which were completely sclerosed, and four of which had fibrocellular crescents. There was mild mesangial sclerosis, occasional capillary collapse and interstitial infiltration of lymphocytes (Figure 1). Direct immuno-



**Fig. 1.** Renal biopsy (light microscopy): in addition to the diffuse interstitial mononuclear cells infiltrations, 20% of glomeruli obtained showed fibrocellular crescents. No findings of arteritis was identified. (PAS stain,  $\times 70$ ).

fluorescent staining of renal biopsy specimens revealed no deposition of IgG, IgM or C3 in the glomeruli (data not shown). Examination of the nasal cavity revealed an oozing ulcer of the septum. Nasal bleeding was stopped after nasal tamponade.

An initial diagnosis of primary SS with crescentic glomerulonephritis was made and she was treated with intravenous methylprednisolone (125 mg/day, three successive days) and followed by plasma exchange (3 l/day, total 6 l). Thereafter she was given oral prednisolone (40 mg/day). These therapies resulted in a marked decrease of MPO-ANCA. Low dose of cyclophosphamide (25 mg/day) was also tried during, but had to be stopped because of myelosuppression. Renal function had markedly improved (BUN 32 mg/dl, Cr 1.8 mg/dl) when she was discharged after 99 days.

**Comment.** The most common renal lesion of SS is interstitial nephritis with interstitial lymphocytic infiltration, fibrosis and tubular atrophy. In contrast, glomerulonephritis is relatively rare [1,2]. The present case had extraglandular manifestations affecting the lungs and kidneys. The present case fulfilled the criteria of primary SS [3], i.e. dry eyes with positive Schirmer's test, abnormal biopsy findings of salivary gland and presence of specific autoantibodies. MPO-ANCA, the serological marker for systemic vasculitis, was also present. Cryoglobulin-mediated glomerulopathy is occasionally found in primary SS [4], although cryoglobulins were detected in our patient, but immunofluorescence study showed no immunoglobulin deposits in the glomeruli.

Antibodies to MPO have been reported in collagen disease such as SLE [5,6], but only two cases of SS with MPO-ANCA-related glomerulonephritis have been reported [7,8].

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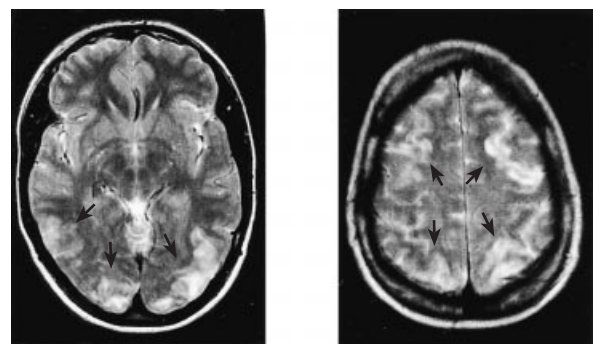
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### Seizures as the presenting feature of post-streptococcal glomerulonephritis

Sir,

During the last decades many diseases have become progressively rare mainly due to better hygiene and vaccination of the population. For this reason diagnosis can be difficult, especially when presenting symptoms are confusing or unusual.

**Case.** A 33-year-old female was admitted to the emergency ward because of seizures and blurred vision. The previous week she had been treated with tablet tetracycline for sinusitis, but was otherwise healthy. On admission she was somnolent, with mild periorbital oedema, and diastolic hypertension, 110–120 mmHg. The rest of the physical examination was unremarkable. A CT (computed tomography) of the brain and a lumbar puncture were performed, followed by an MR (magnetic resonance). Localized oedema was noticed in the occipital, temporal, frontal and parietal lobes (Figure 1). Cerebro spinal fluid (CSF) cell count was normal. Virus encephalitis was suspected and treatment with acyclovir parenterally was initiated but discontinued 2 days later when virologic examination of blood and CSF did not support this diagnosis. A chest X-ray showed bilateral perihilar pulmonary congestion and oedema, particularly in the right lower lobe, while sonography of the kidneys, including renal artery circulation, were normal. The sedimentation rate was 50 mm (0–20), C-reactive protein 33 mg/l (<9 mg/l), serum creatinine 71 µmol/l (60–120 µmol/l), serum albumin 27 g/l (36–48 g/l). Urinalysis showed albuminuria reaching 1.3 g/l and microscopic haematuria. An acute inflammatory reaction and hypoalbuminaemia were found in plasma electrophoresis the following day, with complement C3 and C4 within the lower normal range. Serologic tests for ANA, p- and c-ANCA, anti-GBM antibodies, and RF gave no evidence of connective tissue or vasculitic diseases. A 24 h urine catecholamines sample was normal. Renal crisis due to scleroderma was excluded on the basis of the clinical and laboratory findings. Eye funduscopy and urinary bladder cystoscopy disclosed no abnormalities. The initial patholo-



**Fig. 1.** Axial MR T2 weighted images show focal hyperintensity in the temporal, occipital, frontal and parietal lobes, consistent with oedema (arrows).

gical findings on MR of the brain and chest X-rays were almost completely resolved 4 and 9 days later, respectively.

Simultaneously as her condition improved, her serum chemistry and blood pressure became also normal, the later by treatment with tablet frusemide, 40 mg, and nifedipine, 20 mg, both given twice daily. She also received tablet fenatoin prophylactically against seizures. Due to the spontaneous improvement a renal biopsy was not performed. The patient was discharged 10 days after admission with the presumptive diagnosis of primary hypertonia and secondary hypertensive encephalopathy [1,2]. At the first follow-up 2 months later, at the department of nephrology, the medical history was re-evaluated. At that moment, it appeared that her earlier illness had begun with a sore throat followed by generalized oedema, both of which had passed unnoticed on admission. Anti-streptolysin titer (AST) was 330 U (0–200), and anti-DNAase titer was 400 U (0–200). An electroencephalogram revealed no abnormalities while blood pressure, serum chemistry, and urinalysis were all normal. Almost 5 months after her admission to the hospital all medication could be discontinued with the final diagnosis of post-streptococcal nephritis. After 1 year the patient is doing well, showing no abnormalities in clinical or laboratory examinations.

*Comment.* This interesting case has many instructive points beginning with the presenting symptom which was dramatic and highly suggestive of a cerebral process. The MR findings were first thought to represent an infection, which led to treatment with acyclovir. Hypertensive encephalopathy due to post infectious glomerulonephritis is very rare but the diagnostic approach could be improved by a detailed medical history [3]. The complement levels, which usually decline 3 to 8 weeks from the beginning of a streptococcal pharyngitis, were normal [4]. Our interpretation of this result is that the examination was performed too soon after the onset of symptoms. A low level of suspicion due to the current rarity of post-streptococcal nephritis partially explains the difficulty in making a correct diagnosis.

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### Safety and efficacy of corticosteroids in childhood nephrotic syndrome with concomitant hepatitis B

Sir,

Chronic hepatitis B infection is a well-recognized cause of membranous nephropathy and membranoproliferative glomerulonephritis and generally manifests as nephrotic syndrome (NS) [1,2]. Clinical trials using corticosteroid (C) therapy have been disappointing, in that a benefit has not been demonstrated consistently [3]. Conversely, in several reports therapy has been noted to be, in fact, detrimental, by

increasing viral replication [4]. Moreover, the sudden cessation of C may be associated with rebound activation of the immune system, with resultant acute hepatic decompensation [5].

*Case.* We are reporting our experience in managing a 3-year-old boy with new onset NS who was found to be positive for hepatitis B surface antigen (HBsAg) with a hepatitis B DNA titre (by PCR) of greater than 10 525 pg/ml (normal < 5.0 pg/ml). Laboratory work-up confirmed the nephrosis, with mildly elevated transaminases. Liver and kidney biopsies performed subsequently showed evidence of chronic active hepatitis, and much to our surprise, minimal change renal disease (MCD) without immune complexes on electron micrography. Due to concern that C therapy could foster viral activation, he received a 6-month course of interferon alpha (IA) 2-b (3 million units thrice weekly) without improvement. Due to his persistent nephrosis, a trial of C therapy in tapering doses (oral prednisolone 2 mg/kg/day) was initiated, in combination with a second course of IA 2-b. This has resulted in a prompt and sustained remission of his NS, without clinical deterioration of his liver function. He however, continues to have evidence of active viral replication and mild transaminase elevations.

*Comment.* The patient presented herein, differs from children previously reported with hepatitis B associated NS in several aspects, most importantly in that his underlying renal histopathology was that of MCD. Manna *et al.* [6] noted a higher prevalence of HBsAg carriage among male children with MCD compared to controls, although less than half of the patients whom they classified as having MCD had undergone a renal biopsy to confirm the histologic diagnosis. In addition, it is unclear from their data at what stage during the course of the disease hepatitis B serology was initially checked, and whether any of these children had previously received a course of C therapy which potentially, could have altered immune responsiveness, thereby resulting in increased susceptibility to, and chronic carriage of, hepatitis B virus. It is certainly possible that the two conditions could coexist in the same patient without being related pathogenically. The fact that our patient's heavy proteinuria failed to respond to a trial of IA alone, but promptly resolved after initiation of C therapy in spite of persistent hepatitis B antigenaemia, strongly supports an incidental rather than a cause-and-effect relationship between his NS and hepatitis B.

In conclusion, in our opinion all patients with new onset NS should be evaluated for serologic evidence of hepatitis B infection prior to initiation of C therapy, which may enhance viral replication, and that the presence of hepatitis B antigenaemia in the setting of newly diagnosed childhood NS, whether felt to be related or not, is not a contraindication to the use of C in a slow tapering regimen, with concomitant interferon therapy and careful clinical monitoring, and should be offered to patients who have failed a course of IA alone.

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### Treatment of membranous glomerulopathy with cyclosporin A: how much patience is required?

Sir,

Therapies for idiopathic membranous glomerulopathy (MGN) have been investigated for 30 years, but conclusions as to the best choice of therapy have been conflicting and elusive [1]. Cyclosporin A (CyA) has evolved as a promising alternative to more conventional immunosuppressants in a number of non-randomized trials and one randomized controlled trial with eight treated patients [2–8]. However a uniform treatment protocol with regard to the optimal duration of CyA treatment has yet not been established. In the studies cited above, the duration of treatment varies widely. Unfortunately the authors' rationale for choosing the respective duration of treatment is not stated in any of these publications. In a paper published in this journal, Meyrier observed that time to remission was longer in MGN than in minimal change disease (MC) with remission rates in MGN continuing to rise even after 6 months of treatment [9]. A review of the literature shows that the percentage of observed complete remissions increases with duration of treatment (Table 1). In order to avoid the risk of erroneously discarding CyA treatment as ineffective because of premature termination and on the other hand the possible danger of unnecessarily prolonged treatment, we felt that the optimal duration of CyA treatment for MGN should be estimated from existing data as a basis for future prospective studies. We therefore analysed the data of patients treated with CyA for Nephrotic Syndrome (NS) due to primary MGN in order to characterize the incidence and pattern of responses to CyA treatment in relation to duration of treatment. To determine whether the pattern of responses to CyA treatment differs between the various histologies of NS, we performed the same analysis on patients treated for NS with minimal change lesions (MC).

