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Geeralien Derksen-Willemsen
University Medical Centre St Radboud
Department of General Internal Medicine 541
PO Box 9101
6500 HB Nijmegen
The Netherlands
Tel.: +31 (0)24-361 04 59
Fax: +31 (0)24-354 17 34
E-mail: g.derksen@aig.umcn.nl



Alphen aan den Rijn, the Netherlands

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Systemic auto immune diseases: from pathogenesis to treatment

Prof. dr. C.G.M. Kallenberg

Department of Clinical Immunology, University Hospital Groningen, the Netherlands

On February 14, 2003, a symposium took place at the Groningen University Hospital on 'Treatment of systemic autoimmune diseases: a ready-made or made-to measure approach'. This symposium, dealing with the approach of the patient with a systemic autoimmune disease, was organised at the occasion of the establishment of an integrated out-patient clinic at the Groningen University Hospital. In this out-patient clinic, specialists from different disciplines, such as internists, rheumatologists, nephrologists and clinical immunologists as well as dedicated consultants from neurology, dermatology, pulmonology and other specialities, centralise around the patient with a multi-system autoimmune disease.

Multi-system autoimmune diseases, such as systemic lupus erythematosus (SLE) and related disorders as well as systemic vasculitides, may present in many ways. The diversity in presentation, varying from musculoskeletal symptoms to renal or respiratory insufficiency or cerebral manifestations, often leads to delay in diagnosis. Furthermore, subclinical manifestations such as, e.g., interstitial lung disease or cognitive deterioration, frequently are not recognised, particularly when the medical attention is focussed on one specific organ. Although short-term mortality of these diseases has been considerably reduced, long-term outcome in terms of organ damage, disability and mortality, still is poor. Recognition of factors that lead to late morbidity and mortality is just coming on the horizon. It is clear that an integrated approach of the patient with a systemic autoimmune disease as well as more insight into the pathogenesis of these disorders, are needed to further improve outcome and quality of life.

This and coming issues of The Netherlands Journal of Medicine contains contributions, presented at the before mentioned symposium. The papers concentrate on SLE, the prototypical systemic autoimmune disease, and on vasculitis. The multiple factors, genetic and environmental, involved in the pathogenesis of SLE are discussed by Manson and Isenberg with attention given to clinical implications. Lupus nephritis still is one of the most serious manifestations of SLE. Much progress has been made in understanding the immunological events leading to renal inflammation. Berden reviews the immunopathogenesis of lupus nephritis with emphasis on defects in the clearance of apoptotic cells from the body. Finally, in the next issue of The Netherlands Journal of Medicine, Bijl will focus on late sequelae of ongoing immune activation, particularly at the level of the endothelium, presenting SLE as a model for early atherosclerosis. Insight into these processes has direct consequences for the clinical approach to the patient with SLE.

Systemic autoimmune diseases are a diagnostic and therapeutic challenge for internal medicine in general, particularly in view of the systemic nature of these diseases. It is hoped that new insights in pathogenesis and complications will improve long-term outcome for the individual patient for whom careful follow-up is of paramount importance.

Lupus nephritis: consequence of disturbed removal of apoptotic cells?

J.H.M. Berden

Nephrology Research Laboratory, Nijmegen Centre for Molecular Life Sciences and Division of Nephrology (545), University Medical Centre St Radboud, PO Box 9101, 6500 HB Nijmegen, the Netherlands, tel.: +31 (0)24-361 47 61, fax: +31 (0)24-354 00 22, e-mail: J.Berden@nier.umcn.nl

ABSTRACT

In the last decade it has become clear that systemic lupus erythematosus (SLE) is an autoantigen driven T cell dependent autoimmune disease. The nucleosome has been identified as a major autoantigen. Nucleosomes are generated during apoptosis. Either an increased or delayed apoptosis or a reduced clearance of apoptotic cells (which are not mutually exclusive) leads to an increased exposure of (modified, more immunogenic) nucleosomes to the immune system. This generates the formation of nucleosome specific T cells and antinucleosome autoantibodies. After complex formation of antinucleosome or anti-double-stranded (ds)DNA antibodies with nucleosomes, these autoantibodies are targeted to basement membranes, especially the glomerular basement membrane (GBM). This nephritogenic potential is due to the binding of the positively charged histone components of the nucleosome to the negatively charged heparan sulphate (HS) within the GBM. This incites glomerular inflammation.

INTRODUCTION

Formation of antinuclear autoantibodies, especially against double-stranded (ds)DNA, is a hallmark of systemic lupus erythematosus (SLE). Lupus nephritis is one of the most serious complications in SLE, occurring in up to 60% of the patients with SLE. Traditionally, it was thought that lupus nephritis was initiated by the glomerular deposition of DNA/anti-DNA complexes.¹ However, DNA/anti-DNA complexes are hardly nephritogenic.² In 1995 we presented a new hypothesis for the development

of lupus nephritis³ depicted in *figure 1*. The importance of apoptosis and the phagocytosis of apoptotic cells in SLE was recently supported by various observations. In this review we will discuss the support for the different parts of the hypothesis outlined in *figure 1*.

APOPTOSIS AND SLE

The first notion that abnormal apoptosis was associated with lupus came from the discovery that MRL/lpr lupus mice had a functional Fas deficiency. Binding of the Fas ligand to the Fas receptor (CD95), present on activated T and B cells, leads to apoptosis. Also deficiency of the Fas ligand as in *gld* mice, leads to the same lupus phenotype as in MRL/lpr mice. Transgenic correction of these deficiencies prevented the development of autoimmunity. In patients with SLE, Fas-related defects in apoptosis are less clear. Patients with a Fas or Fas-ligand deficiency develop an autoimmune lymphoproliferative syndrome (ALPS). This condition is characterised by lymphadenopathy, splenomegaly, haemolytic anaemia and thrombopenia. Only a quarter of the patients develop antinuclear antibodies and glomerulonephritis is rarely seen. So, unlike the animal models, in human SLE no clear-cut genetic defects in the Fas pathway have been detected so far.⁴ From these data it is difficult to draw an unequivocal conclusion at this moment on the role of apoptosis in human SLE. It seems likely that in SLE the delicate balance regulating apoptosis is lost, resulting in apoptosis which occurs at the wrong time-point and/or in the wrong micro-environment.⁵ Abnormal apoptosis in itself does

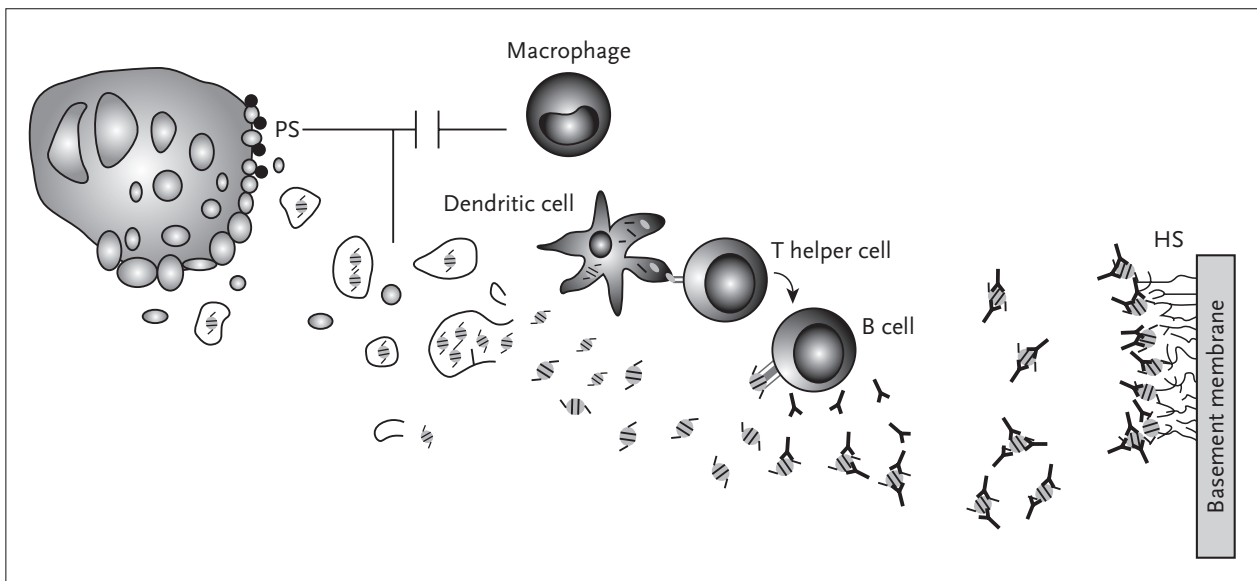


Figure 1
Hypothesis for the development of lupus nephritis

Abnormal apoptosis (in the wrong micro-environment or at wrong time-point) can lead, especially if the phagocytic capacity for apoptotic cells is inadequate or overflown, to the release of modified autoantigens including nucleosomes. These (modified) nucleosomal antigens are presented by dendritic cells to T cells, which provide help for autoreactive B cells. Via this T cell dependent autoantigen driven response various antichromatin autoantibodies are formed including antinucleosome, anti-dsDNA and antihistone antibodies. Nucleosome autoantibody complexes are targeted to the glomerular basement membrane (GBM). This binding to the GBM is the result of binding of the strongly cationic parts of the core histones within the nucleosomes to the anionic heparan sulphate within the GBM (reprinted with permission from J Nephrol).

not need to be detrimental if the removal of apoptotic cells is rapid and complete. Therefore, impairment of apoptotic cell removal is probably more important than disturbances in apoptosis itself.

PHAGOCYTOSIS OF APOPTOTIC CELLS IN SLE

The discovery that autoantigens are clustered in surface blebs, after induction of apoptosis of keratinocytes with UV light, opened new ideas for the pathogenesis of SLE.⁶ In fact all autoantigens targeted in SLE can be found at the surface of apoptotic cells. The smaller blebs contain SS-A (52kD), ribosomal P protein, α -fodrin and Jo-1, while the larger apoptotic bodies contain nucleosomes, SS-A (60kD), SS-B, Sm, SnRNP complexes, PARP and other autoantigens. Since several mechanisms can alter these autoantigens during apoptosis, making them more immunogenic,⁷ it is of utmost importance that these apoptotic cells are removed swiftly and adequately. It is beyond the scope of this review to describe in detail the process of phagocytosis of apoptotic cells, since excellent reviews are available.⁸ In brief, induction of the apoptotic process leads, after intranucleosomal cleavage of chromatin

and nuclear condensation, to a number of surface changes, most notably the expression of phosphatidylserine (PS), which is normally present at the inside of the cell membrane. This and other cell surface changes provide 'eat-me' signals to neighbouring cells and macrophages. Via a large number of receptors including scavenger receptors, the LPS receptor (CD14), the C1q receptor, vitronectin receptor, other β -integrins and lectins, the apoptotic cell binds to the macrophage and is subsequently internalised and degraded. For some of these receptors 'bridging' molecules are necessary such as C1q, β_2 -glycoprotein I (which binds to PS), thrombospondin, C-reactive protein (CRP) and serum amyloid P protein (SAP). The ligands which bind to these bridging molecules or receptors are for the larger part putative.

Because all autoantigens targeted in SLE are either located in small or apoptotic blebs or at the surface of apoptotic cells, it has been postulated that a defective phagocytosis of apoptotic cells may be a pivotal feature in the generation of the autoimmune response. This impaired phagocytosis may lead to the release of nuclear antigens including nucleosomes, since the major pathway for the generation of nucleosomes is apoptosis. In fact, circulating nucleosomes have been found in SLE patients and lupus mice. Indeed,

a defective removal of apoptotic cells has been documented in patients with active SLE.⁹ However, this defect can be secondary to the disease, since autoantibodies could potentially inhibit binding and/or engulfment of apoptotic cells. Therefore, we analysed the phagocytic capacity for apoptotic cells in lupus mouse strains with a sensitive technique.¹⁰ In prediseased mice no constitutive defect was found,¹¹ while in animals with clinical overt disease, phagocytosis of apoptotic cells was impaired. This defect resided in the plasma and was either a shortage of a critical plasma component (complement?) or the presence of an inhibitor (autoantibody?) (Licht *et al.*, unpublished observations).

Recently, a number of studies with well-defined knock-out mice (C1q, SAP, Dnase I) have been reported, documenting the utmost relevance of proper removal of apoptotic cells.¹² In all these knock-out mice three features were observed: 1) an impairment of apoptotic cell removal; 2) generation of antinuclear autoantibodies most notably against nucleosomes; and 3) development of glomerular deposits containing immunoglobulins and complement factors and in some models histological signs of glomerulonephritis. These observations show that inadequate removal of apoptotic cells and/or chromatin may lead to lupus.

IMMUNOGENICITY OF NUCLEOSOMES

Since naked dsDNA has long been regarded as the major autoantigen in SLE, many attempts have been made to immunise with dsDNA in all sorts of forms and conditions. However, these procedures failed to induce anti-dsDNA antibodies with lupus specific characteristics. The first positive result was obtained after immunisation with dsDNA complexed to histone-like DNA-binding proteins from either viral or protozoal origin. The antibodies formed were directed against dsDNA and nucleosomes.¹³ Seminal studies by Datta and colleagues showed that in the SNF1 murine lupus model 50% of the pathogenic T helper cells were directed against nucleosomes. These T helper cells did not only provide help for the production of nucleosome specific antibodies, but also for anti-dsDNA and antihistone antibodies, a phenomenon known as antigen spreading.¹⁴ This observation shed new light on the initiation of the anti-dsDNA antibody response: not dsDNA but the nucleosome is the driving autoantigen in SLE. Subsequently, similar observations have been reported in human SLE.^{15,16} These nucleosome specific T cells respond to histone epitopes on MHC class II molecules presented after processing of nucleosomal material by antigen presenting cells (APC).^{17,18} So, these data indicate that T cells towards nucleosomal epitopes

are present in both human and murine lupus. In fact, in murine lupus this T cell reactivity can be demonstrated long before any serological or clinical sign of the disease.¹⁴ These observations posed the question whether anti-nucleosome antibodies are present in SLE. This anti-nucleosome reactivity was first demonstrated for monoclonal antibodies derived from lupus mice.¹⁹ Subsequently, they were also detected in the great majority of lupus mice^{20,21} and patients.^{22,23} From these studies, it also appeared that the formation of antinucleosome antibodies preceded that of other antinuclear specificities such as anti-dsDNA and antihistone. From subsequent studies it became clear that measurement of antinucleosome reactivity is preferable and more specific than anti-dsDNA. Moreover, it was recently demonstrated that anti-dsDNA reactivity, as measured with the gold standard, the Farr assay, was for a large part due to histone containing immune complexes.²⁵

NUCLEOSOME-MEDIATED AUTO-ANTIBODY-BINDING TO THE GBM

Nucleosomes are not only important for the induction of the autoimmune response but also play a decisive role in the development of tissue lesions, in particular lupus nephritis. The first clue for this notion came from the observation that anti-dsDNA antibodies could cross-react with an intrinsic component of the GBM, namely heparan sulphate (HS).²⁶ HS is the strongly anionic side-chain of agrin, the major heparan sulphate proteoglycan (HSPG) of the GBM.²⁷ HS determines the charge-dependent permeability of the GBM. Injection of monoclonal anti-HS antibodies instantly induces a massive proteinuria.²⁸ So far, in various proteinuric diseases a number of HS alterations have been identified.²⁹ The binding of antinuclear antibodies to HS was not due to cross-reactivity, as thought initially, but was mediated by nucleosomes.³⁰ If monoclonal anti-dsDNA antibodies, which reacted in ELISA with HS, were treated with DNase and were subsequently purified under high salt conditions on a protein-A column, all HS reactivity was lost. Addition of the protein A column effluent restored the binding to HS. Subsequent analysis revealed that histone/DNA complexes (i.e. nucleosomes) were responsible for the binding to HS. Also *in vivo*, in renal perfusion studies in the rat, nucleosomes could mediate the binding to the GBM, while noncomplexed antinucleosome and anti-dsDNA antibodies did not bind.³¹ This nucleosome-mediated binding occurred via binding of the cationic N terminal tails of the core histones to the strong anionic charges of HS. This was deduced from a number of observations. First, removal of HS, by prior intrarenal perfusion of heparanase (which cleaves HS), strongly reduced the binding to the

GBM of subsequently perfused nucleosome/autoantibody complexes.³¹ Second, binding of antihistone antibodies to the N terminal parts of the core histones to a great extent prevented the binding of nucleosome/antihistone complexes to the GBM. In contrast to this, complex formation of nucleosomes with either anti-dsDNA or antinucleosome autoantibodies created a nephritogenic complex.³² Because the epitopes of antihistone antibodies are mainly localised on the N terminal regions, their binding masks the positive charges on these histone tails, thereby preventing the binding to anionic HS. These positive charges on the N termini of histones can not be neutralised by the binding of anti-dsDNA or antinucleosome antibodies. In fact, their binding to the nucleosome has the opposite effect, since they neutralise in part the anionic charges of dsDNA, which makes the complex even more nephritogenic. Third, once we realised the importance of the cationic regions on the core histones for the binding to HS, we argued that neutralisation of these positive charges on the histone tails with an HS 'look a-like' molecule could perhaps prevent binding to HS. Since heparin is such an HS decoy molecule, the effect of heparin was analysed in different ways. *In vitro*, heparin could inhibit dose-dependently in ELISA the binding to HS of nucleosome complexed anti-dsDNA or antinucleosome antibodies.