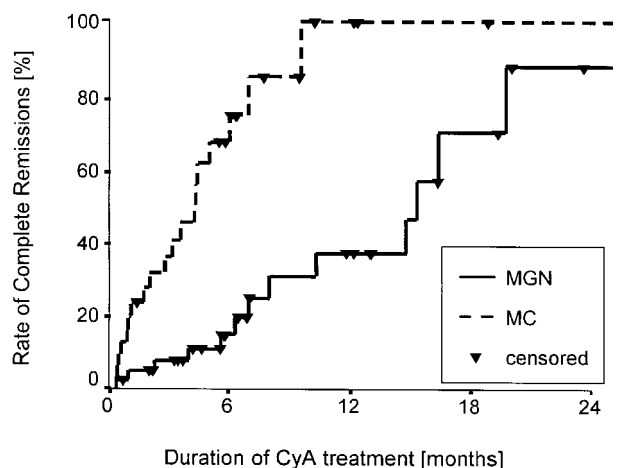
Data on patients treated for NS with CyA in 39 participating centers between 1985 and 1994 were collected retrospectively by the German Cyclosporine in Nephrotic Syndrome Study Group. Patient data were collected for the duration

**Table 1.** CyA treatment for nephrotic syndrome in membranous glomerulopathy: outcome in prospective studies correlated to duration of CyA treatment

Investigators	Duration of CyA treatment	Rate of complete remissions
Guasch <i>et al.</i> [6]	12 weeks	0/14 patients (0%)
Zietse <i>et al.</i> [5]	3 months	0/6 (0%)
Rostoker <i>et al.</i> [4]	4–6 months	4/15 (27%)
De Santo <i>et al.</i> [7]	6 months	4/5 (80%)
Cattran <i>et al.</i> [8]	1 year	6/8 (75%)

of CyA treatment and patients had been treated as long as the attending physicians deemed appropriate in each individual situation. From this database all patients fulfilling the following five selection criteria were selected for the present analysis: (i) adult (age over 16 years); (ii) nephrotic range proteinuria (>3.5 g/d) at initiation of CyA treatment; (iii) verification of the primary renal disease by renal biopsy prior to CyA treatment; (iv) histological diagnosis either membranous glomerulopathy (MN) or minimal change lesions (MC); (v) no evidence for secondary glomerular disease. Of the 168 patients in the database 74 patients fulfilled the selection criteria. Forty-one patients were classified as MGN and 33 patients as MC. The characteristics of these patients are summarized in Table 2. Complete remission of proteinuria (CR) defined as proteinuria <0.5 g/day was chosen as the primary end-point for assessment of response to treatment.

MGN patients were treated for a median of 353 days (quartiles 159 days and 586 days) with an average CyA dose of  $3.3 \pm 1.1$  mg/kg/day (initial dose of  $3.4 \pm 1.4$  mg/kg/day) while MC patients were treated for a median of 370 days (quartiles 193 days and 693 days) with an average CyA dose of  $3.8 \pm 1.3$  mg/kg/day (initial dose of  $3.9 \pm 1.6$  mg/kg/day). There was no significant difference in these CyA-treatment characteristics between both groups. 26/41 (63%) patients in the MGN group and 23/33 (70%) patients in the MC group were concomitantly treated with steroids (average dose: MGN group,  $27.5 \pm 21.2$  mg/day; MC group,  $27.3 \pm 23.7$  mg/day). 18/41 (44%) patients in the MGN group and 21/33 (64%) patients in the MC group received ACE inhibitors as co-medication. Fourteen (34%) of the 41 patients with MGN reached a complete remission during CyA treatment (urinary protein loss decreased from baseline to end of observation by  $5.9 \pm 6.5$  g/d,  $P < 0.001$ ), compared to 20 (61%) in the 33 patients with MC (urinary protein loss decreased by  $8.5 \pm 9.3$  g/d,  $P < 0.001$ ). The median treatment-time until occurrence of the first CR was significantly longer in patients with MGN than in patients with MC (225 days (quartiles 120 days and 459 days) versus 89 days (quartiles 28 days and 147 days),  $P = 0.012$ ). The incidence of CR per year of treatment was 30.8% in the MGN group compared to 43.1% in the MC group. The pattern of occurrence of



**Fig. 1.** Time to complete remission of proteinuria (CR) in patients with nephrotic syndrome due to membranous glomerulopathy (MGM) or minimal change lesions (MC) during treatment with cyclosporine A. (Patients not reaching CR excluded).

**Table 2.** Patient characteristics at baseline<sup>a</sup>

	MGN	MC	P-value <sup>b</sup>
Number of patients	41	33	
Sex	25 female/16 male	17 female/16 male	n.s.
Pre-treated with immunosuppressants	28 (68%)	29 (88%)	0.041
Age	42.7 ± 14.7 years	39.6 ± 17.4 years	n.s.
Body-weight	78.3 ± 16.1 kg	70.1 ± 17.7 kg	0.04
Time since diagnosis	2.3 ± 3.2 years	2.2 ± 4.5 years	n.s.
Creatinine	116.4 ± 53.3 µmol/l	83.7 ± 29.1 µmol/l	0.001
Urinary protein loss	10.9 ± 5.7 g/d	11.3 ± 9.4 g/d	n.s.
Mean arterial pressure	109.0 ± 12.4 mmHg	104.0 ± 12.5 mmHg	n.s.

<sup>a</sup>Means ± SD.<sup>b</sup>n.s. = not significant.

first CR in relation to duration of treatment is shown in Figure 1 separately for MGN and MC.

In the MGN group 30 adverse events were observed in 15 of 41 patients, the most frequent being gingival hyperplasia ( $n=4$ ), nausea ( $n=4$ ) and muscle cramps ( $n=4$ ). The absolute number of adverse events observed in the 16 patients with early termination of CyA treatment (duration <6 months) was 14, while 16 adverse events were observed in the 25 patients with longer treatment (6 months and more). The number of observed adverse events per patient did not correlate with duration of CyA treatment ( $r=0.046$ , Pearson). The rise in serum creatinine from baseline to end of observation was not significantly different between patients with early termination of CyA treatment and those on longer treatment ( $37 \pm 35 \mu\text{mol/l}$  vs  $26 \pm 38 \mu\text{mol/l}$ ,  $P=0.35$ ).

As the MGN patients in this study were all nephrotic and most had at least one additional risk-factor for disease progression, they belonged to a population with a low chance of spontaneous remission and an incidence of remissions lower than 10% per year had to be expected without treatment [10–12]. Therefore, the observed CR-incidence of 30.8% per year can be attributed mainly to a treatment effect.

The need to tailor specific treatment-protocols for the various histologic forms of glomerulonephritis is emphasized by the distinctly different time-patterns of response to treatment observed. The number of MGN patients reaching a complete remission of proteinuria rose steadily with increasing treatment time up to well over 12 months and the majority of CRs occurred after more than 6 months of treatment. Although baseline characteristics, duration and dosage of CyA treatment were similar in the MGN and the MC groups, the time to occurrence of CR was significantly longer in the MGN group. The initially observed gap between cumulative incidences of CR for MGN and MC patients narrowed with increasing duration of CyA treatment. Meanwhile, the comparison of short- and long-term treated patients showed no significant differences in the safety profiles. Thus, duration of treatment seems to be a crucial factor in the assessment of the efficacy of CyA for a given histological form of glomerulonephritis.

We conclude, based on this retrospective evidence, that withdrawal of CyA treatment after less than a year should be avoided in patients with MGN. However, the value of CyA treatment of MGN needs to be confirmed in a large controlled study.

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### Acute cholestasis during long-term treatment with fluvastatin in a nephrotic patient

Sir,

Pharmacologic therapy of nephrotic hyperlipidaemia is needed in some patients because prolonged hyperlipidaemia is a risk factor for accelerated vascular disease and for progression of renal damage. Hydroxymethylglutaryl (HMG) coenzyme A reductase inhibitors have become the treatment of choice for nephrotic hyperlipidaemia. However, the long-term efficacy and safety in these patients are unknown. Adverse effects such as liver dysfunction and myopathy may occur.

*Case.* A 71-year-old man with creatinine 98  $\mu\text{mol/l}$  and high LDL-cholesterol (5.6 mmol/l) secondary to a nephrotic syndrome caused by membranous nephropathy started treatment with fluvastatin (20 mg/day) in September 1996. He received prednisone 20 mg once daily. Six months later, hepatic function was normal, and because of persistently high LDL-cholesterol levels (5.9 mmol/l) the dose was increased to 40 mg/day. In May 1997, anicteric hepatitis with ALT of 210 IU/l (normal <40 IU/l), GGT of 1818 IU/l (normal <40 IU/l) and alkaline phosphatase of 472 IU/l (normal <270 IU/l) was detected. Abdominal ultrasonography was normal. Viral serology was negative. Fifteen days after withdrawal of fluvastatin the patient's biochemical pattern returned to normal. Fluvastatin was reintroduced (20 mg/day) with a new rise of GGT 532 IU/l, which prompted definitive withdrawal of fluvastatin and substitution for simvastatin (20 mg/day), so far no abnormal liver function has been noted.

*Comment.* The acute cholestatic hepatitis initially observed appears to be a dose-dependent effect, even though the new rise of GGT at lower doses, not reproduced with simvastatin, suggests idiosyncratic reaction. We are not aware of other reports of hepatotoxicity during treatment with fluvastatin. To our knowledge the adverse hepatic effects have consisted in a slight rise of transaminases, which in no case was over three times the upper normal limit [1].

Fluvastatin is the only entirely synthetic agent in this class, with high hydrophilicity and liver extraction during the absorption phase [2]. The hepatotoxicity profile of fluvastatin is such that liver-enzyme testing, required with all HMG coenzyme A reductase inhibitors, is less frequently needed with this agent than with the other inhibitors [3]. Although this agent has been proven safe in clinical trials [4,5], like any drug, it also carries the risk of adverse effects. A recent study by Marcelino and Feingold [6] suggested that less than half of the patients on a statin had an annual liver panel to monitor for hepatotoxicity. Monitoring of hepatic function in patients on a statin is advisable even when, during the first months, no rise of hepatic enzymes has been detected. Monitoring is particularly indicated when the dose has been increased.