In the renal perfusion system addition of heparin to nephritogenic nucleosome/autoantibody complexes completely prevented GBM-binding. Based on these observations the protective effect of daily heparin injections on lupus nephritis was analysed. Treatment of MRL/lpr mice from week 8 onwards with heparin or noncoagulant heparinoids prevented the development of proteinuria and 80% of the animals had no histological signs of glomerulonephritis at the age of 22 weeks. This is in contrast to PBS-treated MRL/l mice, 80% of which developed proteinuria and glomerulonephritis. The mechanism behind this renoprotective effect was revealed by immunofluorescence. In PBS-treated mice extensive deposits along the glomerular capillary loops and in the mesangium were seen while in heparin(oid)-treated mice only mesangial deposits were observed.³³ So, neutralisation of the positive charges of the histones within the nucleosome/autoantibody complex by heparin prevented binding of these complexes to HS in the GBM.

If nucleosomes are important for the targeting of autoantibodies to the GBM, they should be present in glomerular deposits in murine and human lupus nephritis. Using polyclonal and monoclonal antibodies to the various components of the nucleosomes as probes, nucleosomes were indeed identified in human lupus nephritis, predominantly in the diffuse proliferative form (WHO class IV).³⁴ With elution studies of isolated glomeruli from MRL/lpr mice antinucleosome antibodies were identified.³⁵

A time study revealed that these antinucleosome antibodies were deposited first, with subsequent deposition of anti-dsDNA antibodies. This sequence suggests that after the nucleosome lodges in the GBM, it acts as a planted antigen for subsequent binding of anti-dsDNA. In concordance with the above-mentioned studies that nucleosome/antihistone complexes are less nephritogenic, the amount of antihistone antibodies was low and did not increase when the severity of the glomerular lesion progressed. An analysis of various glomerular diseases with monoclonal antibodies against HS and the HSPG core protein revealed an almost complete absence of HS staining in the GBM in 90% of the biopsies from patients with proliferative lupus nephritis.³⁶ A similar observation was made in murine lupus nephritis,³⁷ which allowed a further analysis of the responsible mechanism. In a time study in MRL/lpr mice an inverse correlation was found between HS staining and albuminuria and between HS staining and immunoglobulin deposits in the GBM. This suggested masking of HS by immune complexes. Measurement of the HS content in isolated glomeruli from these mice showed a normal amount of HS, which indicated that the decrease in HS staining was not due to a reduction in the HS content in the glomerulus. Further proof for the masking of HS by deposited glomerular immune complexes came from three observations: 1) *in vitro* pre-incubation of HS-coated ELISA plates with nucleosome/autoantibody complexes inhibited the binding of the anti-HS monoclonal to HS dose-dependently;³⁷ 2) heparin treatment of MRL/lpr mice not only prevented glomerular deposition as mentioned before, but also prevented the loss of HS staining;³³ and 3) in human lupus nephritis an inverse correlation was seen between GBM-HS staining and the amount of nucleosome deposits.³⁴ So, this decreased HS staining in lupus nephritis indicates, although indirectly, the presence of nucleosome/Ig complexes in the GBM. Taken together, these results document the presence of nucleosomes, antinucleosome antibodies and nucleosome/autoantibody complexes in glomerular deposits in lupus nephritis. They underline the relevance of nucleosome-mediated targeting of autoantibodies to the GBM, as identified in experimental animal studies.

Because of their nephritogenic potential, it could be helpful to identify nucleosome/autoantibody complexes in the circulation of SLE patients. Using an ELISA, plasma samples of SLE patients were screened for anti-HS reactivity. Onset³⁸ or exacerbation³⁹ of lupus nephritis was indeed associated with higher anti-HS reactivity. Using a GBM-based ELISA similar results were found.⁴⁰ With a more direct approach, by measuring nucleosome/Ig complexes, an association was found in MRL/lpr mice between these nucleosome/autoantibody complexes and development of proteinuria.⁴¹

NOTE

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Renal replacement therapy for acute renal failure on the intensive care unit: coming of age?

E.F.H. van Bommel

Department of Internal Medicine, Albert Schweitzer Hospital, PO Box 444, 3300 AK Dordrecht, the Netherlands, e-mail: e.f.h.vanbommel@asz.nl

ABSTRACT

The introduction and development of continuous renal replacement therapy (CRRT) represents one of the most substantial changes in patient management on the intensive care unit (ICU). Several issues, however, are still unresolved. Adequacy of dialysis in critically ill patients involves more than simple control of urea (although considered reflective of toxic uraemic compounds). It also concerns various (other) biochemical and clinical parameters. This article addresses important questions such as the different aspects of 'adequate' dialysis and its timing and intensity ('dialysis dosing'). Dialytic treatment should now be tailored to the patient, influenced by patient characteristics, urgency of treatment, haemodynamic tolerance and vascular access. For this, intermittent haemodialysis and CRRT should be regarded as complementary techniques, to be used interchangeably in critically ill patients with acute renal failure (ARF) according to circumstances. While awaiting scientific criteria for the initiation of renal replacement therapy in ARF patients, it seems reasonable to prefer prevention of physiological derangements to their *post-hoc* correction. This would mean early initiation of dialytic treatment as renal support rather than its initiation as renal replacement therapy for uraemic complications. The amount of dialysis ('dialysis dose') should preferably be prescribed on an individualised basis, especially when considering that the delivered dialysis dose may make a difference. Despite its limitations, simplified urea kinetic modelling, as outlined in this article's appendix, may be used as a bedside method to establish the required dose with CRRT. If not, at least the weight-adjusted ultrafiltration (UF) flow rate should be used as a surrogate for the prescribed dialysis dose (i.e., ml/kg/h).

As the prescribed dialysis dose is usually less than the delivered dose, this should also be taken into account. In addition, nutrition should be viewed as an integral part of the dialysis prescription. Continuing effort should be made to develop 'evidence-based' guidelines for the appropriate prescription and delivery of renal replacement therapy to treat ARF in the ICU. This should include efforts to determine a validated dialysis dose methodology in ARF patients to address further the dose/outcome relationship. Based on existing data, some guidelines for the prescription and delivery of adequate (C)RRT are provided.

INTRODUCTION

Although in part masked by a change in the patient population, adequate comparative data indicate that outcome of acute renal failure (ARF) patients has improved over the last two decades.^{1,2} Advances in resuscitation techniques, mechanical ventilation, nutrition and haemodynamic monitoring which we have seen during the last two decades may explain this better outcome. In addition, we now have a complete armamentarium of extracorporeal techniques available to replace renal function in the critically ill patient with ARF.

Indeed, the introduction and development of continuous renal replacement therapy (CRRT) represents one of the most substantial changes in patient management on the ICU.³ However, despite more than 250 published papers concerning the various aspects of CRRT, some important questions still need to be answered. This particularly

concerns aspects of 'adequate' dialysis and the timing and intensity ('dialysis dose') of dialytic treatment. This article addresses these questions and, as an increasing number of nondialysis hospitals are implementing CRRT,² attempts to provide some guidelines for internists providing nephrological care on the ICU.

ADEQUACY OF DIALYSIS

In contrast to end-stage renal disease (ESRD) patients, there is no definition of 'adequate' dialysis in critically ill patients. We can only rely on personal experience, clinical intuition and some preliminary data to define adequacy. Of course, adequacy of dialysis in critically ill patients concerns more than simple control of urea (although considered reflective of toxic uraemic compounds). It also concerns various other biochemical and clinical parameters (*table 1*).

Table 1
Different aspects of adequate dialysis in acute renal failure

BIOCHEMICAL PARAMETERS	CLINICAL PARAMETERS
Adequate small-solute clearance	Control of fluid balance
Correction of electrolyte disturbances	Cardiovascular stability
Attaining acid-base homeostasis	No respiratory compromise
Adequate clearance large(r) solutes?	Adapted to nutritional needs
No depletion syndrome	No aggravation of renal/splanchnic ischaemia

Biochemistry

Accumulating data suggest that CRRT is superior to intermittent haemodialysis (IHD) in terms of control over the patient's biochemistry and fluid status.^{3,5} One factor is that the 'dialysis dose' actually delivered with IHD is less than that prescribed, predominantly due to repeated hypotensive episodes necessitating a decrease in blood flow or earlier termination of the procedure.^{4,5} Recirculation is another important factor, depending on site, blood flow and reversal of lines.^{4,5} CRRT not only enables a significantly higher dialysis dose to be delivered when compared with IHD, more mass of urea is also removed in CRRT than in IHD at similar Kt/V_{urea} (mathematical expression of dialysis dose, where K represents clearance, t time and V volume distribution of urea) (see *appendix* on page 246).^{4,5} This apparent inefficiency of IHD compared with CRRT is related to the nonlinearity of diffusion-based solute removal, compartmentalisation phenomena and flow-related disequilibrium.⁴ However, the prescribed dialysis dose with CRRT is also less than the

delivered dose. As the actual mean duration of CRRT often does not exceed 18 to 19 hours (e.g. due to filter clotting, surgical procedures), a prescribed UF rate of 33 ml/min is not necessarily equivalent to a delivered dialysis dose of 48 l/day.^{3,5}

Fluid balance

The amount of fluid removed during IHD is also limited to approximately two to three litres a day. This contrasts sharply with CRRT which, by providing the option of being able to remove fluid any time of the day or night, gives us the potential for continuous fine-tuning of the intravascular volume.^{3,5} This is also important in view of the often massive fluid resuscitation required in the early phase of septic shock; fluid which is sequestered in part into the interstitial tissue because of capillary leakage. During recovery from sepsis and re-establishment of capillary integrity, sequestered fluid shifts back from the interstitial space into the vascular space. In this stage, high negative fluid balances are required if renal failure (i.e. oliguria) is still present, which can only be attained with CRRT.⁶

Acid-base homeostasis

Adequacy of dialysis also concerns the adequate correction of acid-base homeostasis. Lactate-based CRRT is associated with superior correction of acidosis in comparison with standard bicarbonate-based IHD. As lactic acidosis is often present in concurrence with decreased lactate metabolism, one may question whether bicarbonate – although more costly – should (also) be preferred as the buffering anion with CRRT.^{3,5,7} In one prospective, randomised trial comparing continuous venovenous haemofiltration (CVVH) with either bicarbonate-based or lactate-based replacement fluid, superior acidosis correction and reduced cardiovascular events were observed with use of the bicarbonate-based replacement fluid.⁸ Others have noted an increased urea generation rate with use of lactate-buffered replacement fluid, possibly because of a catabolic effect of D-lactate.^{9,10} Lactate can be used safely as the buffering anion in most patients; no hyperlactataemia has been reported with a lactate flux of up to 65 mmol/h in ICU patients.³ However, no data exist on the effect of a large lactate load with CRRT using high UF flow rates (>4 l/h). In cases of severe liver dysfunction (e.g. cirrhosis, fulminant liver failure) bicarbonate should preferentially be used as the buffering anion. Of note, high dialysate or ultrafiltration flow rates with CRRT may result in alkalosis, which may complicate weaning the patient from the ventilator.

Choice of membrane

Adequacy of dialysis also concerns the choice of the membrane. Blood-membrane interactions may lead to several unwanted effects; the less biocompatible the membrane, the more unwanted effects will occur.^{11,12}

Several data suggest that use of bioincompatible cellulosic membranes (cuprophane) with IHD is associated with delayed recovery of renal failure and decreased survival in ICU patients compared with the use of biocompatible low- and high-flux synthetic membranes.¹³ No superiority of synthetic membranes compared with modified cellulosic membranes (cellulosic tri-acetate) in terms of renal or patient outcome with IHD has been observed.^{11,14} Although the use of high-flux synthetic or modified cellulosic membranes is advocated with IHD, this issue is still much debated.¹⁵ With the exclusive use of (semi)synthetic membranes in CRRT and despite potential differences in characteristics (e.g. adsorptive vs. nonadsorptive membrane surfaces), no superiority of any specific membrane has been demonstrated.^{3,11}

Anticoagulation

Ongoing anticoagulation is needed with CRRT to prevent clotting of the extracorporeal circuit. Frequent filter clotting is one of the most important factors decreasing the delivered dialysis dose, thereby jeopardising the adequacy of dialysis with CRRT.¹⁶ In patients who are often at high risk of bleeding, finding the optimal anticoagulation regime which leads to prolonged filter life (≥ 24 hours) while preventing (aggravation of) bleeding is an important part of the dialysis prescription with CRRT. Given the association of new haemorrhagic episodes and even haemorrhage-associated death with use of conventional low-dose heparin in high-risk patients treated with CRRT,^{16,17} regional citrate anticoagulation is being increasingly used.¹⁸ Besides a lower risk of bleeding, it is also associated with increased filter life and avoidance of heparin-induced thrombocytopenia.^{16,18} However, whatever the anticoagulation regime, proper monitoring and adequate vascular access are of utmost importance in preventing filter clotting with CRRT.¹⁶ Contrary to CRRT, IHD can be safely and adequately performed with or without anticoagulation. As such, it may be an alternative for CRRT in patients at high-risk of bleeding. Pros and cons of the different anticoagulation regimes are beyond the scope of this article and the reader is referred to some excellent reviews on this subject.^{16,17,19}

Complications

In addition to being superior as renal replacement *per se*, CRRT avoids complications such as (aggravation of) hypotension, cardiac arrhythmias, an increase in oxygen consumption or cerebral oedema and splanchnic ischaemia, which may be seen with IHD.^{3,5} However, while significant improvements in intermittent treatment may ameliorate some of these complications (*table 2*), CRRT may offer some potential disadvantages (*table 3*). Indeed, sustained low-efficiency dialysis (SLED) may be seen as the ultimate hybrid technique, combining advantages of conventional dialysis with those of CRRT.²⁰

Table 2

Improvements in intermittent treatment of acute renal failure on the intensive care unit

Sequential ultrafiltration/dialysis
Volumetric-controlled ultrafiltration
High-flux biocompatible membranes
Sodium profiling [®]
Low-temperature dialysate
Intermittent haemofiltration
On-line blood volume monitoring
Acetate-free biofiltration [#]
SLED (sustained low-efficiency dialysis)*

[®] Use of variable dialysate sodium concentration with mirrored UF.

[#] Complete avoidance of acetate may result in improved haemodynamics.

* Extended duration of IHD to 6-12 hours with decreased blood (100-200 ml/min) and dialysate flow rate (200-300 ml/min).