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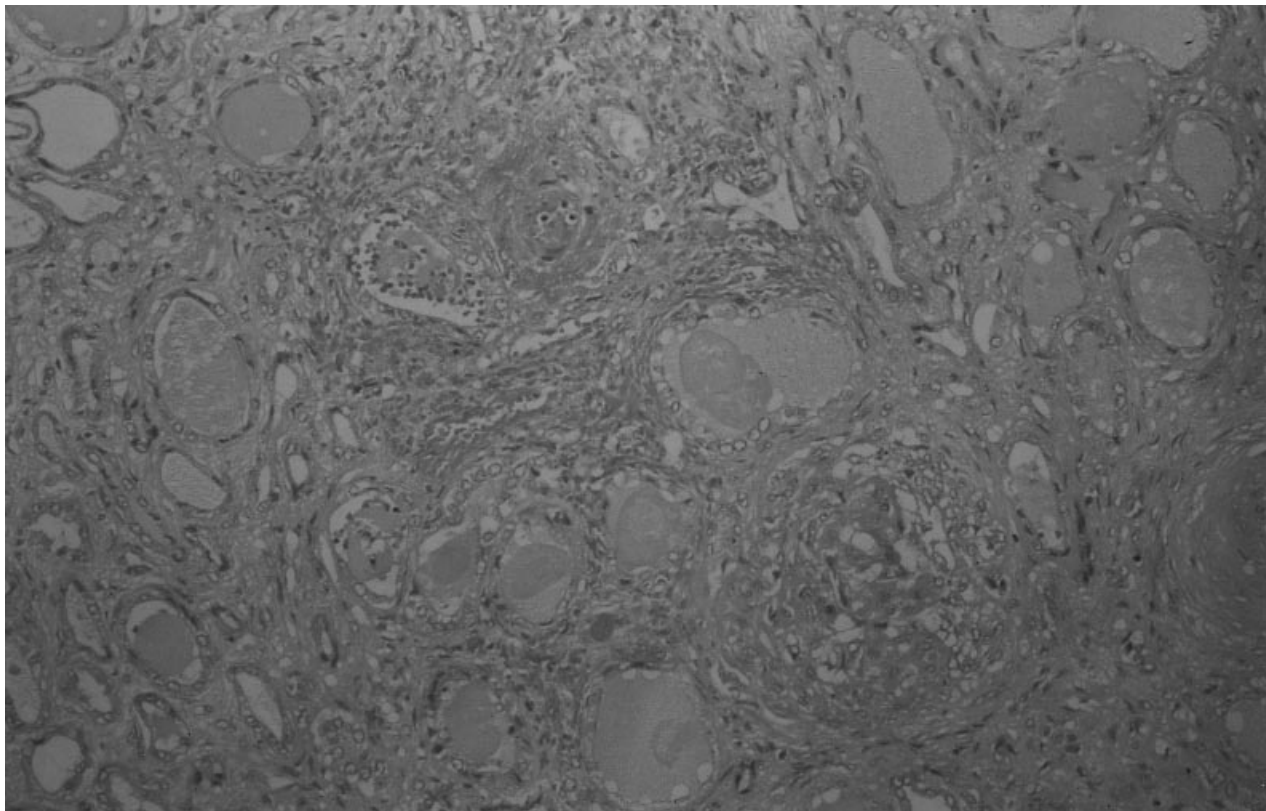
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### Microscopic polyangiitis associated with non-Hodgkin's lymphoma

Sir,

Some cases of vasculitis associated with malignant lymphoproliferative processes have been described. They tend to be leukocytoclastic vasculitis with cutaneous but no visceral involvement. We observed a case of microscopic polyangiitis [1] with renal, pulmonary and splenic but not cutaneous involvement in the context of non-Hodgkin's lymphoma.

*Case.* The patient was a 40-year-old female who was well until December 1990 when monocytoid cell lymphoma was diagnosed with involvement of spleen and tonsils and with generalized retroperitoneal and peripheral lymphadenopathy. She was treated with CHOP and remission of the disease was achieved. In February 1992 the disease relapsed and was treated with prednisone, chlorambucil and radiation therapy with good response. In August 1995 she was admitted for evaluation because of another relapse, now with renal insufficiency and microcytic anaemia. Physical examination revealed: BP: 130/70 mmHg, bilateral and multiple supraclavicular, axillary and inguinal lymph nodes (approximately 2 × 2 cm) and palpable spleen. Blood analysis: ESR, 139 mm; creat., 1.7 mg/dl; Hb, 6.4 g/dl; MCV, 72 fl; direct Coombs test positive; polyclonal hypergammaglobulinaemia; total proteins, 7.6 g/dl; albumin, 3 g/dl; cholesterol, 171 mg/dl; LDH, 262 U/l; urine, 100 red blood cells/field; protein excretion, 3693 mg/24 h. A bone biopsy showed paratrabecular and non-paratrabecular focal infiltration due to small cell lymphoma and presence of the three haematopoietic series in different stages of maturity. The patient was discharged on oral corticoids 30 mg/48 h. Three months later, during follow-up, renal function continued to deteriorate with creat: 2.6 mg/dl and anaemia. Treatment with 2-deoxycophormicin 6 mcg/week was started. Three days after the second dose of 2-deoxycophormicin, the patient was admitted presenting with progressive dyspnea and orthopnea without haemoptysis, decreased diuresis and lid oedema. Blood pressure was TA: 160/90 mmHg. The patient was conscious and oriented. She had orthopnea, pale skin and mucous membranes, congested jugular veins, but no malleolar edema. Bilateral basal crackling was noted. Blood analysis: leukocytosis 15 100/mm<sup>3</sup> (91% GR); Hb, 7.2 gr/dl; MCV, 74 fl; platelets, 213 000/mm<sup>3</sup>; PT, 100%; creat., 11.7 mg/dl; urea, 280 mg/dl; Na<sup>+</sup>, 129 mmol/l; K<sup>+</sup>, 5.5 mmol/l; GOT, 105 U/l. Blood gas analysis (FiO<sub>2</sub>: 0.21): pH, 7.37; pCO<sub>2</sub>, 30 mmHg; pO<sub>2</sub>, 55 mmHg; bicarbonate, 18.2 mmol/l; O<sub>2</sub> sat., 87%. Chest X-ray showed a bilateral interstitial pattern with Kerley B lines. Abdominal sonography: discrete splenomeg-



**Fig. 1.** Small vessel with fibrinoid necrosis and crescentic glomerulonephritis (H-E  $\times$  220).

aly. The patient had one dialysis session via femoral catheter. On the second day she developed psychomotor agitation with disorientation, and died of accidental bleeding through the femoral catheter. At post-mortem nodular infiltration of bone marrow by lymphoma was noted as well as fibrosis of lymph nodes with sinusoidal dilation. In addition diffuse proliferative extracapillary glomerulonephritis and necrotizing small vessel vasculitis were found (Figure 1). There was also extrarenal vasculitic involvement concerning the spleen and the lungs (septal capillaritis and alveolar haemorrhage).

**Discussion.** Vasculitis associated with neoplasias is infrequent and has been described particularly in patients with lymphoproliferative and myeloproliferative diseases, predominantly in leukaemias, less frequently in patients with solid tumours [2]. The most common type of vasculitis is cutaneous leukocytoclastic angiitis, and rarely, systemic vasculitis, develops, mainly in association with hairy cell leukaemia. The types of vasculitis include polyarteritis [3] and Schönlein–Henoch purpura [4]. In patients with lymphoma, Schönlein–Henoch purpura [5] and cryoglobulinemia [6] have been described, but cutaneous angiitis is the most frequent form. Glomerular disease is rare in lymphoma [7]. Membranous, mesangio-proliferative glomerulonephritis, minimal changes, focal glomerulosclerosis and more rarely, focal necrotizing glomerulosclerosis can be observed. The latter, may be associated with cutaneous angiitis [8]. In our case, the patient presented with small vessel vasculitis involving lung and spleen as well as diffuse proliferative extracapillary glomerulonephritis with vasculitis lesions. There was no evidence of renal infiltration by lymphoma at post-mortem. At the time the patient presented with vasculitis, she was treated with 2-deoxycophormicin. A case of small vessel systemic vasculitis

with fatal evolution was described in a patient on 2-deoxycophormicin, but this may have been only a predisposing factor [9]. There was neither peripheral eosinophilia nor fever suggesting hypersensitivity to the medication. The lesions described correspond to microscopic polyangiitis with pulmonary and glomerular capillaritis in the context of non-Hodgkin's lymphoma resistant to therapy. This is the first case in which such an extensive vasculitic lesion associated with lymphoma has been demonstrated by histology.

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## Hantavirus nephropathy in a child

Sir,

A new case of haemorrhagic fever with renal syndrome (HFRS), is described in an 11-year-old boy from Northeastern Greece, caused by hantavirus infection. This is the first case of the HFRS syndrome in a child detected in Greece.

Haemorrhagic fever with renal syndrome is an acute febrile nephropathy, caused by closely related zoonotic viruses of the genus Hantavirus, family Bunyaviridae [1]. Over the last 15 years, approximately 200 cases of HFRS have been serologically confirmed in Greece [2]. In 1987, a Hantaan-like virus (Porogia) was isolated from the urine of a severely ill HFRS patient [3].

*Case.* An 11-year-old boy, resident of Komotini village, located close to the Greek–Bulgarian borders (Northeastern Greece), was initially admitted to the country hospital and then, on 25 July 1997, was transferred to the 4th Pediatric Department of AHEPA (American Hellenic Educational Progressive Association) Hospital in Thessaloniki, Greece. The patient presented with 7-day illness including fever (39°C), abdominal pain, back pain and tenderness of the renal area, nausea, vomiting, loose stools, thrombocytopenia (91 000/mm<sup>3</sup>), anaemia and azotaemia.

On admission, his physical examination was unremarkable, except he was feverish. His laboratory findings were as follows: white blood cell count of 7100 cells/mm<sup>3</sup> (54% neutrophils, 37% lymphocytes and 9% monocytes); haematocrit of 32%; haemoglobin of 10.9 g/dl and platelet count of 110 000/mm<sup>3</sup>. The sedimentation erythrocytes rate (SER) was 70 mm and C-reactive protein (CRP) 1.15 g/l (normal value <0.50). Creatinine and urea levels progressively increased to 23 mg/l and 930 mg/l, respectively. No elevation of liver enzymes were observed. The urine output was 250 ml/24 h with proteinuria and microscopic haematuria. The glomerular filtration rate (GFR) was 47.3 ml/min/1.73 m<sup>2</sup>. No petechiae was observed, nor did internal haemorrhage occur.

On day 12, haematocrit was 36%, hemoglobin 12 g/dl and platelet count 364 000/mm<sup>3</sup>. Serum creatinine and urea levels were 6.5 mg/l and 325 mg/l respectively, with a urine output 2500 ml/24 h and normal GFR. The patient was discharged after 15 days of hospitalization.

Sera taken on day 9 of illness from the patient were tested at 2-fold dilutions (initial dilution 1:16) by immunofluorescence assay (IFA) with fluorescein-labelled goat anti-human immunoglobulin (GIBCO Diagnostics, Madison, WI) on spot slides containing Vero E6 cells (ATCC CRL 1586), infected with strain 76–118 of prototype Hantaan virus. Titers were recorded as the greatest dilution of serum at which characteristic cytoplasmic immunofluorescence was detected. The IgG and IgM Hantaan virus IFA antibody titers were 1:16 384 and 1:512 respectively. Screening for antibodies to other virus-related HFRS was negative as well

as for antibodies to leptospirosis. Management included careful monitoring of electrolytes and fluid intake and output with correction, especially during the oliguric and diuretic phases. Plasma expanders were used as well.

Four months later (November 1997), he remained well and in good condition, with his laboratory findings in normal ranges. Six months later our patient was without any symptoms. The IgG Hantaan virus antibody titer was 1:2048. No IgM antibody titer was quantified. His renal function was normal.

*Comment.* HFRS is endemic in the Balkan Peninsula and epidemic outbreaks and isolated cases have been reported during the last decades. From a retrospective serological and genetic study of the distribution of hantaviruses in North Greece, it was found that the virus which was responsible for all the PCR positive cases was Dobrava virus, which is endemic in the Balkans [2,4]. The principal rodent host is *Apodemus flavicollis*, the yellow-necked mouse.

HFRS in the Balkan region ranges from the severe form usually attributable to Hantaan-like infection to mild cases more typical of Puumala-like infection. The mean age of HFRS patients in Greece is 36 years, ranging from 21- to 71-years-old. The clinical course of the HFRS can be divided into five phases (febrile, hypotensive, oliguric, diuretic, convalescent). Some of the patients do not develop all the above phases of the syndrome. Asymptomatic cases of HFRS also seem to be quite common [5].

The exact location at which the boy acquired the hantavirus infection is not known, but the residency may play a role since the village of Komotini country is thought to be an endemic area. Antoniadis *et al.* performed a prospective study to determine hantavirus-associated HFRS in this Greek region. HFRS appears more frequently from May to October (our case was admitted in July). Besides, the patient's parents are farmers and used to take him into the fields or into the woods, where he was possibly infected by inhaling aerosolized rodent excreta or by ingesting material contaminated with rodent excreta. Our patient had never left Greece, suggesting acquisition of an indigenous virus strain. HFRS should be considered in the differential diagnosis of cases with unexplained high fever, even when the patient is very young. Hantavirus infection should be considered even in paediatric patients who have acute renal failure.

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### Chronic renal dysfunction after Hantavirus infection

Sir,

The long-term renal prognosis of Hantavirus infection (HI) is unclear [1,2]. In 1991–95, 879 patients with HI were identified (11.2 per 100 000 population) in the Penza region of Russia (Central Volga, total population, 1 560 000; total area, 43 000 km<sup>2</sup>). Puumala is the most common Hantavirus sero-type in European Russia. For all patients the diagnosis was confirmed by documentation of elevated antibody titers to Hantavirus in serum using indirect immunofluorescence (diagnostic kits of the Institute of Poliomyelitis and Viral Encephalitides, Moscow, specifically for Puumala, Hantaan and Seoul antigens). Sixty-three (7.2%) patients had severe acute renal failure (ARF) necessitating haemodialysis. The overall mortality rate from HI was 0.3%. Among patients with severe ARF it was 1.6%. Long-term observation is not available for all persons with a history of HI. Nevertheless out of 63 patients with severe ARF (mean age 32.1 years; range 15–67; 55, i.e. 87.3% men) 19 patients (30.2%) had arterial hypertension and 4 (6.3%) elevated had serum creatinine concentration (range 189–423  $\mu\text{mol/l}$ ) 1 month after discharge from the hospital. As far as 1–7 years after illness, all the patients with elevated serum creatinine levels had arterial hypertension and serum creatinine ranged from 165 to 685  $\mu\text{mol/l}$ . In the past we had documented a higher prevalence of chronic renal failure (CRF) in the population living in the forest province of the Penza region, where morbidity rate of HI is more than five times higher than in the steppe province [3]. The overall prevalence of known CRF was low, however, because territorial hospitals do not have complete information concerning CRF.

The development of CRF after severe HI with severe ARF is not surprising. Persisting renal dysfunction may occur after ARF of different aetiologies [4]. Glass *et al.* noted an association between positive HI serology (virus Seoul) and chronic hypertensive renal disease [5]. This finding was made on the American continent, where severe renal manifestation of HI are infrequently observed. In contrast in our region HI is the most common cause of ARF (as a rule patients did not require dialysis) and Hantavirus antibodies are present in 4.9% of the population living in the Penza region of Russia.

We conclude, that long-term renal prognosis after HI is not uniformly benign.

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### LDL apheresis as intensive lipid-lowering therapy for cholesterol embolism

Sir,

With the development of the interventional therapy for cardiovascular diseases, cholesterol embolism (CE) has been recognized as a serious problem after coronary angiography or percutaneous transluminal coronary angioplasty (PTCA). In these procedures, CE is caused by the subsequent release of cholesterol crystals to the microcirculation causing distal ischaemia. The incidence of CE in this setting is rapidly increasing. According to the range of embolization, the clinical findings of CE are highly variable. Even by nephrologists, the diagnosis of CE may not be made in patients with transient renal dysfunction. Premortem diagnosis of CE is difficult if not suspected and can be made only by skin or kidney biopsy [1]. In the benign form of CE, e.g. the blue toe syndrome without renal failure, a few cases of successful with the HMG CoA reductase inhibitor lovastatin have been reported [2]. On the other hand, more than 80% of patients with generalized CE and renal involvement will die illustrating the need for new methods in the diagnosis and treatment of CE. We describe two patients with rapidly progressing renal dysfunction and livedo reticularis due to CE. They were treated with low density lipoprotein (LDL) apheresis using dextran sulphate cellulose columns (Liposorber LA-15, Kaneka Corporation, Osaka) [3] performed once or twice a week over 2 months (a total of 10 treatments). Improvement of livedo reticularis and extremity pain was noted immediately after some sessions of LDL apheresis. In each treatment session approximately 3 l of plasma were treated. In both cases, there was no history of lipid-lowering therapy (Figure 1).

Patient 1 was a 68-year-old man complaining of chest pressure. He was treated for hypertension and diabetes mellitus. Coronary angiography showed critical stenosis of three vessels and he underwent coronary bypass surgery and warfarin therapy. After surgery, renal function deteriorated but subsequently returned to baseline. One month after surgery, he developed progressive renal failure, cyanotic toes, and livedo reticularis on both lower extremities. A renogram showed prolongation of the vascular phase and the loss of the excretory phase, which may reflect nephron damage due to a shower of cholesterol crystals. A kidney biopsy specimen showed about a quarter of 20 glomeruli to be globally sclerotic due to ischaemic changes. The other glomeruli were intact. No inflammatory changes or crescents were detected. Needle-shaped cholesterol crystals in the intraluminal clefts were recognized in small arteries. Crystals were also found in a skin biopsy of acrocyanotic toes. He subsequently required HD. LDL apheresis was initiated at this point. After LDL apheresis, the pain from the gangrenous toes, livedo reticularis of the lower extremities and level of consciousness rapidly improved, but renal function was unchanged.

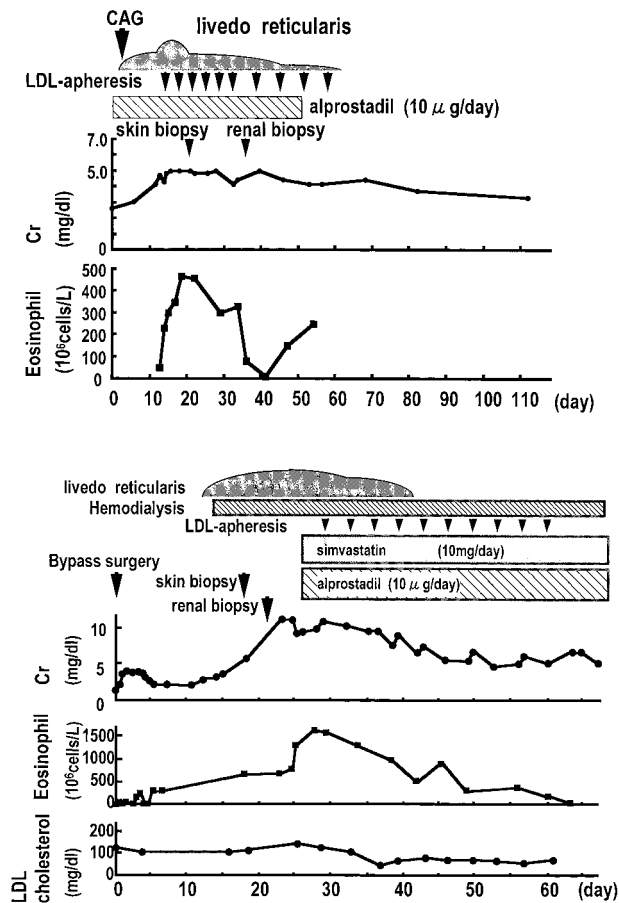


Fig. 1. Clinical course of patient 1 (bottom) and patient 2 (upper).

Patient 2 was a 68-year-old man in whom percutaneous transluminal angioplasty of the femoral artery had been performed 6 months previously and warfarin therapy was begun. He had no coronary risk factors such as diabetes mellitus or cigarette smoking. He was admitted with bilateral painful acrocyanosis and a serum creatinine concentration of 2.6 mg/dl with almost normal sized kidneys. On the second day after admission, coronarography and femoral angiography were performed by the brachial artery approach. After angiography, acrocyanosis worsened and 10 days later, marked livedo reticularis of the trunk and lower extremities appeared along with an increase in the serum creatinine concentration. The progressive renal dysfunction and livedo reticularis were thought to result from CE, and LDL apheresis was performed at once. Following apheresis, the level of consciousness improved and livedo reticularis improved in parallel as did the pain from the acrocyanotic toes. Renal function did not recover, however, cholesterol crystals were noted in skin and kidney biopsy specimens.

In CE patients as well as arteriosclerosis obliterans, the short-term effect of LDL apheresis on ischaemic toe pain, livedo reticularis and level of consciousness can be interpreted mechanistically as follows; (i) improvement of blood and plasma viscosity, and of deformability of red cells secondary to reduction of lipoprotein concentrations, (ii) generation of bradykinin, nitric oxide derivatives [4] and prostaglandins (PG) e.g. PGE<sub>2</sub> and PGI<sub>2</sub>, secondary to improved hemorheology and microcirculation [5]. Recently single sessions of LDL apheresis have been reported to improve

endothelial function by reducing the concentration of total LDL and oxidized LDL [6]. LDL apheresis may be more beneficial for CE induced damage in skin and brain than kidney. In the former tissues collateral arteries can develop. After recovery, it does make sense to treat with simvastatin or alprostadil concomitantly with LDL apheresis. Renal failure due to CE is progressive and carries an extremely poor prognosis. Even in surviving patients, it generally takes over 8 months to recover renal function and discontinue HD [7]. Renal function may recover after restoration of a blood supply to damaged but viable glomeruli.

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### Does colchicine also induce a clearance of the established amyloid deposits?

Sir,

The issue of whether amyloid deposits are cleared is still controversial. We had the opportunity to follow a case which is relevant in this context.

**Case.** A 26-year-old woman was admitted to our hospital in 1989 for the evaluation of a massive anasarca-type pitting oedema that had become apparent over the month before admission. She also had a 6-month history of frothy urine. She was married for 11 years but had no pregnancy in that time. On physical examination she had signs of pleural effusion, ascites, hepatomegaly as well as massive peripheral and sacral pitting oedema. The positive laboratory findings included a microcytic anaemia with a haemoglobin of 8.5 g/dl and MCV of 72.2; ESR was 120 mm/h and total serum protein and albumin levels were remarkably low with values of 4 g/dl and 2 g/dl, respectively. Urinary protein excretion (24-h) was 7 g/day and creatinine clearance was 75 ml/min. ANA, HBsAg, antiHCV were all negative. Abdominal ultra-

sound revealed slight enlargement of both kidneys (right kidney: 111 × 50 mm; left kidney: 138 × 50 mm) with increased echogenicity in parenchyma and a 5 × 4 cm mass lesion in the portal area. A renal biopsy, an excisional biopsy of the mass as well as a biopsy from the nearby enlarged lymph nodes were performed and all of them revealed amyloidosis. The diagnosis of AA amyloidosis was confirmed by potassium permanganate stain. Bone marrow biopsy that was performed showed only bone marrow hyperplasia. Her oedema improved after she was started on diuretics and after the institution of colchicine in the dose of 1.5 mg/d she was discharged to follow-up. A decrease in proteinuria was observed with 24-h urinary protein excretion decreasing to 2 g/day by July 1990. After she was started on colchicine therapy, she had two successful pregnancies in 1991 and 1993 which she delivered uneventfully on term. Repeated ultrasound examination of the abdomen in 1994 showed the decrease in the size of both kidneys (right kidney: 108 × 40 mm; left kidney: 117 × 50 mm). Her renal function improved with a creatinine clearance of 95 ml/min, and proteinuria was 0.5 g/day. She remained on follow-up and by March 1998 her 24-h urinary protein excretion had come down to nil. The repeated renal biopsy that was performed revealed scarcely distributed amyloid in the glomeruli with the significant decrease in the amount of amyloid deposits compared to previous biopsy.