Table 3

Potential disadvantages of continuous renal replacement therapy

Need for continuous anticoagulation
More difficult drug dosing
Prolonged immobilisation of patient
Low efficiency in terms of unit/time (e.g. severe hyperkalaemia)
Hypophosphataemia/(ionised) hypocalcaemia more frequent
Nonselective solute removal: depletion syndrome with prolonged use of high Q_f [®]
Adverse effects hyperlactataemia with lactate-based continuous renal replacement therapy using high Q_f [®]

[®] Few if no data available concerning these important issues, Q_f = ultrafiltration flow rate.

The IHD versus CRRT debate

Some still consider the choice of treatment modality on the ICU a matter of ongoing debate. While a protagonistic view as to the preferential use of CRRT on the ICU is supported by several clinical data, antagonists of the preferential use of CRRT on the ICU point to the similar mortality of ARF patients in studies comparing IHD with CRRT, including three prospective randomised trials and two meta-analysis.²¹⁻²⁵ However, guidelines for providing adequate dialysis should direct the choice of treatment modality. Defining a superior treatment modality based on often biased views and inconsistent data (e.g. intensivists vs. nephrologists; physicians from nondialysis vs. dialysis hospitals) will hamper establishing valid guidelines. Most would agree that CRRT is the preferred treatment modality for a significant proportion of haemodynamically unstable ICU patients. In patients stable enough to tolerate either form of dialysis treatment, benefits and complications of

both treatment modalities should be weighed carefully against each other. Therefore, a reasonable approach is to regard IHD and CRRT as complementary techniques, to be used interchangeably in critically ill patients with ARF according to circumstances (figure 1).

WHEN TO START RENAL REPLACEMENT THERAPY?

The optimal 'timing' of renal replacement therapy is not known. Several earlier studies, including one prospective, randomised trial, comparing outcome of ARF patients

who were dialysed on established indications with the outcome of ARF patients who were dialysed 'early' (i.e. at a lower serum urea level), showed a clear survival advantage of patients who were dialysed 'early' (table 4). However, lack of adjustment to differences in case mix, illness severity, nondialytic therapies and/or dialysis intensity may have confounded these positive results.^{12,23,26,27} There are no recent studies investigating the timing of renal replacement therapy in a controlled fashion. In a retrospective comparative study, a shorter time interval from ICU admission to start of CRRT was found in surgical ARF patients who survived compared with similar patients who died (4.5 vs. 6.8; p=0.01).⁷ These findings were not observed in ARF patients treated

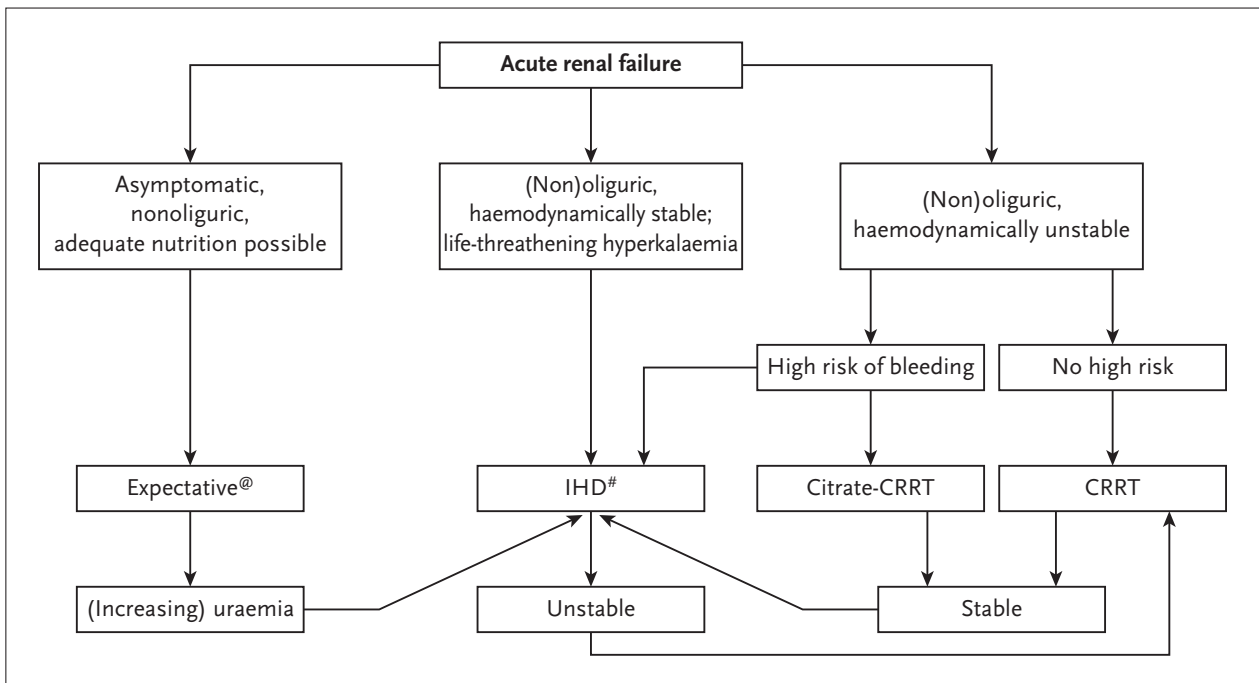


Figure 1

Algorithm for the dialytic treatment of acute renal failure according to circumstances

IHD = intermittent haemodialysis, CRRT = continuous renal replacement therapy. @ Delay initiation of dialytic treatment to maximise the odds of native renal recovery, # if no citrate-protocol for CRRT, heparin-free IHD may be used as alternative treatment.

Table 4

Impact of early ('prophylactic') dialysis on outcome in acute renal failure

AUTHOR, YEAR	PREDIALYSIS UREA (MMOL/L)		MORTALITY (%)	
	CONTROLS#	EARLY	CONTROLS#	EARLY
Parsons, 1961	71	43	15/17 (88)	4/16 (25)
Balslev, 1963	67	52	22/42 (52)	31/54 (57)*
Fischer, 1966	83	54	65/84 (77)	40/78 (51)
Kleinknecht, 1972	58	33	73/173 (42)	43/147 (29)
Conger, 1975 ²⁷	43	18	8/10 (80)	3/8 (36)

Historical controls treated with intermittent haemodialysis for clinical deterioration (severe electrolyte, acid-base or fluid disturbances) and/or very high urea levels, * no significant difference.

with contemporary IHD. There was no difference in serum creatinine levels between survivors and nonsurvivors upon initiation of CRRT.⁷ In another retrospective study, 'early' start (mean urea 15.2 ± 4.6 mmol/l) of CRRT was associated with a shorter time interval between hospital admission and initiation of renal replacement therapy (10.5 vs. 19.4 days; $p=0.01$) and improved outcome (39% vs. 20%; $p<0.0001$) when compared with 'late' starters (urea 33.7 ± 10.1 mmol/l).²⁸

It may be that patients treated later developed ARF with a more protracted course or developed ARF as part of multi-organ dysfunction syndrome (MODS). Otherwise, one might suggest that earlier intervention with CRRT favourably affects outcome. Commonly observed cardiac and/or pulmonary system failure accompanying ARF may be exacerbated (or provoked) by overhydration and increases the risk of dying.^{5,7} Therefore, the prevention or rapid reversal of any existing overhydration with the early initiation of CRRT may lead to a diminution of additional vital organ dysfunctions. The 'early' institution of CRRT may also down-modulate the body's exaggerated response to severe septic or nonseptic insults for which various mechanisms may be responsible: reduction of interstitial oedema by continuous intravascular 'refilling'; decrease in core body temperature in hyperthermic patients; correction of (lactic) acidosis; and perhaps the continuous removal of toxic substances (urea, proteases, inflammatory mediators, myoglobin, and maybe others).^{29,30} All this may lead to less established organ damage (ARDS, acute tubular necrosis) and a more favourable clinical course. Indeed, while awaiting scientific criteria for the initiation of renal replacement therapy in ARF patients, it seems reasonable to prefer prevention of physiological derangements to their *post-hoc* correction. In recent years, indications and timing of dialysis seems to be shifting from renal replacement *per se* to renal support, the latter eventually being more targeted – although unproven³¹ – for overall support.

WHAT DIALYSIS DOSE SHOULD BE PROVIDED?

Dialysis intensity

The issue of dialysis intensity ('dialysis dosing') has been studied extensively in patients with chronic renal failure (see *appendix* on page 246). Indeed, a consistent correlation has been shown between dialysis dose (expressed as Kt/V_{urea}) and survival, even after adjusting for important comorbid factors, such as diabetes, nutritional status and hypertension.²⁷⁻³¹ Based on these data, it is advised to deliver a Kt/V of at least 1.2 per session to chronic dialysis patients.³²⁻³⁶ However, little attention is paid to the intensity of dialysis in ARF. A controlled study from the 1980s,

comprising only a small number of patients, failed to show any significant benefit from intensive IHD using cuprophane membranes in ARF patients.³⁷ However, it may be that the possible beneficial effects of this approach were offset by the side effects associated with IHD using bioincompatible (BIC) membranes, such as hypotension and the prolongation of ARF. Indeed, some data do suggest that the dialysis dose may affect patient outcome. Tapolyai *et al.*³⁸ found a higher delivered dialysis dose in ARF patients treated with (more) contemporary IHD (bicarbonate-based, synthetic membranes) who survived compared with similar patients who died (Kt/V_{urea} 1.09 vs. 0.89; $p<0.05$). In a prospective randomised study comparing daily with alternate-day intermittent haemodialysis in ARF patients ($n=160$), intensive haemodialysis (weekly Kt/V_{urea} 5.8 ± 0.4 vs. 3.0 ± 0.6) reduced duration of renal failure (9 ± 2 vs. 16 ± 6 days; $p=0.01$) and improved survival (72% vs. 54%; $p=0.01$).³⁹

Diffusive or convective clearance ?

Another important question concerns the principal method of solute removal, i.e. diffusion or convection. Some retrospective data suggest a correlation between the ultrafiltration volume (i.e. convective purification rate) and recovery rate of renal failure and patient outcome, respectively.⁴⁰ Paganini and co-workers found an inverse correlation between the delivered dialysis dose (expressed as Kt/V_{urea}) and mortality in patients with intermediate illness severity, whether treated with contemporary IHD or CRRT.⁴¹ As might be expected, this impact of a higher delivered dialysis dose on outcome was not seen at either extremes of illnesses.⁴¹ Improved survival was also observed in a prospective randomised study in CVVH-treated ARF patients ($n=425$) with increasing ultrafiltrate volumes.⁴² Data suggested that the weight-adjusted UF volume should be at least 35 ml/h/kg.⁴² An 'attractive' explanation often put forward is an improved clearance of toxic middle- and large-molecular-weight solutes with convection-based techniques, from which the patient with an exaggerated inflammatory response (e.g. septic shock) may benefit.^{29,30} However, as data suggest a correlation between dialysis dose and patient outcome with both diffusion-based and convection-based techniques, more data are needed to substantiate this point. In addition, data from formal comparisons of convection-based and diffusion-based CRRTs, e.g. CVVH vs. CVVHD (continuous venovenous haemodialysis) or low vs. high volume CVVH in ARF patients have yet to be published. Nevertheless, if not using more 'sophisticated' dialysis dosing, it seems appropriate to use the weight-adjusted UF volume as a surrogate for the dialysis dose (ml/kg/h vs. ml/h). Using the above-mentioned UF flow rate of 35 ml/kg/h one can easily see the difference in required dialysis dose,

depending on the patient's weight: e.g. a daily clearance of 71 l/day for a patient with a bodyweight of 85 kg and 57 l/day for a patient with a weight of 68 kg.

PROTEIN AND CALORIE ADMINISTRATION DURING RENAL REPLACEMENT THERAPY

Nutritional support directly influences the required dialysis dose and amount of fluid removal with renal replacement therapy. Both the amount of nonprotein calories administration and the amount of protein administration correlate strongly with the urea generation rate, thus influencing the required dialysis dose.⁴³ In contrast to IHD, CRRT facilitates the unrestricted supply of protein and energy sources without the risk of exacerbating azotaemia or fluid overload. However, these techniques also have an impact on nutrient balance itself. Urea nitrogen losses with the ultrafiltrate represent 70 to 80% of the eliminated nitrogen.^{44,45} Non-urea nitrogen losses occur as a result of convective removal of free amino acids (AA) (MW 75-240 Da),^{44,45} their clearance being directly proportional to the serum concentration and ultrafiltration/dialysate flow rate (≈ 10 to 12% of nutritional input). Therefore, although AA losses with CRRT are not great, this should be taken into account when prescribing nutritional support.

Thus far, protein requirements of ARF patients receiving renal replacement therapy have not been studied carefully. Some studies suggest that positive nitrogen balance can not be achieved with full (par)enteral nutrition.^{44,46} However, levels of protein administration in these studies were relatively low (0.5-1.0 g/kg per day). It is suggested that a positive nitrogen balance may be achieved with the administration of 1.5 to 1.8 g protein/kg per day.⁴⁷ Of note, at this increased level of protein administration, lower levels of energy administration (25 to 35 kcal/kg per day) appeared to be associated with improved nitrogen retention and a more favourable nitrogen balance.⁴⁷ Recent data in highly catabolic ARF patients treated with CVVHDF (continuous venovenous haemodiafiltration) suggest that even higher levels of protein administration (2.5 g/kg/day) may be required to improve nitrogen balance.⁴⁸ Although benefits of aggressive nutritional therapy in ARF for renal recovery are unknown and its impact on morbidity and mortality remains unproven, it seems intuitive that early initiation of nutritional support is warranted. Indeed, pre-existing and/or hospital-acquired malnutrition have been identified as important factors contributing to the persistent high mortality of ARF patients.⁴⁹ Therefore, the dose of dialytic therapy – whether IHD or CRRT – should always be adapted to the nutritional needs (i.e. no protein restriction to avoid daily haemodialysis; no

'standard' UF volume without considering the amount of calories and protein administration). However, one must also realise that any excess protein intake beyond basic requirements will result in an additional increase in urea production, the production of other nitrogenous waste products and in potentially more pronounced negative nitrogen balance.^{44,46}

In short, nutrition should be viewed as an integral part of the dialysis prescription (table 5). Most authors suggest administration of at least 1.4 g protein and 35 to 45 kcal/kg a day in patients with complicated urea ARF (for instance a highly catabolic patient with severe septic shock) receiving renal replacement therapy.^{26,44,47} Urea kinetic modelling (UKM) may also assist in establishing protein requirements through determination of the protein catabolic rate (see appendix on page 246). It should be noted that dialysis – particularly CRRT – may have an impact on other nutritional substrates as well (e.g. vitamins, minerals).^{44,46}

Table 5
Factors influencing prescription of dialysis dose

Patient size and weight [®]
Degree of catabolism (assumed or calculated PCR)
Amount of protein and calorie administration
Delivered dose < prescribed dose
Desired level of metabolic control

[®] Adjust ultrafiltration rate to the patient's weight (ml/kg/h) or use Kt/V . PCR = protein catabolic rate (see appendix).

ADEQUATE PERFORMANCE OF CRRT

Inadequate knowledge of or expertise with CRRT will directly affect its performance and impact negatively on the adequacy of dialysis. For example, repeated filter clotting – the Achilles' heel of CRRT – may not be related to the anticoagulation regime *per se* but more often to incorrect monitoring and absence of standardised procedures.⁵⁰ For all people involved (intensivists, nephrologists, renal and critical care nurses), it is important to recognise each other's responsibilities and expertise.^{50,51} Regardless of the ICU format (closed vs. open), severely ill and complex patients with ARF offer ample opportunity for a collaborative interaction between the nephrologist and intensivist.^{52,53} Unlike CRRT, IHD is performed by renal nurses under the direct supervision of the nephrologist and requires no active participation from the critical care nurse in the dialytic care of the patient.

However, what about hospitals without non-CRRT dialysis facilities and absence of nephrologists (and renal nurses)

with extensive knowledge of and experience with different dialytic treatment modalities? The first and most important question is the required minimal number of patients to be treated on a yearly basis to safely adopt CRRT on the ICU. In other words, how many patients should be treated to gain (and keep) enough experience with the technique? To date, no such practice guideline exists but is urgently needed. In addition, all measures should be taken to keep pace with (rapid) changes in technology and technique, to provide adequate and continuously updated protocols, and to establish areas for potential improvement.^{50,54} These and other important issues that need to be considered are summarised in *table 6*. The mere implementation of some form of CRRT ('Wow, a new technique, let's do it')⁵⁵ without considering or adhering to these issues is to be strongly discouraged.

CONCLUSIONS

It seems as if renal replacement therapy for the treatment of ARF on the ICU is coming of age. Dialytic treatment can now be tailored to the patient, influenced by patient characteristics, urgency of treatment, haemodynamic tolerance and vascular access. However, current practice at many institutions is still to prescribe generally similar amounts of renal replacement therapy to ARF patients regardless of patient size and degree of catabolism. The amount of dialysis ('dialysis dose') should preferably be prescribed on an individualised basis, especially when considering that the delivered dialysis dose may make a difference (*table 5*). Despite its limitations,⁵⁶⁻⁶¹ simplified UKM may be used as a bedside method to establish the required dose (see *appendix* on page 246). If not, at least the weight-adjusted UF flow rate should be used as a surrogate for the prescribed dialysis dose (i.e., ml/kg/h). As the prescribed dialysis dose is usually less than the delivered dose, this should also be taken into account. It is the author's view that improved clearance (particularly of larger solutes), better control of blood flow and ultra-

filtration rate and avoidance of arterial cannulation make pump-driven venovenous techniques the treatment of choice in critically ill haemodynamically unstable patients. Since the blood pump can augment blood flow and thus the ultrafiltration rate, it seems inefficient to add dialysate before the blood flow is maximised. In addition, CVVHD and CVVHDF are more labour intensive than CVVH. Results from a Dutch survey indicate that this judgement is shared by others.² One should also recognise that there are still specific situations for the preferential use of intermittent techniques on the ICU (*figure 1*). Continuing effort should be made to develop 'evidence-based' guidelines for the appropriate description and delivery of renal replacement therapy to treat ARF in the ICU. This should include efforts to determine a validated dialysis dose methodology in ARF patients to address further the dose/outcome relationship.^{8,59} Based on existing data, some guidelines for the prescription and delivery of adequate CRRT are suggested (*table 7*).

Table 7
Some guidelines to deliver adequate CRRT on the ICU

Start 'early': oliguria >24 hours or anuria ≥12 hours; uraemia ≥25-30 mmol/l
Prescribe 'adequate' dialysis dose: daily Kt/V ≥1.2; UF volume ≥35 ml/kg/h
Use (semi)synthetic biocompatible high-flux membranes
Use the venovenous approach, preferably internal jugular vein [#]
Maximise UF flow rate, before adding slow-dialysis
In case of severe liver dysfunction, use bicarbonate as buffering anion
Judicious use of anticoagulation to improve delivered dialysis dose [@]
Prescribe ≥1.2-1.4 g protein/kg/day to improve nitrogen balance
If the patient is stabilised, switch to intermittent treatment

CRRT = continuous renal replacement therapy, IHD = intermittent haemodialysis, UF = ultrafiltration. [#] Cannulation of jugular vein associated with less recirculation, hence improved dialysis adequacy. [@] if repeated clotting consider switch therapy (e.g., post- to predilution CVVH; other filter type; CVVH to CVVHDF) or switch to other anticoagulation protocol.

Table 6
Factors affecting successful implementation and continuation of CRRT

FACTORS AFFECTING POTENTIAL IMPLEMENTATION OF CRRT	FACTORS AFFECTING PERFORMANCE OF CRRT
# intensive care unit beds; # acute renal failure patients on intensive care unit/year; # dialysed patients on intensive care unit/year	Clear delineation of nursing responsibilities (e.g. CRRT set-up, initiation, monitoring, trouble shooting)
Dialysis services (non-CRRT dialysis facilities, nephrological support, renal nurses)	Physician's responsibilities and interaction
Intensive care unit staffing support (# intensivists, # part-time critical care nurses)	Formal and continuous instruction (lectures, 'hands-on' training, skill assessment, patient care experience)
Intensive care unit staff training support	Standardised and updated protocols
Level of intensive care unit (CBO terms)	Continuous identification of areas for improvement (e.g. new knowledge)

Appendix

UREA KINETIC MODELLING (UKM)

Mathematically derived biochemical concept of adequacy of intermittent dialysis in end-stage renal disease (ESRD), assuming:^{35,36}

1. a steady-state process;
2. negligible urea generation during dialysis;
3. eubolic state (protein catabolic rate reflects daily protein intake);
4. absence of residual renal function;
5. with 'single-pool' kinetics, it is also assumed that urea is distributed in one well-mixed pool of volume.

Dialysis dose is expressed as Kt/V_{urea} , where:

K = diffusive and/or convective clearance, derived from the manufacturer's specifications of the dialyser clearance with actual delivered blood- and dialysate flow rates (ml/min);

t = time (min);

V_{urea} = urea distribution volume (L), for which different equations are available.

Intensifying dialysis by increasing Kt/V per dialysis session is consistently associated with lower morbidity and mortality in ESRD patients. It is suggested that the target dialysis dose, as assessed by UKM-derived single-pool Kt/V , should be increased from the traditional 1.0 to 1.2 and even 1.4 per session. No further improvement in outcome was noted beyond a Kt/V of 1.5.

Several simplified formulas are now available to evaluate Kt/V of intermittent treatment at the bedside. For several reasons calculation of Kt/V with CRRT is much easier (continuous nature, exact body clearance, linearity of treatment). Of note, Kt/V is only a marker of treatment efficiency of small molecules.⁵⁶⁻⁵⁹

Hypothesis: In the absence of other data, ARF patients should at least receive a similar dialysis intensity per dialysis session to that recommended for ESRD patients: $Kt/V \geq 1.2$.⁵⁶⁻⁵⁹

Limitations of using UKM in ARF patients:⁵⁶⁻⁶⁰

- no steady-state situation;
- only crude approximation of variables (e.g. fluid overload, hypercatabolism);
- prescribed dialysis dose usually less than actually delivered;
- high(er) and variable urea generation rate (PCR 1.0 vs. >1.4 g/kg/day).

CLEARANCES WITH CONTINUOUS THERAPIES

CAVH/CVVH

Clearance, $K = Q_f \times C_f / C_{pi}$, where:

Q_f = ultrafiltration flow rate (ml/L);

C_f and C_{pi} = ultrafiltrate and prefilter plasma solute concentration (mmol/L).

Sieving coefficient, SC (C_f / C_{pi}) for urea = 1.0 so $C_f = C_{pi}$.

$$(1) K_{\text{urea}} = Q_f$$

CAVHD/CVVHD

$K = (Q_{do} \times C_{do}) - (Q_{di} \times C_{di}) / C_{pi}$, where:

Q_{di} and Q_{do} = dialysate inflow and outflow rate (ml/min);

C_{di} and C_{do} = solute concentration in inflowing and outflowing dialysate (mmol/L).

If $C_{di} = 0$ (e.g., urea) then $K = Q_{do} \times C_{do} / C_{pi}$.

If $Q_b \gg Q_d$ almost complete (90-95%) small solute saturation of outflowing dialysate occurs⁶¹ and therefore

$C_{do} = C_{pi}$,

$Q_{do} = Q_{di}$.

$$(2) K_{\text{urea}} = Q_{do}$$

CAVHDF/CVVHDF

$K = (Q_{di} \times C_{do} / C_{pi}) + (Q_f \times C_{do} / C_{pi})$.

$$(3) K_{\text{urea}} = Q_{di} + Q_f = Q_{do}$$

Kt/V with CRRT

Example (1): female patient 73 kg, CVVHDF; Q_d 1 l/h, Q_f 0.5 l/h.

$K_{\text{urea}} = 1.5$ l/h = 25 ml/min;

$t = 1440$ min;

$V_{\text{urea}} = 0.58 \times G = 42.3$ L, where G is pre-ICU weight with added resuscitation fluid and estimated oedema component (kg).

Prescribed daily $Kt/V_{\text{urea}} = 0.86$ (weekly Kt/V 6.0).

Note: if G 85 kg then prescribed Kt/V_{urea} is lower: 0.72.

Note: if actual duration 18 hours (e.g., due to filter clotting), delivered dialysis dose is significantly lower:

$Kt/V_{\text{urea}} = 0.6$.

Example (2): male patient 89 kg, CVVH; Q_f 3 l/h.

$K_{\text{urea}} = 3$ L/h = 50 ml/min;

$t = 1440$ min;

$V_{\text{urea}} = 0.58 \times G = 51.6$ L.

Prescribed daily $Kt/V_{\text{urea}} = 1.4$ (weekly Kt/V 8.8).

Note: if actual duration 19 hours, delivered dialysis dose is lower: $Kt/V_{\text{urea}} = 1.1$.

UREA GENERATION RATE AND DIALYSIS DOSE

Another approach to determine the required dose makes use of the urea generation rate.⁵⁷

For IHD with significant variations of urea concentrations, urea generation can not be readily assessed at the bedside. For continuous techniques, however, assuming that no significant alterations in urea concentrations occur during the day (i.e., after 48 to 72 hours of treatment), the rate of urea removal from the body can be determined as:

(4) R_{urea} (mmol/min) = C_{urea} ($K_{\text{urea}} - Q_{\text{net}}$), where:
 C_{urea} = serum urea concentration (mmol/L);
 K_{urea} = urea clearance (ml/min);
 Q_{net} (ml/min) = net rate of plasma volume reduction or the rate of ultrafiltration (Q_f) minus the rate of substitution fluid replacement (i.e. to correct for haemoconcentration).

At steady-state urea levels and assuming negligible residual renal function, urea generation rate equals urea removal rate ($G_{\text{urea}} = R_{\text{urea}}$) or:

$$(5) G_{\text{urea}} \text{ (mmol/min)} = C_{\text{urea}} (K_{\text{urea}} - Q_{\text{net}})$$

The steady-state serum urea level (C_{ss} , mmol/l) equals the ratio between G_{urea} (mmol/day) and K_{urea} (L/day):

$$(6) C_{\text{ss}} = G_{\text{urea}}/K_{\text{urea}}$$

This equation can be inverted to determine the necessary clearance to obtain a certain 'goal' steady-state urea concentration (C_{goal}):

$$(7) K_{\text{urea}} = G_{\text{urea}}/C_{\text{goal}}$$

Example (3): patient 85 kg, 3^d of CVVH; Q_f 2 L/h; net ultrafiltration 200 ml/h.

$K_{\text{urea}} = 2$ L/h or 48 L/day;

$C_{\text{urea}} = 20$ mmol/L or 56 mg/dl ('steady-state');

$Q_{\text{net}} = 200$ ml/h or 4.8 L/day.

Current $G_{\text{urea}} = 20(48-4.8) = 864$ mmol/day (0.6 mmol/min) or $560(48-4.8) = 24$ g/day

If desired serum urea level (C_{goal}) is 16 mmol/L and assuming stable urea generation, than required clearance is: Desired $K_{\text{urea}} = 864/16 = 54$ L/day or 38 ml/min.

Knowledge of G_{urea} (g/day) permits the protein catabolic rate (PCR) to be derived :

$$(8) G_{\text{urea}} = 0.154 \times \text{PCR (g/day)} - 1.7 \text{ or } \text{PCR} = (G_{\text{urea}} + 1.7)/0.154$$

For this patient $\text{PCR} = 24 + 1.7/0.154 = 167$ g/day or 1.9 g/kg/day.

Note: all this implies a simplified approach to UKM using some crude approximations to provide a bedside method to determine the required dialysis dose. More sophisticated methods of UKM are beyond the scope of this article and the reader is referred to other articles on this subject.^{57,58}

CAVH = continuous arteriovenous haemofiltration, CVVH = continuous venovenous haemofiltration, CAVHD = continuous arteriovenous haemodialysis, CVVHD = continuous venovenous haemodialysis, CAVHDF = continuous arteriovenous haemodiafiltration, CVVHDF = continuous venovenous haemodiafiltration.

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Low cobalamin (vitamin B₁₂) levels in multiple myeloma: a retrospective study

L.Th. Vlasveld

Department of Internal Medicine, Bronovo Hospital, Bronovolaan 5, 2597 AX The Hague, the Netherlands

ABSTRACT

Background: In patients with multiple myeloma a variety of metabolic events may occur. One of these are changes in the serum cobalamin (vitamin B₁₂) concentration. Elevated as well as decreased serum cobalamin levels have been reported. The prevalence and clinical consequences of low cobalamin levels are largely unknown.

Objective: To investigate the prevalence of low serum cobalamin levels in patients with multiple myeloma and to describe the clinical features, haematological parameters and outcome in patients with multiple myeloma with low and normal serum cobalamin levels.

Methods: A retrospective study was conducted in the Deaconess Hospital in Eindhoven. Thirty-two patients were identified who fulfilled the diagnostic criteria for multiple myeloma and had at least one serum cobalamin level tested during the diagnostic or treatment period. A number of clinical characteristics, haematological parameters and outcome were scored.

Results: Twenty-one (66%) patients had a normal serum cobalamin level, nine (28%) patients had a low one and two (6%) patients had an elevated serum cobalamin level. Between the group with a normal and a low serum cobalamin level there were no differences in patients characteristics such as sex and age, tumour characteristics such as the type of paraprotein, tumour load or tumour stage nor in haematological parameters such as haemoglobin level, mean corpuscular volume and megaloblastic changes in the bone marrow. The median survival was not statistically different between both groups.

INTRODUCTION

Multiple myeloma is characterised by a clonal expansion of malignant plasma cells which produce monoclonal heavy and/or light chain immunoglobulins. The malignant plasma cells reside primarily in the bone marrow leading to suppression of the normal haematopoiesis and increased bone turnover eventually resulting in osteolysis. The relationship between malignant plasma cells and bone marrow stromal environment is complex.¹ Plasma cells produce a variety of cytokines, such as interleukin 1 and tumour necrosis factor (TNF), which influence the growth and activity of bone marrow cells such as osteoblasts and osteoclasts. The increased activity of these cells results in increased bone turnover and production of interleukin 6, which acts as a growth-promoting factor for the plasma cells. Common metabolic sequelae of the plasma cell expansion include hypercalcaemia, hypogammaglobulinaemia, and renal failure, either due to the hypercalcaemia or due to deposition of immunoglobulins in the kidney. There are a variety of less common or less well-known metabolic events in myeloma patients. One of these is a change in the serum cobalamin (vitamin B₁₂) concentration. Elevated as well as decreased serum cobalamin levels have been reported in small series of patients.^{2,7} In these reports the prevalence of low cobalamin levels ranges from 0 to 70%. To investigate the prevalence and clinical characteristics of a low cobalamin level in patients with multiple myeloma a retrospective study was performed in myeloma patients treated in the Deaconess Hospital in Eindhoven during the period from 1996 to 2001.

PATIENTS AND METHODS

Patients potentially eligible for the study were identified using the laboratory data system (LABOSYS) which found patients who had undergone immunoelectrophoresis; the records of the bone marrow examinations were screened for results reporting more than 10% plasma cells. To be included in the study the patients identified had to fulfil the diagnostic criteria for multiple myeloma according to Durie and Salmon⁸ and the serum cobalamin concentration had to be determined at least once during the diagnostic period or during the course or treatment of the disease. At the time of determining the serum cobalamin concentration the following data had to be available: haemoglobin level, total leucocyte and thrombocyte count, mean corpuscular volume of the erythrocytes, and serum paraprotein, creatinine, calcium and folic acid levels. In addition the serum concentration of IgG, IgM and IgA, the percentage of plasma cells in the bone marrow, urine analysis for the presence of light chains, and radiographic evaluation of the skeleton had to be recorded. The presence of megaloblastic changes in the erythropoiesis in the bone marrow was scored by an independent investigator (J. Bury) who was unaware of the results of the serum cobalamin concentration. A low cobalamin level was defined as a serum concentration below 120 pmol/l. The results were compared using the Student's *t*-test of unpaired observations.