*Comment.* Amyloidosis secondary to familial Mediterranean fever (FMF) may occur in patients who present with only mild or occasional attacks or even in those who never experienced an acute febrile episode before [1–4]. Although our case did not have previous history of characteristic FMF manifestations, the fact that she originated from central Anatolia region led us to suspect FMF. There is an unexplained difference in the prevalence of amyloidosis among the different ethnic groups of patients with FMF [2,5]. In Turks, amyloidosis reaches an incidence of 60% among the subjects affected by FMF [5]. In the patients with a well-established amyloidosis, colchicine may induce complete remission of proteinuria or the nephrotic syndrome that can last as long as 10 years [4,6]. It is well known that colchicine prevents the development of amyloidosis in almost all patients compliant to therapy and also reverses the clinical manifestations of organ involvement in established amyloid cases [1,2]. However, it is generally believed that although the amyloidosis seems to be clinically cured by colchicine therapy, a large amount of amyloid deposits still remains in the involved organs [5]. Our case demonstrated that colchicine therapy in this patient with the frank, biopsy-proven amyloidosis of both the kidneys and the liver not only improved her clinically and enable her to become fertile but also induced a decrease in the amount of deposited amyloid that was demonstrated on the repeated renal biopsy. We concluded that colchicine does not only prevent the FMF attacks, the subsequent development of secondary amyloidosis and the reversal of the clinical picture but also seems to induce the clearance of amyloid deposits in the previously involved organs.

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### Defective erythropoietin production in the anaemia of malaria

Sir,

Falciparum malaria is one of the most common parasitic diseases causing high morbidity and mortality in the tropics. The origin of malaria-induced anaemia is quite complex including: red blood cell destruction and phagocytosis, hyperplenism, autoimmune mechanisms, inhibition of red cell production, ineffective erythropoiesis due to release [1] of interferon gamma and tumour necrosis factor, and interleukin 1 despite an increase in erythropoietin (Epo) production [2]. The aim of the present study was to evaluate serum Epo levels in patients suffering from acute *Plasmodium falciparum* infection to gain insight into Epo response to different degrees of anaemia.

The study was performed at the Sololo Catholic Hospital (Kenya, East Africa) and the Bissau Simon Mendez Hospital (Guinea Bissau, West Africa).

Fifty-two patients (26 males and 26 females; age range 1–37 years) took part in the study. Microscopy on thick blood film lead to a diagnosis of *P falciparum* malaria in all cases. Patients were treated both as either as (i) ambulatory outpatients (uncomplicated malaria) with oral amodiaquine or sulfadoxine+pyrimethamine or (ii) severe inpatients (complicated malaria) with intravenous quinine.

Blood samples were taken at the time of admission to determine serum haemoglobin and Epo. Epo levels were evaluated by *in vitro* enzyme-immunoassay (Quantikine IVD, R & D System, Minneapolis, MN, USA); normal Epo values were 3.3–16.6 mIU/ml. Statistical analysis was performed by regression line and Pearson's correlation coefficient.

The results showed severe anaemia (Hb < 5 gr/dl) in 4 of 52 patients (7.7%), moderate anaemia (Hb 5–8 gr/dl) in 19 (36.5%), mild anaemia (> 8 gr/dl) in 18 (34.6%) and normal Hb values in 11 patients (21.2%), according to the anaemia classification of Clinical Guidelines [3]. 43.5% of the cases with severe or moderate anaemia occurred in malaria patients under the age of 9 and another 34.8% of these cases occurred during pregnancy. Anaemia secondary to malaria was an important cause of hospital admissions in children and pregnant women.

Patients received antimalaria drugs and both iron and folic acid. None of the patients had acute or chronic renal failure. Nevertheless, in some cases severe or moderate anaemia did not improve but rather persisted despite pharmacological treatment. The Epo and Hb values for each patient are indicated by the squares in Figure 1.

The mean of Epo value was 264.6 ± 530.24 mIU/ml (range 5.4–3094). Moreover, in all of the cases considered, there was a good inverse correlation between log-Epo and Hb: log [Epo] = 3.133 – (0.148 × Hb); r = 0.607; P < 0.001. This demonstrated that in falciparum malaria anaemia is an efficient stimulus for Epo generation.

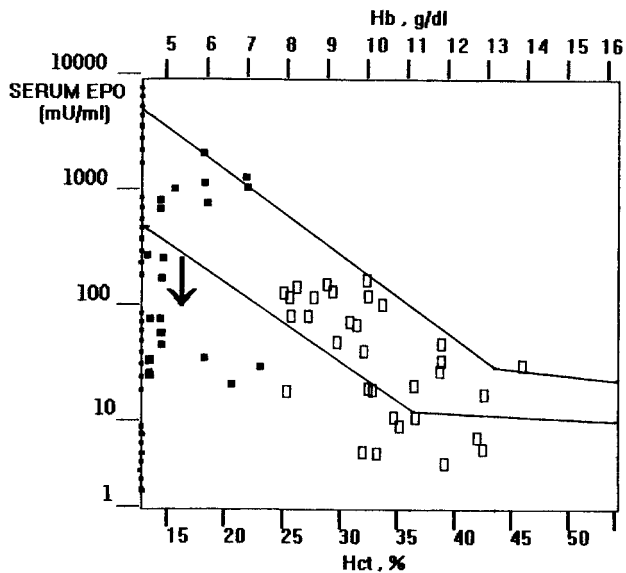


Fig. 1. Relationship (squares) between serum Epo levels and haemoglobin (above) in each malaria case and relationship between serum Epo levels and haematocrit in reference subjects (from the paper by Cazzola and Beguin) [4]. Lines are the 95% confidence limits. Values below this reference range (arrow ↓) indicate inappropriate Epo response to anaemia.

In the most of the cases (12/20; 60%) at the lowest Hb values (<8 g/dl: black squares in Figure 1), Epo values were blunted and shifted to the left (Figure 1, arrow ↓) when the values were evaluated by comparing the Cazzola and Beguin regression curve [4] between serum haematocrit and Epo levels (see Figure 1).

Blunted Epo production, demonstrated in various inflammatory disorders such as rheumatoid arthritis, AIDS and in malaria-free pregnancy [5], might occur in our cases of refractory anaemia. Nevertheless we cannot rule out any effect of antimalaria drugs on Epo production [6].

Effectively, these low Epo values appear inappropriate to the degree of anaemia and our results agree with those reported by Burgmann *et al.* [6]. In conclusion, our observations might provide the basis for further study into the choice of therapeutic strategies, i.e. treatment with Recombinant Human Epo, to correct refractory malaric anaemia occurring predominantly in children and pregnant women.

The study could not have been carried out without the interest and help provided by the Catholic Sololo Hospital staff members directed by Drs M. T. Reggente and G. Giaccaglia, and by Dr M. I. Manè of Bissau Simon Mendez Hospital.

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### The elderly haemodialysis patient with abdominal symptoms and hypovolemic shock—splenic rupture secondary to splenic infarction in a patient with severe atherosclerosis

Sir,

Extensive atherosclerotic vascular disease in diabetic haemodialysis (HD) patients is common, but splenic infarction is rarely observed in these patients. In fact, in the literature revised there are only four diabetic patients recorded on peritoneal dialysis, one of them with polycythaemia [1–3]. In the general population, patients with splenic infarct under the age of 40 years typically have an associated haematologic disorder. In elderly patients, thromboembolic disease predominates, but is uncommonly encountered [4]. We report a case of a diabetic elderly man on HD who developed splenic rupture secondary to splenic infarct. This diagnosis should be considered in HD patients with acute abdominal pain, especially in diabetic patients. We are not aware of other reports of splenic infarct in HD patients.

*Case.* A 68-year-old diabetic man on HD for 3 years was admitted for fever, left upper abdominal pain and nausea. The pain was described as constant and dull. There was no radiation of pain to the left shoulder. The patient developed mild upper abdominal pain and nausea 15 days prior to admission. No association of this pain with meals, or change in bowel habits was observed. There was no history of recent trauma. He had severe peripheral vascular disease and retinopathy secondary to longstanding diabetes mellitus, but no history of cerebral vascular disease or coronary artery disease. The patient was treated with dialysis three times a week with cellulose triacetate and bicarbonate dialysate. The percentage of urea reduction 61% and PCR 1.14. The abdominal examination was significant for pain with deep palpation in the left upper quadrant. There was voluntary guarding in this area and flank tenderness on palpation. The bowel sounds were normal. Rectal examination demonstrated haemocult negative stool. Laboratory evaluation showed a white blood cell count of 10.100/μl, with 90.4% segmented neutrophils. Haematocrit was 29.1%. Prothrombin time was 13.5, with a TTPA of 26.4 and fibrinogen of 831 mg/dl. Serum amylase normal, with a mild increase of SGOT 56 IU/l, SGPT 57 IU/l and LDH 504 IU/l. An electrocardiogram showed normal sinus rhythm. Multiple abdominal X-ray studies demonstrated a non-specific bowel gas pattern, with atherosclerotic calcification of the abdominal aorta, and splenic artery. An abdominal ultrasonography was unremarkable, with perisplenic hyperechogenicity. The spleen was normal.

The patient's abdominal pain increased over the first 24 h of hospitalization and fever persisted. On the second hospital day abdominal pain persisted with rebound tenderness and without bowel sounds. A fall in blood pressure and hypovola-

emic shock developed. A severe acute anaemia (haematocrit 16.2%), metabolic acidosis (pH 7.10), and increased LDH (8500 IU/l) were detected. The patient improved with a rapid fluid infusion and blood transfusion. A second ultrasonography showed splenic rupture with free intraperitoneal haemorrhage. At operation, an extensive atherosclerosis in the splenic arterial tree, with thrombotic occlusion as well as an extensive splenic infarct with rupture splenic and subcapsular haemorrhage was detected. Splenectomy was necessary. Twelve days postoperatively the patient was discharged from the hospital without complications.

**Comment.** Splenic infarction usually occurs in association with emboli of cardiac origin or haematologic disorders, but in three diabetic patients on peritoneal dialysis it was due to atheromatous disease of the splenic artery [1,3]. There are some similarities between the three patients reported with splenic infarct on peritoneal dialysis [1,3] and the patient reported by us. All four cases were diabetics with atherosclerotic disease. However, the three patients on peritoneal dialysis died, but our patient after splenectomy was maintained on HD and did well. Moreover, splenic rupture has been reported to result in massive haemoperitoneum and shock in a patient on peritoneal dialysis [5] and another patient on HD, but without splenic infarction [6]. We have not found any other case of splenic rupture secondary to splenic infarct in patients on HD in the literature revised.

Clinical symptomatology of splenic infarct consists primarily of left upper abdominal pain. Physical findings associated with splenic infarct include fever and left pleural effusion. Other physical findings could be clinical signs of peripheral vascular disease. In some patients anaemia, leucocytosis and elevated LDH may occur. Techniques for diagnosing splenic infarcts include ultrasonography, computed tomographic scan, nuclear imaging, and angiography. Ultrasound is less sensitive in acute infarction as occurred in our case. Once liquefaction of the infarcted tissue occurs, ultrasound becomes much more sensitive and is useful to follow the possibility of complications developing. There are potential complications of splenic infarct such as the development of pseudocyst, abscess, haemorrhage, subcapsular haematoma or splenic rupture [4]. Splenectomy in these cases may be necessary.