RESULTS

A total of 32 patients fulfilled all the above-mentioned criteria and were included in this retrospective study. Twenty-one (66%) patients had serum cobalamin levels within the normal range (130 to 850 pmol/l), nine patients (28%) had a low cobalamin level and two (6%) had a serum cobalamin concentration of more than 1476 pmol/l. In six of the nine patients with a low level of cobalamin, this low level was present at the time of diagnosis of multiple myeloma, while in three patients the low cobalamin level developed during the treatment and the course of the disease. The characteristics of the patients with a normal and a decreased cobalamin concentration are summarised in *table 1* and show no differences between the two groups. As a measure for the tumour load the stage of the disease according to the Durie and Salmon criteria,⁸ level of the serum paraprotein, level of the remaining serum IgM and percentage of plasma cells in the bone marrow were used. As depicted in *table 2* patients with low cobalamin levels had no greater tumour load than patients with a normal serum cobalamin level. The haematological parameters are shown in *table 3*. There was no difference in the serum haemoglobin level, mean corpuscular volume of the erythrocytes, and total leucocyte and

Table 1

The clinical characteristics of patients with multiple myeloma with a normal and low serum cobalamin level

	NORMAL COBALAMIN N=21	LOW COBALAMIN N=9
Cobalamin (pmol/l)		
Mean	300.4	93.8
Range	125-845	46-114
Age (years)		
Mean	66.5	68.8
Range	44-84	55-86
Sex		
Male	6	4
Female	15	5
Paraprotein		
IgA	4	5
IgG	10	4
Light chain	6	-
Nonsecreting	1	-

Table 2

The tumour load in patients with multiple myeloma with a normal and low serum cobalamin level

	NORMAL COBALAMIN N=21	LOW COBALAMIN N=9
Stage		
I	1	2
II	4	-
III	16	7
M component (g/l)		
Mean	27.6	27.3
Range	4.3-65.3	11.9-76.3
IgM (g/l)		
Mean	0.4	0.26
Range	0.02-1.32	0.02-0.74
Bone marrow plasma cells (%)		
Mean	51.75	52.2
Range	15-100	15-100

Table 3

Haematological parameters in patients with multiple myeloma with a normal and low serum cobalamin level

	NORMAL COBALAMIN N=21	LOW COBALAMIN N=9
Haemoglobin (mmol/l)		
Mean	6.9	7.1
Range	3.7-8.7	5.4-8.6
Mean corpuscular volume (fl)		
Mean	93.4	96
Range	80-110	89-104
Leucocytes (10⁹/l)		
Mean	6.6	5.6
Range	2.9-13.8	2.7-12.3
Thrombocytes (10⁹/l)		
Mean	240	181
Range	101-591	83-286
Megaloblastic features		
Present	5	1

thrombocyte counts in the two groups. In addition there was no difference in the number of patients with megaloblastic changes in the erythropoiesis in the bone marrow. The serum folic acid levels did not differ between the two groups (data not shown). The median survival in patients with a normal cobalamin was 20.5+ months (range 1 to 76+ months) and in those with a low cobalamin level this was 16+ months (range 6 to 61+ months), which was statistically not significant ($p=0.715$).

Two patients had an elevated serum cobalamin level at the time of diagnosis. Both had an IgA paraprotein-producing myeloma with very high concentrations (69.6 and 77 g/l). One patient was lost for follow-up. In the other patient the serum cobalamin level normalised during cytostatic treatment with reduction of the serum IgA level.

DISCUSSION

In this study a low level of cobalamin was found in more than one fourth (28%) of the patients with multiple myeloma. The presence of low cobalamin levels was not related to patient characteristics such as sex and age or tumour characteristics such as the type of paraprotein or tumour load. As reported by others,⁴ the presence of a low cobalamin level could not be predicted by haematological parameters. In contrast to selected reported cases^{3,9} no association with megaloblastic haematopoiesis in the bone marrow was found in this study and previous reports.^{2,6} In addition, the presence of a low cobalamin level seems no poor prognostic factor since the median survival was not significantly impaired.

Cobalamin is an essential vitamin for DNA synthesis and consists of a number of analogues of which methylcobalamin and deoxyadenosylcobalamin are metabolically active in humans.¹⁰ Cobalamin is primarily present in a protein-bound form in foods of animal origin. After digestion cobalamin is released from the protein by gastric acid and peptic enzymes and bound to cobalamin-binding proteins such as the gastric intrinsic factor (IF). After resorption of the intrinsic factor-cobalamin complex in the terminal ileum through endocytosis by the mucosal cells, cobalamin is intracellularly bound to transcobalamin II (TC II) and the intrinsic factor shed into the lumen of the bowel. Cobalamin is transported by binding onto TC II which is produced by hepatocytes, endothelial cells and probably by enterocytes. The TC II molecule binds methylcobalamin as well as deoxyadenosylcobalamin. However, only 5 to 20% of cobalamin is bound to TC II. Only the TC II-bound cobalamin can enter the cell to be metabolically active. Methylcobalamin acts as a co-factor for methionin synthetase which regulates the formation of methionin from homocysteine whereas deoxyadenosylcobalamin acts as a co-factor of methylmalonic-coenzyme A mutase, which regulates the formation of succinyl CoA

from methylmalonic CoA.

The remaining 80 to 95% of cobalamin is bound to haptocorrines (HC), which are mainly produced by myeloid cells, and consist of a sialic poor and a sialic rich analogue. The physiological role of HC is not fully established.

A number of clinical, especially haematological, conditions are associated with changes in the serum cobalamin concentration. Strongly elevated serum cobalamin levels are mainly found in myeloproliferative disorders such as chronic myeloid leukaemia, polycythaemia vera and the hypereosinophilic syndrome.¹⁰ The elevation of the serum cobalamin level in chronic myeloid leukaemia is the result of an increased production of HC by the proliferating myeloid cells.¹¹ Also in lymphoproliferative diseases such as plasma cell disorders as multiple myeloma, changes in the serum cobalamin, TC II and HC are found.^{12,13} As indicated in this study too, myeloma patients may have strongly elevated serum cobalamin levels. These increased serum cobalamin levels are thought to be the result of elevated TC II levels.^{12,13}

In the past, several hypotheses have been postulated on the cause of the low levels of cobalamin in myeloma patients. Initially it was thought that the low cobalamin level was the result of gastric malabsorption due to pernicious anaemia, which is occasionally found,^{14,16} or to hypochlorhydria or achlorhydria as frequently seen in old age.⁴ There was scattered evidence of a pseudodeficiency of cobalamin as the result of an increased plasma volume in some myeloma patients⁶ and it has also been hypothesised that the decreased serum cobalamin levels result from binding of cobalamin to the paraprotein.¹⁷ Some investigators have found a decreased HC serum level in association with a decreased serum cobalamin level.⁴ From the reported studies and our data it is not clear whether the low level of serum cobalamin found reflects an actual cobalamin deficiency or is merely the result of changes in the cobalamin binding proteins.^{4,6,17,18}

An *in vitro* study provided some evidence for the assumption that the myeloma cells themselves may consume cobalamin.⁵ In comparison with healthy controls the concentration of cobalamin in bone marrow suspension of myeloma patients was significantly higher with a positive correlation between the cobalamin concentration and the amount of bone marrow plasma cells. In addition, the investigators found an increased transcobalamin II-mediated cobalamin uptake in bone marrow cells of myeloma patients in comparison with healthy controls.

The consequences of low cobalamin levels found in myeloma patients are unclear. This study shows that this condition does not seem to influence the prognosis. Theoretically, low cobalamin levels may have an effect on the bone turnover contributing to the myeloma-associated osteoporosis. Older studies in nonmyeloma patients with cobalamin deficiency provided scattered evidence for a

diminished osteoblastic activity leading to osteoporosis, which is reversible after supplementation with cobalamin.¹⁹⁻²² Several *in vitro* and clinical studies indicate that cobalamin may indeed have a direct or indirect effect on the osteoblast and osteoclast activity. Firstly, the activity and proliferation of human bone marrow stromal osteoprogenitor and osteoblastic cells have been shown to be dependent on the cobalamin concentration.²³ Furthermore, clinical studies have shown that cobalamin deficiency results in a significantly increased homocysteine as well as TNF- α level.²⁴ The elevated homocysteine levels may be caused by an insufficient activity of methionine synthetase which may be the result of a decrease in methylcobalamin, a cobalamin analogue that is disproportionately decreased in myeloma patients.¹⁸ It has been demonstrated that high serum homocysteine levels may be associated with impaired cross-linking of collagen.²⁵ As mentioned previously, experimental studies indicate that TNF- α has a regulatory effect on the osteoclast activity.¹ Taken together, these data may suggest that, if the low cobalamin level were to reflect an actual cobalamin deficiency, the low cobalamin level in myeloma patients may have a contributory effect on the increased and pathological bone turnover observed in myeloma patients.

In conclusion, changes in serum cobalamin levels is a frequent finding in patients with multiple myeloma. Especially a low cobalamin level is a common metabolic feature in this disorder. The reason for this low level of cobalamin is not fully understood and the question whether cobalamin substitution is warranted in myeloma patients with an established low cobalamin level cannot be answered. A well-defined study is needed to establish whether a low cobalamin level reflects an actual cobalamin deficiency, to evaluate the metabolic consequences of the observed low cobalamin level and to explore the potentially additional role of a low cobalamin level in the bone turnover in patients with multiple myeloma.

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Cervical mediastinoscopy in the Netherlands: past or present? A retrospective analysis of 218 procedures

P.W. Plaisier*, H.J. Mulder, J.H. Schouwink, P. de Smit

Departments of General Surgery and Pulmonology, Medisch Spectrum Twente, Enschede, * corresponding author, Department of Surgery, Albert Schweitzer Hospital, PO Box 444, 3300 AK Dordrecht, the Netherlands, tel.: +31 (0)78-654 11 11, fax: +31 (0)78-654 22 64, e-mail: p.w.plaisier@asz.nl

ABSTRACT

Background: Cervical mediastinoscopy (CM) has been considered the gold standard for the evaluation of mediastinal lymph nodes in the staging of non-small cell lung cancer (NSCLC) for many years. Recent publications on the value of PET scanning might reduce the use of CM in the near future. The aim of this study was to analyse the data of our CM procedures for their reliability and contribution in the assessment of mediastinal lymph nodes.

Methods: In the period 1995-1999, 219 patients underwent CM. Data were available on 218 procedures and were analysed retrospectively. CM was performed in 162 men and 56 women with a median age of 56 years [range 29 to 80 years].

Results: Median hospitalisation time was three days. There was no mortality and morbidity was 6%. In 96% of procedures representative lymphoid tissue was obtained. In 24%, biopsies contained malignancy.

Conclusions: CM is a relatively safe procedure with a high diagnostic yield. As long as PET scanning remains available at a limited level, CM remains the gold standard in the Netherlands for patients with apparently operable NSCLC.

INTRODUCTION

Cervical mediastinoscopy (CM) has been considered the gold standard for the evaluation of mediastinal lymph nodes in the staging of non-small cell lung cancer

(NSCLC) for several decades. Furthermore, CM is useful to obtain histological samples in cases of primary mediastinal lymph node enlargement. Relative disadvantages of the procedure are its invasive character and the need for general anaesthesia. Recent studies on the value of PET scanning¹⁻³ have demonstrated that reliable preoperative staging may be performed without CM in selected patients. It seems reasonable to expect a reduced need for CM in the very near future, although it will remain indicated in a considerable number of patients. In this retrospective study, data from 218 CM procedures were analysed for their reliability and contribution in the assessment of mediastinal lymph nodes.

PATIENTS AND METHODS

In the period 1995 to 1999, 219 CMs were performed in Medisch Spectrum Twente, a large community hospital in the Netherlands (1995: 49; 1996: 45; 1997: 42; 1998: 50; 1999: 33). The same procedure was performed as was described several decades ago.⁴ Data could be retrieved for 218 procedures (99.5%) and were analysed retrospectively. Patient characteristics are depicted in *table 1*. The majority of patients (n=212; 97%) were referred from the Department of Pulmonology. The others were referred from the Departments of Internal Medicine (2) and Neurology (2) and from other hospitals (2). In 202 cases (93%) there was apparent pulmonary malignancy and in 16 cases (7%) primary mediastinal pathology. During the study period CM was mandatory prior to any thoracotomy for pulmonary malignancy. No patients had had CM or other mediastinal surgery previously.

Table 1
Characteristics of 218 patients undergoing cervical mediastinoscopy in the period 1995 to 1999

Male/female	162/56 (74/26%)	
Median Age Range	65 years 29-80 years	
Percentage smokers*	72	
Percentage COPD patients	31	
Percentage smoking COPD patients	67	

* Smoking defined as active smoking or not stopped less than ten years prior to mediastinoscopy.

Table 2
Indications for cervical mediastinoscopy as a result of the final diagnosis

Pulmonary			
Malignancy	187		86%
Primary			
Squamous		97	
Adenocarcinoma		48	
Undifferentiated large cell		21	
Small cell		9	
Mixed type		3	
Bronchoalveolar		1	
Carcinoid		1	
CIS (carcinoma in situ)		1	
Metastasis		6	
No classifying diagnosis	11		5%
Unknown	9		4%
Benign diseases	7		3%
Tuberculosis		6	
Sarcoidosis		1	
Other malignancies	4		2%
Non-Hodgkin		1	
Hodgkin		1	
Thymoma		1	
B cell		1	

RESULTS

The final diagnosis after CM and thoracotomy is depicted in *table 2*. The results of CT scanning are depicted in *table 3*. Histology from Naruke stations 7 (subcarinal), 4R and 4L (right and left tracheobronchial angle, respectively) was obtained in 79% (154/195), 86% (171/198) and 66% (130/196), respectively. The combinations 7/4R, 7/4L and 7/4R/4L were biopsied in 68% (133/195), 57% (112/195) and 50% (98/195) of cases. The primary lung lesion was located 1.3 times more often in the right lung. Biopsies contained representative lymphoid tissue in 96% of the cases (193/201). Of 201 procedures, 51 (24%) contained malignant tissue in at least one station biopsied. There was no difference in malignancy yield whether all three stations were biopsied or not: 24% (23/98) and 26% (23/90), respectively. Of 60 patients who had enlarged mediastinal lymph nodes (i.e. >10 mm in the shortest diameter) as diagnosed on CT, 24 (42%) had malignant lymphoid tissue on CM. Of 21 patients without enlarged mediastinal lymph nodes on CT, four (19%) had malignant lymphoid tissue. Of 38 peripherally localised squamous cell carcinomas, four (12%) had mediastinal metastases proven by CM. Median hospitalisation time was three days, including day of admission and discharge. Significant morbidity occurred after 6% of the procedures (*table 4*). There was no mortality. Subsequent thoracotomy was performed in 145 patients (67%): 4 wedge resections (3%), 67 lobectomies (46%), 11 bi-lobectomies (8%), 49 pneumonectomies (34%) and 14 explorative thoracotomies (10%). In 73 cases (33%) CM was the final procedure. In 58, biopsy results excluded patients from thoracotomy: malignancy (n=51), benign disease (n=7). In two cases, thoracotomy was not performed due to complications related to CM: one patient developed congestive heart failure and one needed mechanical ventilation for several days after CM.

Table 3
CT scanning in 218 patients undergoing cervical mediastinoscopy

CT performed?	Unknown	15		
	Known	203		
	Performed		154	- 76%*
	Not performed		49	- 24%
Lymph nodes identified?	Unknown	4		
	Known	150		
	Identified		82	- 55%
	Not identified		68	- 45%
Identified lymph nodes enlarged?	Unknown	1		
	Known	81		
	Enlarged		60	- 74%
	Not enlarged		21	- 26%

* 59% (1995), 63% (1996), 74% (1997), 80% (1998), 79% (1999), respectively.

DISCUSSION

The optimal strategy for evaluation of the mediastinum in patients with apparently operable lung cancer is still a matter of debate.^{5,6} Some authors regard CM a safe procedure yielding essential information for proper staging. Therefore, it should precede any thoracotomy for NSCLC.⁶⁻⁸ With CM included in the preoperative staging procedure, percentages of explorative thoracotomies without resection (so-called 'futile thoracotomies') decrease to levels less than 5%⁸ and resection ratios increase from 0.60 to 0.94.⁹ Others have suggested refraining from CM in patients with mediastinal lymph nodes less than 1 cm on CT scan.⁵ Although CT is noninvasive and relatively simple to perform, it has clear limitations. Confirmation and exclusion of mediastinal lymph node metastases has shown to be not reliable and, therefore, not advocated as decisive in the assessment of mediastinal lymph nodes on a large scale.^{1,10} Moreover, it has been shown that CM is still obligatory in tumours and patients with certain characteristics even in the absence of enlarged lymph nodes on CT.^{10,11} In general, CM is considered essential in the preoperative staging of NSCLC, except for small (<3 cm) peripheral squamous cell tumours.¹²

Recent publications regarding the role of PET scanning in the staging of NSCLC are promising.^{1,3,13} There is a large body of evidence showing the superiority of PET over CT for staging of NSCLC in the mediastinum.¹⁴ Moreover, the combination of both procedures is more accurate than either procedure alone.¹⁴ The combination of CT and PET scanning may, therefore, reduce the need for CM. Two aspects of preoperative staging are improved by the use of PET scanning. First, its negative predictive value of mediastinal involvement is sufficiently high to allow CM to be omitted. Second, detection of unexpected distant metastases may make CM redundant. However, it seems unlikely that the introduction of PET scanning on

a large scale will totally replace CM. First, because PET-positive mediastinal locations will still need histological confirmation. And, furthermore, because PET's negative predictive value of mediastinal involvement is not high enough in cases of primary tumours directly adjacent to the mediastinum (i.e. central tumours).

We reviewed our results of CM and confirmed that CM is a relatively safe procedure with a high diagnostic yield, irrespective of the localisation of the primary tumour. The surgical complication risk (2.8%) was comparable with the literature: in two large studies (2259 CMs) there was a cumulative morbidity of 2%.^{7,15} When the medical complications are included, a 6% complication rate still seems acceptably low. Even indirect information is provided by CM on whether patients are suitable to undergo subsequent thoracotomy: in our series two patients developed serious medical complications rendering them unfit for further surgical therapy.

A malignancy yield of 24% in our series seems adequate from a historical point of view: Tantua found 32% in 1973,⁴ Luke *et al.* 30% in the period 1979 to 1984⁷ and Coughlin and co-workers 27% in the period 1975 to 1983.¹⁵ In recent publications malignancy yields are often unclear.^{5,10} Inoue found 10.8%, but studied small cell lung cancer only.¹⁶ We demonstrated a higher histological yield at the right tracheobronchial angle (4R) as compared with the left (4L). This may be explained by the fact that the primary tumour was more often located in the right lung. Another explanation may be better accessibility of the right tracheobronchial angle.⁴

In our series, only half the patients were biopsied in all three accessible stations. Although this seems rather low, this observation has been made before.¹⁷ No differences were found in diagnostic yield between cases in which biopsies were taken from all three stations as compared with

Table 4
Morbidity in 218 patients undergoing cervical mediastinoscopy in the period 1995 to 1999

		NUMBER	%
Surgical	Recurrent nerve palsy	6	2.8
	Significant drop in haemoglobin level	3	1.4
	Pneumothorax	2	0.9
		1	0.5
Medical	Pneumonia	7	3.2
	Congestive heart failure	3	1.4
	Atelectasis	1	0.5
	Transient ischaemic attack	1	0.5
	Atrial fibrillation	1	0.5
		1	0.5
Total		13	6.0

patients in whom less than three stations were biopsied. Nonetheless, a selection in stations to be biopsied should not be advised on the data of this study only.

In our hospital the use of CT increased during the study period (*table 3*). CT was not performed according to protocol and not performed in all patients. Since data were also either lost or insufficient, this study does not seem suitable for addressing any questions on the value of preoperative CT scanning for the assessment of mediastinal lymph node involvement.

In conclusion, CM is a safe procedure with a high diagnostic yield in the preoperative assessment of potentially operable NSCLC patients. With the evolving availability of PET scans the number of CMs will certainly reduce. However, in cases of central tumours, suspected mediastinal involvement on PET scan or the unavailability of PET scans, CM still should be performed.

NOTE

The data from this study were discussed at the Convention of the Dutch Society of Pulmonary Surgeons in Vaals, 2001.

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Skin lesions on the foot

M.G. Netea¹, J. van Aken², A.H. Mulder³, J.W.M. van der Meer¹

¹Department of General Internal Medicine, UMC St Radboud, Nijmegen, the Netherlands,

²Department of Internal Medicine, Hospital De Gelderse Vallei, Ede, the Netherlands,

³Department of Pathology, Rijnstate Hospital Arnhem, the Netherlands

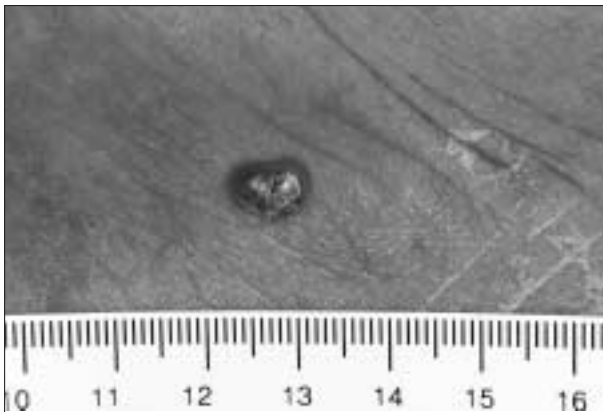
CASE REPORT

A Turkish 62-year-old man, since 1964 living in the Netherlands, known to have type 2 diabetes, presented with discrete bluish/purple skin lesions on his legs. Some of the lesions, especially on his feet were painful, whereas others were indolent. Otherwise, he was in good health. He had no fever and had not lost any weight. Except for insulin therapy he used no medication.

On examination a somewhat adipose man (weight 78.8 kg, length 175 cm) was seen with 14 discrete skin lesions with diameters of approximately 0.5 cm (*figure 1*), mainly on his lower legs. There were two lesion on the right thigh and one on his arm. Two lesions were exophytic. There were no palpable lymph nodes, and further examination was unremarkable.

WHAT IS YOUR DIFFERENTIAL DIAGNOSIS?

See page 269 for the answer to this photo quiz.



A colour version of this photo quiz can be found on our website
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J.W.M. van der Meer was not involved in the handling and review process of this photo quiz.

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Emergency resection of an extra-adrenal phaeochromocytoma: wrong or right? A case report and a review of literature

J.C. Bos^{1*}, A.W.F.T. Toorians², J.C. van Mourik³, R.J.M. Strack van Schijndel⁴

Departments of ¹Internal Medicine, ²Endocrinology, ³Surgery and ⁴Intensive Care, Free University Medical Centre, De Boelelaan 1117, Amsterdam, the Netherlands, *corresponding author, Academic Medical Centre, Department of Internal Medicine (F4), Meibergdreef 9, PO Box 22660, 1100 DD Amsterdam, the Netherlands, e-mail: j.c.bos@amc.uva.nl

ABSTRACT

Phaeochromocytomas are rare neuroendocrine tumours that produce symptoms through excess release of catecholamines. Treatment of choice is elective, complete surgical removal after pretreatment with α -adrenergic blocking drugs, to prevent dangerous haemodynamic fluctuations. In rare cases a 'catecholamine crisis' develops presenting with pulmonary oedema and circulatory shock. We report such a case of a patient with familial extra-adrenal phaeochromocytoma who successfully underwent emergency surgery. Pathophysiological mechanisms are discussed. Although pretreatment with α -adrenergic blocking drugs seems advisable in terms of morbidity and mortality, the concept is based on theory rather than clinical evidence. Surgical management of a catecholamine crisis is associated with high mortality rates. However, proof of better outcome by avoidance or discontinuation of emergency surgery is not available. Based on literature and on this case, we conclude that emergency surgery in phaeochromocytoma does not have to be structurally avoided and may be considered under life-threatening circumstances.

INTRODUCTION

Phaeochromocytomas (PCHC) are rare neuroendocrine tumours that arise from paraganglionic cells, either inside or outside the adrenals, and produce symptoms through excess release of catecholamines. Familial PCHC exists in syndromes such as multiple endocrine neoplasia (MEN) type 2A and 2B, Von Hippel Lindau disease

(VHL) and type 1 neurofibromatosis (NF1). The term 'phaeochromocytoma' refers to the brown (Greek: phaios) colour of the cells that emerges after oxidation of catecholamines with chromium salts. Its use should be restricted to clinically overt tumours, whereas the term 'paraganglioma' is used for the tumour independent of the occurrence of disease. The adrenal form of PCHC is considered 'classical'.¹

The clinical picture is that of acute illness, predominantly appearing as paroxysms of headache, sweating, pallor, palpitations, hypertension and anxiety, or a more or less moderate form with sustained hypertension,^{1,2} representing less than 1% of all causes of hypertension.³ In rare cases its presence is unveiled by the dramatic and sudden onset of a 'catecholamine crisis', a medical emergency often leading to death. Under these circumstances the disease presents with signs mimicking an acute abdomen, or severe sepsis with circulatory shock and pulmonary oedema (POD).⁴⁻⁶

Since PCHC is a curable cause of hypertension and a potentially fatal disease, a high level of clinical suspicion is needed to establish early diagnosis. Elective, complete surgical removal is the treatment of choice. It is generally believed that surgery should be preceded by pharmacological control of effects of excessive adrenergic stimulation with α (and β) adrenergic receptor antagonists, as this has shown to be associated with low morbidity and mortality. Surgery in undiagnosed and unprepared severely ill patients, however, is associated with high morbidity and mortality rates and should therefore be avoided.^{2,7}

We report a case of a patient with familial extra-adrenal PCHC, manifesting as acute onset POD and circulatory

shock, who successfully underwent emergency surgery without pretreatment with α (and β) adrenergic receptor blocking drugs and fully recovered. Pathophysiological background and decision making are discussed.

CASE REPORT

A 31-year-old woman was admitted in an acutely ill condition to our emergency room. Half an hour earlier she had suddenly started to feel weak and vomited several times. As the weakness progressed rapidly, she had decided to seek immediate medical help. On arrival she complained of muscle weakness and vague abdominal pain. Blood pressure was 160/80 mmHg, pulse rate 100 beats/min and regular, and body temperature 36.5°C.

In less than five minutes she became dyspnoeic and coughed up small amounts of bloodstained sputum. Blood pressure had dropped to 90/50 mmHg, pulse rate had increased to 130 beats/min and respiratory rate to 36 /min. The skin appeared normal, cardiac examination was unrevealing, but rales were heard throughout all lung fields. Examination of the abdomen was normal. The chest X-ray showed bilateral diffuse infiltration, compatible with oedema. Electrocardiography was normal. Arterial blood gas analysis, drawn while the patient was breathing oxygen at 10 l/min, showed pH 7.24, pCO₂ 40 mmHg, bicarbonate 17 mmol/l, base excess -9.8 mmol/l, pO₂ 67 mmHg and SO₂ 90%. The patient rapidly deteriorated into circulatory shock and respiratory failure and artificial ventilation was started while dopamine was given by vein, almost immediately followed by norepinephrine. At the same time blood cultures were drawn and broad-spectrum antibiotics were given intravenously.

Additional history-taking revealed that the patient had been feeling well that morning and that she had been healthy until then, except for episodic vomiting when she was younger. At the time, gastroscopy had turned out to be normal.

Erythrocyte sedimentation rate was 35 mm in the first hour, haemoglobin 6.1 mmol/l, white blood cell count $34 \times 10^9/l$, differential count 94% neutrophils, platelet count $229 \times 10^9/l$, sodium 144 mmol/l, potassium 3.1 mmol/l, creatinine 120 mmol/l, lactate 5.0 mmol/l and glucose 8.3 mmol/l. A specimen of urine tested for hCG was negative. Abdominal ultrasound revealed a round mass of 5 cm in diameter, located medially of the left kidney. The aorta appeared normal. New information became available when the patient's sister told us that she had had an operation five years earlier because of an adrenal tumour that was said to have been the cause of years of unexplained fainting. During transport to radiology the patient's pulse rate decreased and on arrival resuscitation was needed for cardiac arrest. CT scanning of the abdomen revealed a

round mass, 6 cm, retroperitoneally, caudally of the left kidney and another one, 4 cm, located ventrally of the sacrum. No abnormalities were detected in the adrenal glands, in the liver, nor in other abdominal organs. As an abdominal emergency was suspected, we decided to proceed to laparotomy. During the operation two tumours were found on the locations described above, but haemorrhage and/or rupture was absent. Both tumours were removed. During removal blood pressure remained low despite administration of high doses of dopamine and norepinephrine.

Postoperatively oxygenation remained difficult. The patient needed high positive end-expiratory pressure (PEEP) up to 20 cm H₂O in a prone position. Nevertheless, her condition ameliorated very quickly and she spent a total of only three days on the intensive care unit. After discharge her blood pressure remained normal. She told us she had endured attacks of palpitations, nausea and vomiting that had begun when she was about thirteen years of age. They occurred during periods of exertional activity and usually faded when this was stopped. Subsequently, she systematically avoided situations that would precipitate such an attack.

Histological examination of the specimens showed appearances typical of PCHC. There were no signs of haemorrhage or necrosis. In the blood sample drawn on arrival to the emergency room, before vasopressors were given, serum epinephrine and norepinephrine concentrations both exceeded the upper detection level of 10 nmol/l (normal <1.0) and 200 nmol/l (normal <10), respectively. Cultures of blood remained negative. Our patient left the hospital in good condition one week after the onset of her dramatic symptoms. There was no need for antihypertensive treatment. ¹³¹I-metaiodobenzyl guanidine (MIBG) scintigraphy showed no pathological accumulations of the tracer.

DISCUSSION

Although most clinicians recognise the classic symptoms of PCHC consisting of paroxysms of headache, palpitations, pallor, anxiety and hypertension, diagnosis appears to be far more difficult when less commonly encountered symptoms, such as nausea, abdominal discomfort, weakness and visual impairment occur. This is not surprising as the prevalence of the disease in the community is very low and its incidence is estimated between 1 to 8 per million.^{3,8,9} Unfamiliarity with the wide variety of symptoms can prove fatal when the tumour masquerades under the guise of POD or circulatory shock.