Several risk factors for atherosclerotic disease have been recognized in dialysed patients, particularly age and diabetes mellitus. Diabetic patients with ESRD or undergoing dialysis are particularly prone to develop accelerated atherosclerosis. The incidence and prevalence of end-stage renal disease (ESRD) from diabetic nephropathy type II increased over recent years [7] and vascular comorbidity is prominent in this patients. Splenic infarct is a rare complication of atherosclerotic arterial occlusive accidents in dialysed patients. However, splenic infarct should be included in the differential diagnosis of elderly diabetic patients on HD with atherosclerosis disease who present acute abdominal pain, especially if left upper quadrant pain occurs. This option may be valued, if the progressively increasing number of elderly diabetic patients starting dialysis in recent years is considered.

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### Effect of ferric polymaltose complex as a phosphate binder in haemodialysis patients

Sir,

Considerable evidence supports a primarily important role of phosphate retention and hyperphosphataemia (HPi) in the development of secondary HPTH [1–3]. Phosphate binders are usually required to achieve good phosphate balance. Aluminum (Al)-containing phosphate binder was the standard treatment before the risk of Al-related toxicity, such as osteomalacia, and encephalopathy, was appreciated [4]. Calcium salts have now become the most frequently prescribed phosphate binders. However, calcium salts increase the incidence of hypercalcaemia, metastatic calcification, changes in bowel habits, and dyspepsia [5,6]. Therefore, there is a continuing interest and also search for other alternatives and among them an iron-containing agent is a promising candidate [7]. We examined the effect of this iron containing compound in HD patients.

Thirty-two uraemic patients (14M, 18F) were included in this study. Their mean age was  $55.6 \pm 4.2$  years (21–72 years old) and the mean duration on HD treatment was  $6.4 \pm 3.6$  years (23–120 months). They all received regular HD (three times per week, 4 h per session) for at least 6 months and were included after giving their informed consent. Before being included, they had HPi ( $> 1.78$  mmol/l) in at least two consecutive times during the routine monthly biochemical examination and took different doses of either  $\text{Al}(\text{OH})_3$  or  $\text{CaCO}_3$  as phosphate binders. None of them was treated with vitamin D in at least three months before study. They were dialyzed with the same hollow fiber (KF-201, 1.8 m<sup>2</sup>, Kuraray Laboratories) and the dialysate before entering the fiber contained 2.8 mEq/l calcium. Subjects were excluded from participation if they had unstable medical conditions, including poorly controlled diabetes, cardiovascular or gastrointestinal illness, or any surgical events complicating the progression of this study. The iron agent used in this study was Ferrum<sup>®</sup> chewable tablet (Hausmann Laboratories, Inc., Switzerland) as a non-ionic ferric polymaltose complex, containing 1.78 mmole elementary iron per tablet.

Patients were divided into study group (I) and control group (II) and they (16 in each) all discontinued the previous phosphate binders for two weeks as clearance. The patients in study group took two Ferrum<sup>®</sup> chewable tablets after each meal (total 10.68 mmol iron per day). The patients in control group took their previous phosphate binders, either  $\text{Al}(\text{OH})_3$  (total 25.89–77.67 mmole elementary aluminum per day) or  $\text{CaCO}_3$  (30–45 mmole elementary calcium per

day). The first phase of study lasted for 8 weeks. After the first phase, they discontinued all the phosphate binders for another 2 weeks as wash-out and then were crossed over to the second phase study. This crossover phase also lasted for 8 weeks. One patient dropped out due to frequent diarrhoea after ingesting Ferrum tablets. One patient dropped out because of moving and another two because of other illness unrelated to calcium-phosphorus homeostasis. So in the second phase of study, there were 15 patients in the new study group and 13 in the new control group. In either phase, all patients were given the prescribed amount of phosphate binder every week and were asked to return those tablets that were not taken. Patients were suggested to keep their protein intake as steady as possible and they were asked to report their diet content to one of our staff. During the whole study periods, all the patients received their maintenance HD as the schedule. Plasma phosphate and ionized calcium levels were examined every week during study. Serum iron, unsaturated iron binding capacity, ferritin, and intact parathyroid hormone (PTH) levels were measured every 2 weeks. All the blood samples were drawn before HD. Ionized calcium levels were measured by  $\text{Ca}^{++}$  Analyzer (CIBACORNING). Ferritin level was examined by enzymatic immunoassay. Serum iron, unsaturated iron binding capacity, and phosphate were measured by colorimetric analysis. Intact parathyroid hormone level was determined by Immunoradiometric Assay kit (Nichols Institute, CA).

There were no significant differences between the two groups at the beginning. However, more diabetic patients, longer dialysis period, and higher baseline intact parathyroid hormone levels were noted in one group (Table 1). The proportion of subjects using either  $\text{Al}(\text{OH})_3$  (31.25% vs 37.5%, 25.89–77.67 mmole elementary aluminum per day) or  $\text{CaCO}_3$  (75.2% vs 81.9%, 30–45 mmole elementary calcium per day) was similar.

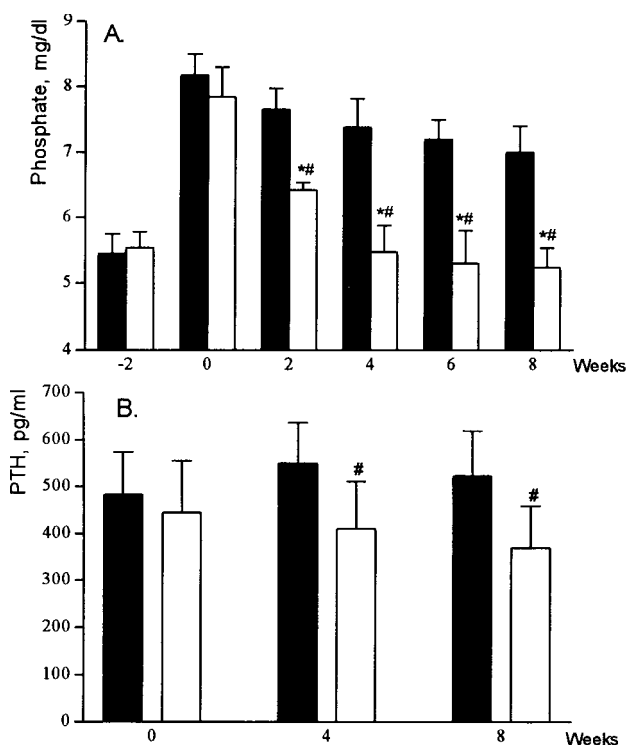
Two weeks before the beginning of the study, the mean serum Pi levels in both groups were comparable (1.76 vs 1.79 mmol/l) but increased significantly (2.64 vs 2.53 mmol/l) after 2 weeks of washout periods. In the study group, the serum Pi level gradually decreased by a mean of 0.38 mmol/l at the end of the 8th week: 2.47 at 2-week, 2.39 at 4-week, 2.34 at 6-week, and 2.26 mmol/l at the 8-week end. In the control group, the Pi levels decreased by a mean of 0.85 mmol/l: 2.07 at 2-week, 1.75 at 4-week, 1.70 at 6-week, and 1.68 mmol/l at 8-week end. The mean decrease of Pi

levels between the two groups (0.38 vs 0.85 mmol/l) was significantly different ( $P < 0.001$ ). Serum ionized calcium concentrations were not changed significantly during the study periods in both groups. The baseline intact PTH levels were comparable ( $484 \pm 156$  vs  $445 \pm 117$  pg/ml), but became significantly different after treatment with various agents:  $511 \pm 135$  vs  $411 \pm 104$  pg/ml ( $P < 0.05$ ) at the end of 4th week and  $524 \pm 168$  vs  $370 \pm 112$  pg/ml ( $P < 0.01$ ) at 8th week (Figure 1). After the second washout period, the mean serum Pi levels in both the new groups increased, from 1.68 to 2.22 mmol/l ( $P < 0.05$ ) in the new study group and from 2.26 to 2.34 mmol/l ( $P > 0.05$ ) in the new control group. In the new study group, the serum Pi level decreased by a mean of 0.25 mmol/l at the end of the 8th week treatment: 2.22 at 2-week, 2.04 at 4-week, 2.03 at 6-week, and 1.97 mmol/l at the 8-week end. In the new control group, the Pi levels decreased by a mean of 0.74 mmol/l: 2.07 at 2-week, 1.82 at 4-week, 1.69 at 6-week, and 1.59 mmol/l at 8-week end. The mean decrease of Pi levels between the two groups (0.25 vs 0.74 mmol/l) was significantly different ( $P < 0.001$ ). Intact PTH levels increased in both groups during washout periods ( $370 \pm 112$  to  $404 \pm 85$  pg/ml in the new study group,  $524 \pm 168$  to  $602 \pm 173$  pg/ml in the new control group). PTH levels increased, though not significantly, in the new study group,  $455 \pm 177$  pg/ml at 4th week and  $446 \pm 201$  pg/ml at 8th week. In contrast, the PTH decreased gradually in the new control group,  $548 \pm 155$  pg/ml ( $P > 0.05$ ) at 4th week and  $485 \pm 99$  pg/ml ( $P < 0.05$ ) at 8th week (Figure 2). The ionized calcium levels were not changed in either group and in either phase. Ferritin, serum iron, and iron saturation were different from the start and the difference was not

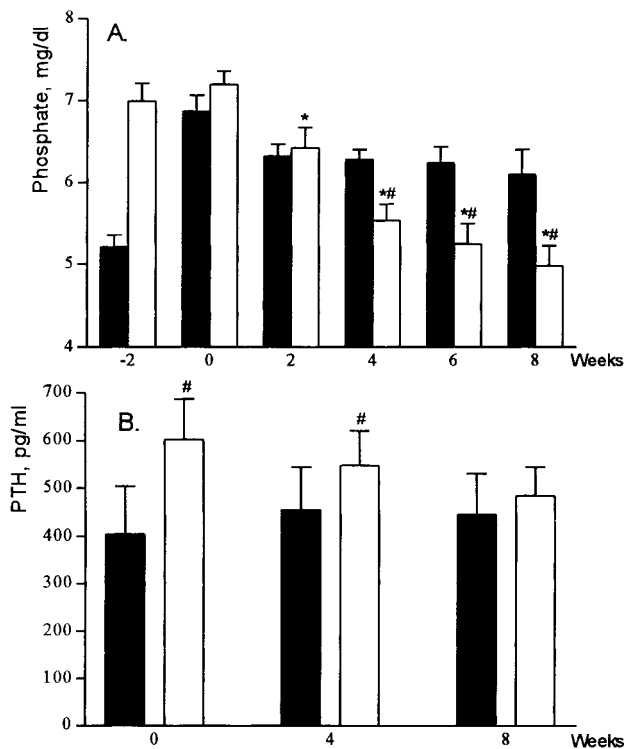
**Table 1.** Baseline characteristics of study subjects

Parameters	Ferrum® group	Control group
HD duration (years)	7.2 ± 3.3	5.7 ± 3.9
Use of $\text{CaCO}_3^a$		
% of patients	75	81
Dose (mmol/day)	35.63 ± 9.38	37.50 ± 6.25
Range (mmol)	30.00–45.00	30.00–45.00
Use of $\text{Al}(\text{OH})_3^a$		
% of patients	31.25	37.5
Dose (mmol/day)	41.42 ± 10.33	46.59 ± 12.37
Range (mmol)	25.89–51.78	14.78–77.67
Ionized calcium (mmol/l)	1.20 ± 0.1	1.18 ± 0.12
Phosphorus (mmol/l)	2.61 ± 0.50	2.52 ± 0.46
Intact PTH (pg/ml)	434 ± 211	356 ± 164
Iron saturation (%)	27.5 ± 8.4	32.8 ± 10.2
Ferritin (ng/ml)	363 ± 201	425 ± 220

<sup>a</sup>Some patients were treated with  $\text{CaCO}_3$  and  $\text{Al}(\text{OH})_3$  simultaneously.