Our patient's illness presented dramatically so, initially without a history of the above-mentioned classical symptoms. The first step was to look for clinical disorders

associated with the adult respiratory distress syndrome (ARDS), which can be defined by the occurrence of bilateral fluffy infiltrates on chest X-ray, severe hypoxaemia unresponsive to low-flow oxygen and a normal pulmonary capillary wedge pressure (PCWP).¹⁰ Sepsis was considered first, being the most common cause of ARDS.¹¹ Although clinical features fitted this presumption, the acute onset and short course of the illness without appearance of petechiae, such as can be found in the Waterhouse-Friderichsen syndrome, and the lack of an immune-compromised medical history, made us doubt this. Secondly, rupture of an aortic aneurysm could be ruled out ultrasonographically. Finally, the question was raised whether the patient was suffering from an abdominal emergency: urine testing ruled out extra-uterine gravidity but both abdominal ultrasonography and CT scanning revealed two abdominal masses without signs of haemorrhage. These findings, combined with the history-taking of the patient's sister, made us think of extra-adrenal PCHC as a possible cause. Our patient, who had developed acute POD and circulatory shock that had proceeded to cardiac arrest, was now depending on mechanical ventilation with PEEP and increasing doses of cardiotoxic medication. Even though PCHC was already suspected at that time, we could not exclude the possibility of the patient harbouring an ischaemic or bleeding tumour of a different origin. Therefore, explorative laparotomy was performed. Two extraperitoneal tumours were found without signs of haemorrhage or rupture into the abdominal cavity. Nevertheless, it was agreed that both tumours, which had been clearly visualised by CT, should be removed given their surgical accessibility and, more importantly, given the patient's critical condition which was believed to be caused by these tumours. The removal was carried out without short-acting α -blocking drugs, as we decided that it was too dangerous to supply drugs that could possibly lower the patient's blood pressure further, while the diagnosis PCHC had not yet been made. No further problems were met during surgery. The postoperative period was difficult for a short period. POD and cardiovascular collapse have been reported as the sole manifestation of PCHC in naive patients, as well as in patients with established diagnosis. The pathophysiological background of POD and circulatory shock arising from catecholamine release is a debatable subject. It has been well recognised that high catecholamine levels can cause focal myocarditis in both humans and experimental animals.^{12,13} Foci of cellular necrosis that become fibrotic after prolonged exposure have been found on several occasions during autopsy.¹⁴ Cardiomyopathy, either dilated or hypertrophic, is also known to occur and downregulation of β -receptors and a net reduction of viable myofibrils have been proposed as causal factors.¹⁵⁻¹⁸ Although decreased myocardial function

has been reported,¹⁹ its clinical significance should be doubted as some studies lack information about pulmonary capillary wedge pressure (PCWP) and some reports indicate that POD can exist without co-existing increased PCWP, thus suggesting a noncardiogenic origin.^{5,7,20} These observations are confirmed by a report of a patient with POD and normal left ventricular function.²¹ Interestingly, a parallel phenomenon has been described for neurogenic pulmonary oedema (NPO). As in PCHC-related POD, massive catecholamine release takes place immediately after brain injury. Strong evidence for the onset of an intense, generalised, but transient vasoconstriction leading to a shift of blood from high-resistance systemic circulation to low-resistance pulmonary circulation, preceded by an only momentarily depressed cardiac function, has been provided by several studies.^{22,23} Nevertheless, increases in left atrial and left ventricular end-diastolic pressure seem to be attributable to the augmented cardiac work rather than on intrinsic alterations in cardiac function.²⁴ As massive infusion of epinephrine in dogs produced a pattern of haemodynamic response indistinguishable from that associated with NPO, it seems likely that indeed NPO and POD share a primarily noncardiogenic origin. As we have no data on our patient's cardiac function during her catecholamine crisis, we can not deliver clinical evidence to support this.

Fatal and near fatal periods of (transient) hypotension, with or without POD, have been observed in different situations, sometimes preceded by a hypertensive episode.^{5,25,26} Major discrepancy is known to exist between the largely increased blood pressure as measured in the aorta and the sometimes immeasurably low blood pressure as measured intra-arterially in the radial artery or with a sphygmomanometer. This observation reflects the extreme peripheral vasoconstriction mentioned above.²⁷ In addition, plasma volume in patients with PCHC appears to be significantly reduced as a result of prolonged high levels of catecholamines and therefore prompt intravascular filling is needed in case of hypotension.^{28,29} Basically, three major problems threaten the PCHC patient when confronted with anaesthesia and surgery: uncontrolled hypertension, hypotension and arrhythmia. Anaesthesia and surgery seem to be precipitating factors. Various anaesthetic agents, especially those with sympathicomimetic properties, can interfere with high circulating concentrations of catecholamines. Although halothane suppresses catecholamine release, it may sensitise the myocardium to the effects of catecholamines, promoting arrhythmia.^{30,31} Succinylcholine may stimulate the sympathetic ganglion and involuntary fasciculations may squeeze the tumour.³² Peritoneal insufflation of air and tumour manipulation during (laparoscopic) surgery can evoke release of catecholamines, thus promoting a crisis.³³ Hypertensive crises during surgery can be controlled by the

use of phentolamine, a short-acting nonselective α -blocking drug. Based on the afore mentioned about extreme peripheral vasoconstriction during a catecholamine crisis, it seems very likely that this condition can be treated with the same agent.³⁹ However, no clinical reports emphasising this could be found. Naturally, a balanced choice of anaesthetics and employment of an experienced surgeon minimises the chance of calamity.

In patients with an established diagnosis, preoperative preparation with α -adrenergic receptor blocking agents is widely accepted as the foundation for successful surgical treatment, as it is believed to minimise morbidity and mortality due to sudden haemodynamic changes. The concept of pretreatment has been developed since 1965, when the anaesthetic management of 92 surgical patients with PCHC was reviewed.^{34,35} Several retrospective studies have been published since then, emphasising the structural need for preoperative pharmacological treatment.^{36,37} Perry and co-workers, who reviewed another 33 patients in 1972, based their conclusions on the occurrence of less hypotension during surgery in pretreated patients, although this did not result in administration of significantly more vasopressors and fluids, nor in increased mortality in non-pretreated patients. However, several other studies failed to demonstrate the advantage of pretreatment.^{30,38} Scott and colleagues, who had already reviewed the cases of 27 patients with PCHC in 1965, found their surgical outcomes to be largely dependent on prompt recognition of symptoms and good-planning of operative removal. Pretreatment with α -blockade was not used in any of the cases.³⁹ Deoreo and associates postulated that preoperative adrenergic blockade is neither advantageous nor necessary as they described their experience with 46 non-pretreated patients operated on between 1952 and 1973.³⁸ More recently, Boutros *et al.* and Ulchaker *et al.* reviewed the surgical outcome of 63 and 127 cases, respectively. They found that using no preoperative medication was as effective as using α_1 -blockade and explained their findings

by suggesting that recent advances in anaesthetic and monitoring techniques, along with the use of faster-acting vasoactive agents, have improved the management of sudden changes in intraoperative haemodynamics.^{40,41} It may, however, be important to realise that to date, the concept of α -adrenergic blocking drugs has a theoretical basis rather than one founded on clinical evidence, since prospective controlled studies of large groups of PCHC patients are lacking.

A definitive statement regarding management of a so-called catecholamine crisis, without or with POD and circulatory shock, as in our patient, is even more difficult to make. Several reviews that involve autopsy-proven cases of patients with PCHC emphasise the hazardous and lethal course of unrecognised and untreated PCHC. St. John Sutton and co-workers described 54 autopsy-proven cases of clinically unsuspected PCHC and found that 27% of them had died from hypertensive or hypotensive crises precipitated by, or occurring during, minor operations for unrelated pathology.⁸ Scott *et al.* reported 27 cases, 16 of which, clinically diagnosed as having PCHC, were successfully operated. From the remaining 11 cases harbouring clinically unsuspected PCHC, four operations were eventually fatal and were thought to be directly related to the tumour.³⁹ Platts *et al.* did a survey of 62 PCHC related deaths and found that 16 patients died from anaesthesia and surgery (*table 1*).⁴² In addition, a number of case reports have demonstrated surgery in unsuspected PCHC to be a situation associated with high mortality.^{43,44} Consequently, it is generally believed that surgery should be discontinued whenever PCHC is suspected and that emergency resection is never indicated. It seems, however, important to underline that fatalities tended to occur in unsuspected PCHC and that some studies were only concerned with patients who had died and had had a complete autopsy. Nevertheless, nine cases of emergency resection in non-pretreated patients with a good outcome have been described, six of which are outlined in *table 2*.

Table 1
Overview of studies that are believed to confirm the high fatality risk during surgery in PCHC

REFERENCE	STUDY TYPE	NUMBER OF CASES	PERIOD	NUMBER OF DEATHS DURING SURGERY IN UNRECOGNISED PCHC (N = OPERATIONS)	NUMBER OF DEATHS DURING SURGERY IN RECOGNISED PCHC (N = OPERATIONS)
St. John Sutton <i>et al.</i> , 1981 ⁸	Retrospective; autopsy proven PCHC/paraganglioma	54	1928-1977	6 (11)	9 (9)
Scott <i>et al.</i> , 1965 ³⁹	Retrospective; cases of PCHC/paraganglioma	27	1950-1975	4 (4)	0 (16)
Platts <i>et al.</i> , 1995 ⁴²	Retrospective; deaths with PCHC/paraganglioma	62	1981-1989	9 (9)	7 (46)

Table 2

Overview of case reports of successful emergency surgery in preoperatively undiagnosed PCHC (in the first three cases PCHC was unexpected)

REFERENCE	CASE	SIGNS AND SYMPTOMS	MEDICATION DURING SURGERY	FINDINGS DURING OPERATION	OUTCOME	HISTOLOGY
Huston JR, <i>et al.</i> , 1965 ⁴⁵	Woman, 20 years Previously asymptomatic mentally retarded, resident of a mental institution	Sudden onset pain left abdomen. Shock, blood pressure 60/40 mmHg, pulse 160 bpm, cold and clammy skin, paralytic ileus White blood cell count 25x10 ⁹ /l	Levarteronol tartrate, plasma saline	Ileus, retroperitoneal mass, 13 cm diameter, left paravertebral gutter No increase in blood pressure while removing the tumour	Direct postoperative dependence on levarteronol tartrate, phenylephrine In addition corticosteroids and packed cells Good recovery	PCHC of left adrenal gland, major part advanced necrosis
Greaves DJ, <i>et al.</i> , 1989 ⁴⁷	Man, 22 years Blunt abdominal trauma	Acute collapse, blood pressure 110/60 mmHg, pulse 130 bpm, pale sweaty discomfort back Amylase elevated After five hours ARDS	Ketamine, suxamethonium, vecuronium, 50% nitrous oxide in oxygen and diamorphine	Normal duodenum and pancreas Vascular tumour 10 cm diameter over bifurcation of the aorta, suspected to be an extra-adrenal PCHC	Immediately after resection drop in blood pressure, adrenaline and isoprenaline Patient progressed well	Extra medullary PCHC of the organ of Zuckerkandl
May EE, <i>et al.</i> , 2000 ⁴⁶	Woman, 34 years Eight pregnancies and six deliveries, hypertension during last pregnancy Fall on ice with sudden onset right flank pain and upper quadrant of abdomen	Blood pressure 190/110 mmHg, pulse 62 bpm Then sudden fall in systolic pressure max. 60 mmHg, pain CT and angiography: right pararenal haematoma, active bleeding, coil embolised, hypertension and tachycardia Clinical diagnosis of PCHC ARDS	Nitroprusside and esmolol initially Not otherwise specified	Retroperitoneal haematoma right with a soft necrotic right adrenal mass 6 cm diameter	Inotropic medication for nine days Uncomplicated pulmonary course after ARDS, three days mechanical ventilation Ejection fraction 70% Lengthy convalescence time	Oedematous, haemorrhagic, partly necrotic PCHC of the right adrenal gland
Newell KA, <i>et al.</i> , 1988 ⁴⁸	Woman, 62 years Poorly controlled hypertension, diabetes mellitus, congestive heart failure, intermittent headache and backache Presentation with syncope, blood pressure 285/140 mmHg, fluctuating nadir 60/0 mmHg. PCHC suspected and confirmed	Deterioration with MOF, DIC, high fever. β -blocking agents, inotropics and broad-spectrum antibiotics	Broad spectrum antibiotics Supportive care with inotropic medication	10 cm right adrenal gland	Protracted postoperative course. Restoration of organ function but remaining quadriplegia and dysarthria	PCHC of right adrenal gland with foci of recent tumour necrosis

Newell KA, <i>et al.</i> , ⁴⁸ (continued)	Woman, 50 year Diabetes mellitus and seizures Presentation with nausea, vomiting, right upper abdominal pain Blood pressure 200/90 mmHg PCHC suspected and confirmed	Deterioration with hypertension, lactic acidosis, renal and respiratory failure high fever Further clinical deterioration of MOF with cardiac failure, with maximal medical therapy	Phenoxybenzamine, 7 cm mass in right adrenal gland phenolamin, nitroprusside and broad-spectrum antibiotics	MOF resolved quickly, postoperatively	Cystic degeneration in right-sided adrenal tumour without necrosistumour without necrosis	
Lamberts R, <i>et al.</i> ⁴⁹ (article in German)	Woman, 66 years Hypertension 18 months, PCHC diagnosed, however refused surgical treatment Currently myelography for sciatica-like pain	Paroxysm of headache, diarrhoea, dyspnoea, systolic blood pressure >200 mmHg Later no abnormal findings in physical examination Haemoglobin decreased ECG acute MI? Echocardiography regional wall movement disturbances Angiography normal Left adrenal mass 5,8 x 5,5 cm Within hours development of septic syndrome, fever and MOF	Dopamine, adrenaline, phenolamine, octreotide, veno-venous haemofiltration	No circulatory disturbances while removing the tumour Bleeding in tumour, extending to bursa omentalis	Proximal muscle weakness, no classifying histological description of muscle biopsy No further information	Necrotic, haemorrhagic PCHC of the left adrenal gland

ARDS = adult respiratory distress syndrome, DIC = disseminated intravascular coagulation, MOF = multiple organ failure, PCHC = phaeochromocytoma.

The three remaining cases (and abstracts) are written in Russian and French and are therefore not included. In two of the outlined cases PCHC was not suspected until surgery.⁴⁵⁻⁴⁹ Apparently, emergency surgery in PCHC can be successful. Based on the afore-mentioned cases and on our own case, it seems to us that it would be more rational to suppose that the optimal surgical approach for clinically suspected PCHC in emergency situations should be tailored to the circumstances. Under life-threatening conditions due to a PCHC catecholamine crisis, when stabilisation of the patient followed by pretreatment with α -blocking drugs does not seem to be a realistic option, emergency resection of the tumour(s) should not have to be *structurally* avoided. Early recognition of the hazards of PCHC is of major importance in this respect and, naturally, complete resection has to be achieved. Preoperative localisation of the tumour(s) by CT or MRI is therefore indispensable. Both CT scanning and magnetic resonance imaging (MRI) are highly sensitive (98 to 100%). Specificity depends on inclusion of patients with previous biochemically confirmed PCHC and has recently been reported as high as 98.4%. With T2-weighted MRI intensity of adrenal PCHC enhances, in contrast to liver tissue. It may also be superior

to CT scanning in demonstrating primary extra-adrenal and metastatic tumours.⁵⁰ Naturally, the positive predictive value will depend on the level of suspicion.

In conclusion, PCHC can produce life-threatening symptoms such as acute POD and circulatory shock, which may not be recognised as such. As in NPO, POD seems to emerge after a sudden fluid shift to the pulmonary vasculature and appears to have a primarily noncardiogenic origin. Treatment of choice is elective, complete surgical removal. Preoperative treatment with α -blocking agents – and in cases of arrhythmia with β -blocking agents – seems advisable in terms of morbidity and mortality, but we have to realise that the concept has a theoretical basis rather than one founded on clinical evidence. Emergency surgery in patients with life-threatening symptoms is generally dissuaded. Although it is certainly not without danger, it has proved to be successful in several cases and our case can be added to that category. The final outcome is probably also influenced by the level of clinical suspicion and by the anaesthetic and surgical technique used. Based on literature and on our own experience, we feel that emergency tumour resection in PCHC does not have to be *structurally* avoided and may be considered under certain circumstances.

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Haemosuccus pancreaticus, a rare cause of upper gastrointestinal bleeding

N.B. Pronk*, W.P. Haanstra, F.G.H van der Kleij

Department of Internal Medicine, Scheper Hospital, Emmen, the Netherlands, *corresponding author, Medisch Spectrum Twente, PO Box 50000, 7500 KA Enschede, the Netherlands, tel.: +31 (0)53-487 20 00, fax: +31 (0)53-487 30 85, e-mail: pronkniels@hotmail.com

ABSTRACT

Upper gastrointestinal bleeding is most commonly caused by lesions in the oesophagus, stomach or duodenum. In a minority of cases the bleeding originates from the pancreatic duct, and is known as haemosuccus pancreaticus. In many cases it is associated with chronic pancreatitis. Diagnostic strategies and therapeutic options are discussed.

INTRODUCTION

Bleeding from the gastrointestinal tract is most commonly caused by lesions in the oesophagus, stomach or duodenum. Rarely, the focus of the bleeding originates from the pancreatic duct, 'haemosuccus pancreaticus'.¹ We describe a patient with recurrent bleeding in the gastrointestinal tract, which appeared to originate from the pancreatic duct.

CASE REPORT

A 40-year-old male was admitted to our hospital after recurrent episodes of melaena over the past 14 days. Four days before coming to the hospital he had vomited blood, which had been followed by melaena the day prior to admission. He was not suffering from nausea or heartburn, but had recurrent complaints of upper abdominal pain radiating to the back. His medical history revealed chronic pancreatitis for three years before admission. The pancreatitis was most probably caused by ongoing alcohol abuse. He had also gone through a period of aggressive, psychiatric

behaviour. During the last two years he was frequently seen with anaemia after haematemesis or episodes with melaena. No diagnosis was made by repeated gastro-duodenoscopy. During one of these bleeding episodes a radioactive labelled erythrocyte nuclear scan suggested a bleeding near the jejunum.

On physical examination his blood pressure was 100/60 mmHg, pulse rate regular at 110 beats/min and central temperature of 38.2°C. His appearance was pale and malnourished. Rectal examination showed a combination of dark red blood and melaena. Laboratory results revealed a haemoglobin of 3.2 mmol/l (normal values: 8.5-11.0), a serum urea nitrogen of 5.9 mmol/l (2.5-6.4) and creatinine of 79 µmol/l (50-100). Liver function tests, serum amylase, glucose and prothrombin time were in the normal range. The patient underwent a gastro-duodenoscopy introducing the scope beyond the duodenum into the proximal jejunum. No sign of a bleeding was seen, the duodenal ampulla was normal and did not show blood. We decided to perform a computed tomogram (CT) angiography of the upper abdomen as this was a quick and less invasive procedure in contrast to angiography according to the Seldinger technique. Spontaneous filling of the pancreatic duct was seen after intravenous contrast had been administered (*figure 1*). It was concluded that a selective angiography of the splenic artery should be made to confirm the presence of a fistula to the pancreatic duct. In that case an attempt could be made to coil the aneurysm. However, active bleeding stopped making the chance of finding a fistula small. Until present, almost a year since admission, the bleeding has not reoccurred.

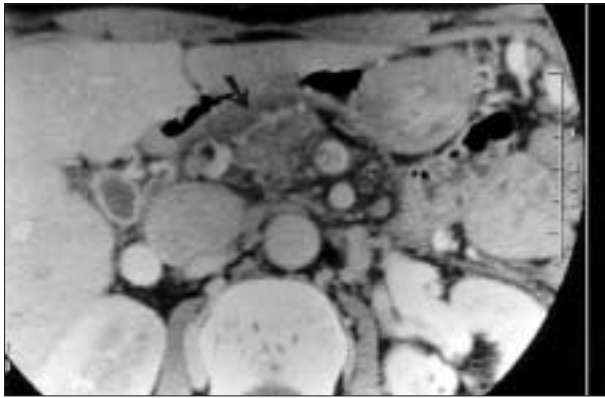


Figure 1
CT angiography; after administration of IV contrast, the pancreatic duct becomes visible (arrow)
The pancreatic head is slightly swollen and the pancreatic duct appears irregular and widened.

DISCUSSION

Haemosuccus pancreaticus, also termed Wirsungorrhaghia or pseudohaemobilia, is a rare cause of upper gastrointestinal (UGI) bleeding. It was first described by Lower and Farell in 1931 and named by Sandblom in 1970.¹ It is estimated that one in every 1500 UGI bleeds are caused by haemosuccus pancreaticus.² In most cases a history of chronic pancreatitis is present. The pancreatic inflammation is thought to lead to erosion of peripancreatic blood vessels forming an aneurysm or spurious aneurysm; secondary fistula formation from the aneurysm to the pancreatic duct causes bleeding. A second cause of bleeding is the direct erosion of a pancreatic pseudocyst into a peripancreatic artery or vein.³ It has been reported that chronic pancreatitis causes an aneurysm in adjacent arteries in 10% of cases.⁴ Rarely, an arteriosclerotic aneurysm or traumatic aneurysm, in most cases of the splenic artery, will rupture into a normal pancreatic duct.² Haemosuccus pancreaticus is often difficult to diagnose, partly because of its rarity and anatomical localisation. Also, the bleeding is often intermittent with sometimes long intervals in between.

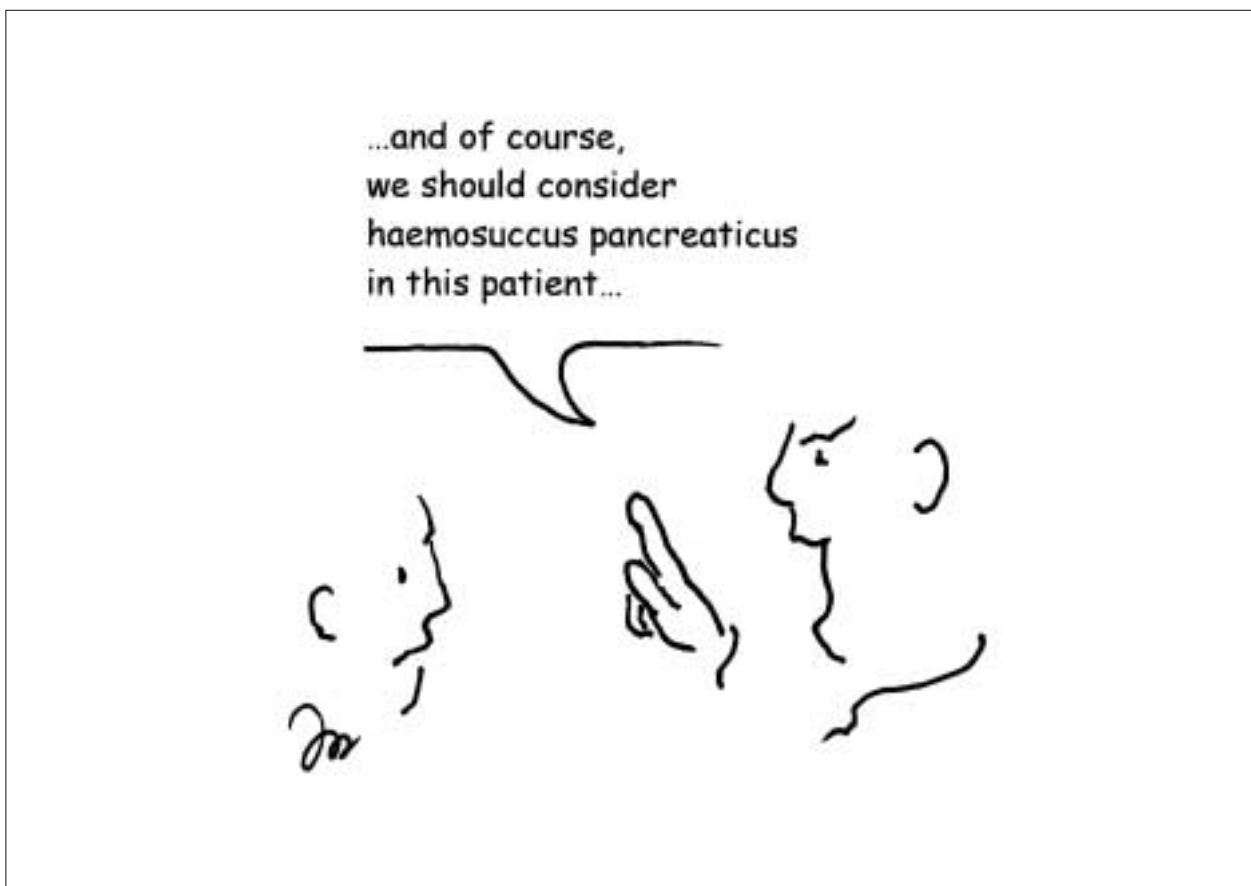
Endoscopy is essential to rule out other causes of UGI bleeding. In rare cases, active bleeding is seen coming from the duodenal ampulla.⁵ In some cases endoscopic retrograde pancreatography shows clots in a dilated pancreatic duct.⁶ On precontrast CT, the characteristic finding of clotted blood in the pancreatic duct, known as the sentinel clot, is seldom seen.⁷ Early angiography or a CT angiography is recommended in cases where endoscopy

is not diagnostic, identifying the presence of an aneurysm or pseudoaneurysm and sometimes showing the fistula between the pancreatic duct and an artery. In contrast sometimes only filling of the pancreatic duct is present as in our case.⁷ Because the bleeding is often intermittent, active bleeding as we saw is rare. Ultrasound of the abdomen can also contribute showing signs of chronic pancreatitis or giving an indication of the size of an existing aneurysm.⁷ Treatment of haemosuccus pancreaticus in a patient with a history of chronic pancreatitis has been surgical in most reports.^{1,5} In most cases proximal arterial ligation, distal pancreatectomy and splenectomy is performed in one surgical setting. When haemorrhage is associated with a pancreatic pseudocyst, pancreatic resection is appropriate. Duodenopancreatectomy is indicated for lesions in the head of the pancreas, and subtotal pancreatic resection for those in the body or tail.² Angiographic intervention of a haemorrhage from a true aneurysm or pseudoaneurysm in haemosuccus pancreaticus, either to stabilise the patient in order to perform elective surgery or as a definitive treatment, is possible. This could particularly be an option in elderly or high-risk patients. In more recent reports experience with this method of treatment has been reported.^{5,8,9} Embolisation of the splenic artery can be complicated by (partial) splenic infarction or abscess formation. Therefore, assessment of the collateral flow should be made prior to the embolisation,⁹ although abundant collateral circulation does not always prevent this complication.¹⁰ A third therapeutic option that has been reported in the treatment of a splenic artery aneurysm is implantation of stent grafts, reducing the risk of splenic infarction or abscess formation.^{11,12} This procedure can be difficult because of a sharp angle of the origin in the celiac axis, a small diameter and tortuosity of the splenic artery, thus making it difficult to introduce currently available stent grafts.¹¹

In conclusion, upper gastrointestinal bleeding in a patient with a history of chronic pancreatitis could be caused by haemosuccus pancreaticus. If gastroduodenoscopy shows no focus for active bleeding, angiographic investigations should be undertaken to search for peripancreatic artery aneurysms. Diagnosis is difficult because of intermittent nature of the bleeding with sometimes long intervals in between. Therapeutic options consist of surgery, embolisation or stenting. A therapeutic strategy should be discussed and also depends on the treating doctor's experience, and the age and the condition of the patient. In case of recurrent bleeding in our patient, we would initially try to embolise an existing aneurysm because of the experience of the radiologist in our centre.

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ANSWERS TO PHOTO QUIZ (ON PAGE 257)

SKIN LESIONS ON THE FOOT

DIAGNOSIS

With no particular differential diagnosis, the patient was referred to a dermatologist who took a biopsy of one of the lesions. The microscopy showed bundles of spindle-shaped cells with atypical nuclei and multiple mitoses. The cells were positive for CD34, vimentin and factor 8, and negative for keratin. SMA is positive in some areas of the biopsy. The picture, also showed on page 257, is diagnostic for Kaposi's sarcoma (*figure 1*). The biopsy showed a positive PCR for herpes virus type 8.

With this diagnosis the HIV status of the patient was tested and found negative. The CD4 lymphocyte count was $0.98 \times 10^9/l$. There were no signs of visceral lesions.

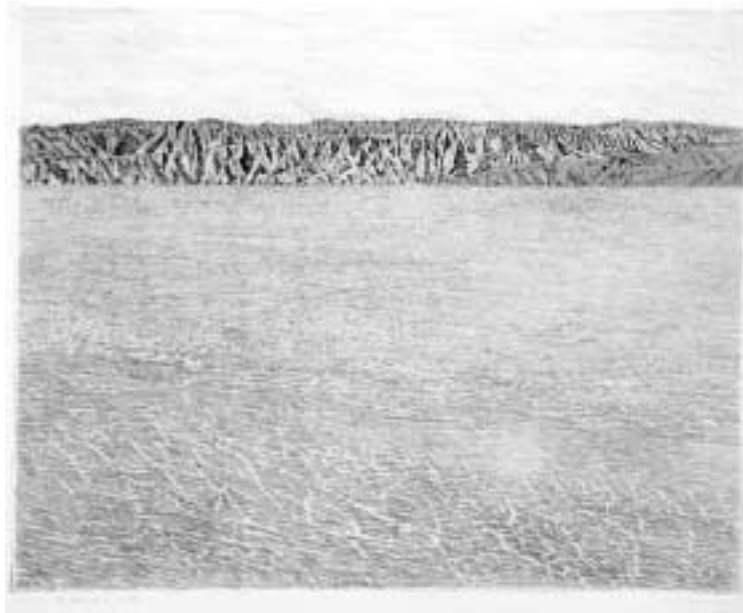
Thus, the diagnosis was Kaposi's sarcoma, in its classical form. This is a rare malignancy, which occurs in elderly males, especially from Mediterranean countries or with Eastern European background.¹ There is also a higher prevalence in Jews. Because of the pain, and since the lesions progressed in the course of two months, it was decided to treat the patient with interferon alpha 6 million IU s.c. three times weekly. This treatment led to regression of the lesions and cessation of pain. Because of malaise and fatigue, the treatment with interferon was stopped after three months. Over the past two years, the patient has been clinically stable, with a few new skin lesions.

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'Haya de Guadia'

Jan Hein van Rooy



This month's cover by Jan Hein van Rooy is inspired by 'The Hoya de Guadix', a kilometres wide folded wall of earth (a 'Cristo' avant la lettre). The landscape behind is invisible and inaccessible. The technique used, is a combination of etching and lithography. His work mainly exists of drawings, graphic and casein paintings. In general he is a landscape painter. Since 1992 he travels to

Spain, where he works with colourful, pigmented earth.

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Manuscripts submitted to the Journal should report original research not previously published or being considered for publication elsewhere. Submission of a manuscript to this Journal gives the publisher the right to publish the paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

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It is the author's responsibility to seek permission from the person or party concerned for the use of previously published material, such as tables and figures. In addition, persons who are recognisable on photographs must have given permission for the use of these.

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The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

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Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process number the pages; also we would appreciate seeing the line numbers in the margin (Word: page set-up - margins - layout - line numbers). Divide the manuscript into the following sections: Title page, Abstract, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

A *Covering letter* should accompany the manuscript, identifying the person (with the address, telephone and telex numbers, and e-mail address) responsible for negotiations concerning the manuscript: the letter should make it clear that the final manuscript has been seen and approved by all authors. Conflicts of interest, any commercial affiliations, consultations, stock or equity interests should be specified. In the letter 1-3 sentences should be dedicated to what this study adds. All authors should sign the letter.

The *Title page* should include authors' names, degrees, academic addresses, address for correspondence including telephone, fax and e-mail, and grant support. Also the

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The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

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The *Discussion* should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

Acknowledgement: All finding sources should be credited here. Also a statement of conflicts of interest should be put here.

References should be numbered consecutively (in square brackets) as they appear in the text. Type the reference list with double spacing on a separate sheet. References should

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Examples:

- [1.] Smilde TJ, Wissen S van, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. *Neth J Med* 2001;59:184-95.
- [2.] Kaplan NM. *Clinical Hypertension*. 7th Edition. Baltimore: Williams & Wilkins; 1998.
- [3.] Powell LW, Isselbacher KJ. Hemochromatosis. In: *Harrison's Principles of Internal Medicine*, 15th Edition, Braunwald E, Fauci AS, Kasper DL, et al. (eds). New York: McGraw-Hill; 2001. p. 2257-61.

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