**Fig. 1.** Changes of serum Pi (A) and PTH (B) levels in the first phase study. The Ferrum® (blank bar) was less effective than aluminum or calcium salts in the control of Hpi, although it stopped the further increase and decreased the Pi level (not significantly). Change of PTH levels followed the alteration of Pi levels. \*:  $P < 0.05$ , ANOVA. #:  $P < 0.05$ , *t*-test.



**Fig. 2.** Changes of serum Pi (A) and PTH (B) levels in the second phase study. The difference of Pi levels soon approached the similar degree after 2 weeks of wash-out period. As in the first phase, the Ferrum® (black bar) was less effective in the control of Hpi. Change of PTH levels followed the alteration of Pi levels. \*:  $P < 0.05$ , ANOVA. #:  $P < 0.05$ ,  $t$ -test.

significantly changed by the use of either phosphate binder. In general, side effect was minimal. Three patients experienced loose stool passage, but only one had to drop out because of this symptom.

Our results in this study showed that daily use of 10.68 mmol iron was less effective than 25.89 mmol aluminum or 30–45 mmol calcium in the control of Hpi. PTH levels fluctuated following the changes of Pi levels. It was not ineffective, though. Use of Ferrum® at least reversed the tendency to accumulate phosphorus and could decrease serum Pi level, although this was not statistically significant. Two important factors that obviously influenced the effectiveness of iron than either aluminum or calcium were the doses and the formula used. The dose of iron used in our study was much smaller than that of either  $\text{Al}(\text{OH})_3$  or  $\text{CaCO}_3$  on a mole-to-mole basis. Second, different iron formulas might have different phosphate binding capacity. For example, ferric citrate was more effective than calcium salts to control Hpi if they were compared in the equivalent weight (personal communication with Dr C. H. Hsu, professor of the University of Michigan, USA). As early as 1940s, Liu and Chu had studied the effect of large doses of ferric ammonium citrate on the calcium and phosphorus metabolism [8]. They accidentally discovered that the serum Pi levels decreased obviously after the use of the iron agent. Other more recent reports also showed such action [9,10]. Taking all these issues into consideration, we have good reasons to believe that iron agents still hold promises to be an effective phosphate binder. More studies are needed to clarify this concept.

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### Fenofibrate-induced rhabdomyolysis in two dialysis patients with hypothyroidism

Sir,

We wish to report two patients with end-stage renal failure on chronic renal replacement therapy who presented rhabdomyolysis while taking fenofibrate prescribed for their dyslipidaemia. Interestingly, for both of them, we later discovered hypothyroidism.

**Case 1.** The first patient was a 57-year-old woman with end-stage renal failure secondary to ischaemic nephropathy treated with continuous ambulatory peritoneal dialysis (CAPD) for about 2 years. Since many months, she was on the following treatment: four daily 2.5l exchanges with Dianeal 2.5% (Baxter Healthcare Corporation, McGaw III Park, IL), omeprazole 20 mg/d, diazepam 5 mg twice a day, metoprolol 100 mg twice a day, and alfacalcidol 0.5  $\mu\text{g}$  every other day. Micronized fenofibrate, 200 mg/d, was recently added to her medication because of an increasingly poor lipid control in spite of a low lipid diet. Indeed, a few months before, her total cholesterol was noted at 11.7 mmol/l (N 4.2–5.2) and total triglyceride at 6 mmol/l (N 0.6–2.3).

Four weeks after beginning fenofibrate and 4 days after a moderate physical exercise, she came to the emergency room complaining of diffuse muscle pain. She did not have any other specific symptoms except for a sensation of weakness and constipation. No specific physical signs were found. The initial biochemistries revealed a serum creatine phosphokin-

ase (CPK) concentration of 8850 U/l (N 0–190), a lactate dehydrogenase (LDH) level of 460 U/l (N 0–170), an aspartate aminotransferase (AST) level of 147 U/l (N 0–40) and an alanine aminotransferase level (ALT) of 113 U/l (N 0–40). Serum sodium was 136 mmol/l, potassium 6.1 mmol/l, chloride 93 mmol/l, total calcium 2.17 mmol/l, phosphate 1.54 mmol/l, albumin 38 g/l, glucose 4.6 mmol/l, urea 30.5 mmol/l, and creatinine 1097 µmol/l. Both total cholesterol and triglyceride were reduced to values of 6.89 mmol/l and 4.04 mmol/l, respectively. Her thyroid-stimulating hormone (TSH) serum concentration was 30.26 mU/l (N 0.30–5.50) and free thyroxine (T4) 11.4 pmol/l (N 11.5–23.2). There was no evidence of cardiac event. Fenofibrate was stopped and she was hospitalized for 3 days with a uneventful clinical evolution. Her serum CPK returned gradually to normal. Thyroid hormone replacement was initiated and her dyslipidaemia improved concomitantly.

**Case 2.** The second patient was a 55-year-old woman with end-stage renal failure secondary to autosomal dominant polycystic kidney disease (ADPK) treated on thrice weekly hemodialysis since 1989. She was known for mixed dyslipidaemia since 3 years. Her medication consisted of isorbide mononitrate 120 mg/d, metoprolol 50 mg twice a day, acetyl salicylic acid 325 mg/d, calcium carbonate 500 mg three times a day, ranitidine 150 mg/d, epoetine alfa 2000 U twice a week, oxazepam 7.5 mg at night, magaldrate 2 tablets three times a day, and sodium polystyrene 60 g/d. Because of an inadequate triglyceride level of 4.1 mmol/l despite the administration of atorvastatine 10 mg/d for more than 3 months, micronized fenofibrate 200 mg/d was recently substituted to atorvastatine.

Three weeks after starting fenofibrate and 1 week following a moderate physical exercise, she was admitted to the emergency room for muscle pain. Except for diffuse muscle tenderness at palpation, there were no other specific clinical signs. Initial investigations revealed a serum CPK level of 11 360 U/l (N 0–190), and increased LDH, AST, and ALT concentrations of 743 U/l, 334 U/l and 164 U/l respectively. Electrolytes were as follows: serum sodium 139 mmol/l, potassium 5.9 mmol/l, chloride 99 mmol/l, total calcium 2.43 mmol/l, and phosphate 2.47 mmol/l. Albumin was 36 g/l, glucose 6.1 mmol/l, urea 40.4 mmol/l and creatinine 1165 µmol/l. TSH level was slightly above normal at 6.51 mU/l (N 0.30–5.50) with a normal free T4 at 12.9 pmol/l (N 11.5–23.2). There was no evidence of cardiac event. Fenofibrate was stopped. She was discharged after three days with a favourable evolution and CPK levels returned to normal. She had not received any thyroid supplements but she did need eventually a new medical treatment for her dyslipidaemia.

**Comment.** Fenofibrate is a derivative of fibric acid. It reduces very low density lipoprotein (VLDL) and plasma triglycerides, while increasing high density lipoprotein (HDL) and lowering low density lipoprotein (LDL) as well as total plasma cholesterol. Fenofibrate is 99% protein-bound with a half-life of about 20 h and is mainly excreted in urine. One of the most serious reported side effects of this drug has been rhabdomyolysis. However, with a normal renal function, the tolerability of this drug seems generally good over the short term as well as over the long term. Only two patients over 7235 patients and only one patient over 131 patients have been reported as presenting raised CPK levels after 12 weeks and 1 year, respectively [1].

Since blood levels of fibric acid derivatives and fenofibrate are increased in patients with renal failure [2,3], it is recom-

mended to adjust dosage in patients with mild to moderate renal impairment [1]. However, very few data are available for end-stage renal failure patients on renal replacement therapy. In fact, in a recent meta-analysis comparing various antilipidaemic therapies in renal diseases, it has been recognized that most of clinical trials on this subject have been too small to provide strong data on the incidence of adverse events, including rhabdomyolysis [2].

In our report, two dialysis patients developed rhabdomyolysis three and four weeks after starting micronized fenofibrate at a dose of 200 mg/d. It appeared that rhabdomyolysis was precipitated by micronized fenofibrate which was prescribed at a dosage higher than recommended for renal failure [1]. However, for both patients, a contributing factor could have certainly been mild hypothyroidism.

Rhabdomyolysis associated with hypothyroidism has been rarely described. However, there have been some reports about hypothyroidism and mild rhabdomyolysis disclosed by a fibrate [4], mainly fenofibrate. The precise pathophysiology remains unclear. With hypothyroidism, there is an inhibition of mitochondrial activity in muscle cells as well as many metabolic pathways such as Krebs cycle, fatty acid catabolism and glycolytic energy production. It seems that these underlying metabolic anomalies may sensitise the patient to the muscular adverse effects of fenofibrate [4].

In summary, in spite of several cases of rhabdomyolysis associated with fibrates derivatives reported in the literature, few cases have been attributed to fenofibrate [4]. Here, it appeared that rhabdomyolysis was precipitated by a dosage of micronised fenofibrate higher than recommended for renal failure. However, for both patients, hypothyroidism also most probably promoted the occurrence of rhabdomyolysis. This association highlights the need to evaluate thyroid function before prescribing fenofibrate and fibric acid derivatives in ESRD patients and the necessity of careful dosage adjustments for patients on renal replacement therapy.

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### **A concept for expanding the donor pool for renal transplantation: non-heart beating donor 1-year retrospective evaluation**

Sir,

Renal transplantation is accepted as a standard treatment procedure for chronic renal failure patients [1]. Grafts are usually supplied from relatives as donation and from brain death patients as a heart beating donor. It is clear that these sources could not respond to the increasing demand for grafts. This led to the search for alternative graft sources

which gave rise to the concept of the non-heart beating (NHB) donor [2]. Patients who died moments before or upon arrival to the hospital are catheterized via femoral route, *in situ* renal cooling preservation initiated [3] and at this time, relatives are asked about donation.

Osmangazi University Research and Education Hospital is a reference hospital located in the central part of Turkey including 765 ward beds, 48 ICU beds and 12 coronary care beds. There are 125 000 admissions to this hospital yearly, of which 15% are hospitalized. The mortality rate for hospitalized patients is 4% according to the 1994 registry. Additionally, this centre houses a renal transplant programme in cooperation with a transplantation centre located in Istanbul for heart-beating and cadaveric donors.

In order to detect the NHB donor potential, all mortality charts from 1997 were examined excluding cases which were found to have malignancies other than primary brain tumours, renal disease at the time of death, uncontrollable hypertension, sepsis and/or suspected i.v. drug abuse. Selected charts were reviewed and age, sex, reason of death, medical and logistic suitability at the time of death, and last known renal functions were recorded. In order to assess the graft function after the post-operative period, medical and logistic suitability scores were assigned according to mortality registry data. Medical suitability was scored according to renal function (last known serum creatinine level) and the identification of several risk factors which determine the outcome of NHB donor kidneys (age over 50, hypertension, diabetes mellitus, and/or arterial vascular disease). Logistic suitability was scored according to the accessibility of the wards (to both ward team and according to availability of *in situ* cooling preservation equipment) in which patients expired. By combining the medical and logistic suitability scores in a total score, the potential of NHB kidney donors and the likelihood that the donation would be successful were determined. Total scores of 2–3, 4, or 5–6 were classified as low (group A), moderate (group B) or high potential (group C), respectively. Medical suitability, logistic suitability, and total score criterias which were adopted from a study by Daeman *et al.* were shown in Table 1 [2].

From a total of 780 in-hospital deaths at the Osmangazi University Hospital in 1997, there were 480 deaths among patients in the 3–65 year age range. Analysis of deaths

revealed that 264 of them were available for kidney donation, of which 120 had incomplete charts and were therefore excluded from the study. The remaining 144 patients were included in study. Medical and logistic suitability of these patients are shown in Table 2. The combined total scores are depicted in Table 3. The latter demonstrated that estimations of potential number of NHB donors available range from 56–144. Thus, 18% of in-hospital deaths were suitable for kidney donation, while 7% had a high potential.

Potential NHB donors were predominantly male (64.2%), the mean age was 49 years, and the mean serum creatinine level was 106.08  $\mu\text{mol/l}$ . Potential NHB donors were found mostly in cardiology, neurology, thoracic/cardiovascular surgery, and neurosurgery wards. Serum creatinine levels of A, B, and C groups were 150, 106, and 70.7  $\mu\text{mol/l}$ , respectively. When comparing the potential donors, high potential NHB donors were found mostly in the cardiology service, followed by the neurology and neurosurgery units, which had creatinine levels of 123.7, 110.5, and 91.9  $\mu\text{mol/l}$ , respectively. When examining the logistic suitability of group C, it was found that 95% of these patients died in intensive care units, coronary care units, or the emergency service after unsuccessful resuscitations; the remaining 5% died of cardiac arrest post-brain-death in the ICU. These wards were accepted as suitable for *in situ* cooling preservation procedures. All patients in group C had serum creatinine levels below 100  $\mu\text{mol/l}$ .

The success of renal transplantation is limited by organ availability. There are several methods for organ donation determined by the population's socio-economic levels, ethical values and their organization for transplantation.

Although the best transplant results are achieved with organs from living donors, it is clear that this source will never suffice the increasing demand [4]. Within Eurotransplant, only 5% of transplantation are achieved from living donors [5]. In our country this ratio approaches 95%. Every year, 65 patients are added to chronic renal failure pool per million population. Resulting in 3000 more patients require dialysis treatment every year. In one of our previous studies including dialysis centres around Eskişehir region we found that there were 220 patients registered to these centres [6].

According to results of this study, it seems that the growing demand for kidneys could be supplied from cadaveric organ pools most effectively. As revealed by this study 144 NHB donors could be added to this pool by developing the equipment and educating the ward personal. As considering

**Table 1.** Non-heart beating evaluation chart

Name:				
Illness:				
Sex:				
Risk Factors:	Age:	Over 50?	Y	N
	HT:		Y	N
	DM:		Y	N
Arterial Vasc Disease:			Y	N
Last BUN/Creatinine level:				
<b>Medical suitability:</b>				
0	Not suitable			
1	Creatinine level above 100 $\mu\text{mol/l}$ and two or more risk factors			
2	Creatinine level below 100 $\mu\text{mol/l}$ and two or more risk factors or creatinine level above 100 micromol/l and 0–1 risk factor			
3	Creatinine level below 100 $\mu\text{mol/l}$ and 0–1 risk factor			
<b>Logistic suitability:</b>				
0	Exited when arrived at hospital			
1	Exited after unsuccessful resuscitation at the wards			
2	Exited after unsuccessful resuscitation at the ICU, CCU, ES			
3	Exited after waiting arrest for brain death at the ICU, CCU, ES			
<b>Potential non-heart beating score:</b>				
<b>Patient group:</b>				

**Table 2.** Medical and logistic suitability of 144 patients

Score	Medical suitability (n)	Logistic suitability (n)
1	20	28
2	56	112
3	68	4

**Table 3.** Total scores and groups of 144 patients

Potential	Total score	Group	n
Low	2–3	A	32
Medium	4	B	56
High	5–6	C	56

that the only 40–50% of chronic renal failure patients are able to undergo renal transplantation this amount (144 grafts for this study) will be enough to supply the graft demand of all chronic renal failure patients in Eskişehir region of Turkey. This will increase with the suitable NHB donors from the other reference hospitals in this region like State Hospital and Social Security Hospitals.

As revealed from this study, the services that have the most extensive potential for NHB donors are cardiology, neurology, neurosurgery and thorax-cardiovascular surgery wards. The other studies also had the same results [7]. It is concluded that it had been better for these clinics to be informed about this subject. When considering the logistic suitability of high potential NHB donors, it was seen that 95% of these patients died in coronary unit, intensive care unit or emergency service where *in situ* cooling preservation could be managed rapidly. Therefore technical equipment of ISP should be intensified in these units. In conclusion it should be stressed once more that, increasing demand for kidney grafts could be decreased by implementing specialized health centres that have personal and technical equipment to interfere the mortal cases in the hospitals around this centre. So NHB may be a way out for graft deprivation for countries which have few numbers of cadaveric organ like our country.

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**The clinical significance of ganciclovir resistance in a renal transplant patient**

Sir,  
 Cytomegalovirus (CMV) is a common opportunistic infection following renal transplantation. Disease severity is dependent on the viral load, the level of immunosuppression and the serostatus of both the organ donor and recipient [1]. Whilst ganciclovir is used to treat established disease it is increasingly used as prophylaxis, to reduce the incidence of disease following transplantation [2]. Such widespread use may encourage the development of resistance. In most cases this is secondary to genetic changes in the UL97 gene, which encodes a protein kinase responsible for the phosphorylation of ganciclovir to its active moiety. To our knowledge, ganciclovir resistance has only rarely been reported in solid organ transplant recipients, usually following lung or liver transplantation [3,4]. We report the clinical course and implications of ganciclovir resistance in a renal transplant recipient with recurrent CMV disease.

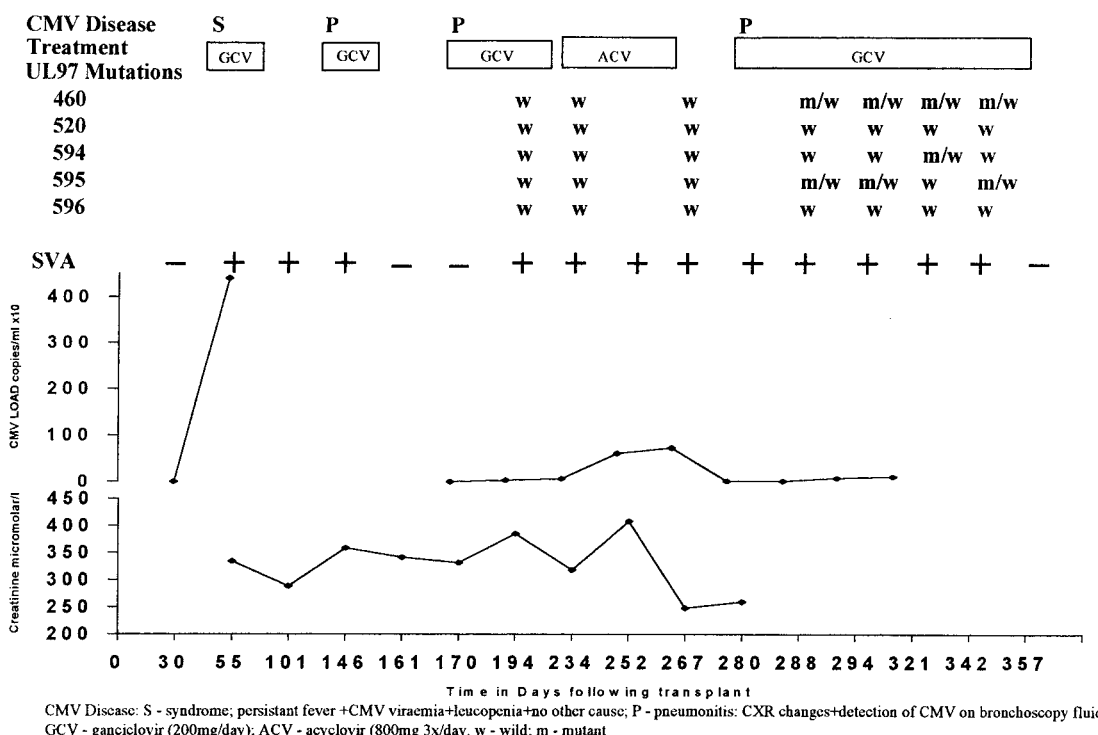


Fig. 1. The relationship between CMV viral load and the appearance of genotypic ganciclovir resistance in a renal transplant recipient.

VS, a 42-year-old woman with end-stage renal failure secondary to the Otorenal syndrome, was transplanted, for the first time, with a CMV seropositive kidney (cadaveric) in April 1995. She was seronegative for CMV antibodies. Her clinical course is summarized in Figure 1. Initial immunosuppression consisted of cyclosporin A (250 mg/day), azathioprine (100 mg/day), prednisolone (20 mg/day). This was reduced to cyclosporin A (100 mg/day) and prednisolone (10 mg/day) on day 170 during her second episode of pneumonitis. During each episode of CMV disease her symptoms resolved completely following either a 10 day (first and second episodes), 21 day (third episode) or 28 day (fourth episode) course of intravenous ganciclovir therapy (220 mg/day; dose adjusted according to renal function). Following successful treatment of her fourth episode of CMV disease, she continued to self administer ganciclovir (220 mg/day) at home through a Hickman line to prevent further episodes of disease. Weekly surveillance samples (heparinized blood) were taken for the shell vial assay following transplantation and EDTA samples for viral load testing using the CMV hybrid capture assay (Murex) were taken when possible.

While our patient was administering ganciclovir at home we became concerned that ganciclovir resistance was developing since CMV was detected by both the shell vial and hybrid capture assays between days 288 and 342. Fortunately, she remained well during this time and did not require treatment with either of the two nephrotoxic alternatives—foscarnet or cidofovir. Using plasma samples we were able to amplify and sequence the main catalytic domain of the UL97 gene of CMV. Mutations in this region appeared in sequential plasma samples after a total of 77 days of ganciclovir therapy (Figure 1). The first to appear were mutations at positions 460 (amino acid change: methionine to valine) and 595 (amino acid change: leucine to serine). The 595 mutation was then replaced transiently by the 594 mutant (amino acid change: alanine to valine). The appearance of these mutants was associated with a modest increase in viral load from  $23 \times 10^3$  to  $12 \times 10^4$  copies/ml.

Despite evidence showing that these mutations are associated with *in vitro* resistance and disease progression in immunocompromised patients [3,5] our patient remained well with no deterioration in her graft function. It is possible that a reduction in immunosuppression plus continuous ganciclovir therapy was able to suppress disease but not the appearance of these mutants. This idea is supported by the

sequence traces which showed a mixture of wild and mutant genotypes. The failure of a fully resistant virus to emerge in the presence of ganciclovir suggests that the mutant strains may have been 'less fit' and unable to outgrow the wild-type. Prolonged continuous ganciclovir therapy is associated with the appearance of resistant mutations and disease progression in immunocompromised patients [3,5]. In our patient each episode of CMV disease responded to a course of ganciclovir, and resistance did not appear until the fourth episode of disease had been treated and continuous therapy started. Despite the presence of the resistant genotypes, we were able to suppress clinically significant disease by a combination of continuous ganciclovir therapy and a reduction in immunosuppression. This is important as the alternative therapeutic options are limited to highly nephrotoxic agents such as foscarnet and cidofovir.

In summary, our patient illustrates the complex interactions between immunosuppression, CMV disease and the development of antiviral resistance. The development of modern laboratory methods such as viral load measurements and DNA sequencing may be required to guide therapy decisions in patients with a history of prolonged antiviral therapy and symptomatic disease.

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