The Th1-Th2 paradigm in 1998: law of nature or rule with exceptions

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Twelve years ago Mosmann and Coffman described individual CD4⁺ T-cell clones in mice that produced distinct profiles of cytokines [1]. A link between the different patterns of cytokine production of the two T helper subsets, termed Th1 and Th2, and their distinctive functions has been observed. Th1 cells are mainly involved in cell-mediated immunity, whereas Th2 cells are commonly found in association with humoral immune responses. In certain situations, Th2 cytokines are antagonistic to Th1 cell development and function and Th1 cytokines inhibit Th2 responses. This Th1-Th2 paradigm has stimulated intensive efforts to understand how CD4⁺ T cell activation program regulates the immune response towards Th1- or Th2-type. Moreover, targeted manipulations of the cytokine network have been suggested for the development of new therapeutic strategies to inhibit allograft rejection, to induce tolerance, to prevent and treat autoimmune diseases, and also to enhance vaccination efficacy. However, in many situations, mechanisms underlying the immune response obviously exist that seem to ignore the Th1-Th2 paradigm.

The Th1-Th2 axis

Strong evidence exists that both Th1 and Th2 cells derive from a common Th0 precursor. Genetic factors and the form, the dose, the adjuvant, and the route of antigen entry influence the microenvironment during the initial stimulation of Th0 cells by antigen-presenting cells (APC) [2]. The pattern of cytokines in this microenvironment dictates whether a Th0 cell will preferentially develop into a polarized Th1 or Th2 cell (Figure 1).

The principal early event that leads to Th1 differen-

tiation is the production of IL-12 by macrophages and dendritic cells responding to antigens or direct infection [3]. Polarized Th1 cells produce IL-2, IFN-γ, and lymphotoxin. These cytokines promote the development of cytotoxic T cells, which support delayed-type hypersensitivity reaction (DTH) and facilitate antibody-dependent cellular cytotoxicity (ADCC) serving as effector mechanisms against intracellular pathogens and allotransplants (Figure 1).

Stimulation of naive CD4⁺ T cells by T cell receptor ligation in presence of IL-4 leads to Th2 differentiation [4]. Besides naive T cells themselves, mast cells and a rare population of NK1.1⁺ CD4⁺ T cells are believed to be the initial source of IL-4. Polarized Th2 cells produce IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 and have important effects on immunoglobulin isotype expression. In mice, Th2 responses stimulate IgE and IgG1 production by B cells and activate eosinophils, thereby promoting anti-helminthic and allergic immune responses (Figure 1).

A large body of evidence suggests that Th1-dominated immune response inhibits the Th2-dominated arm and vice versa [5]. For example, the Th1 cytokine IFN-γ blocks antigen-induced proliferation of Th2 cells and inhibits IL-4- and IL-5-dependent B lymphocyte differentiation. In contrast, IL-4 inhibits Th1 cell development by antagonizing many of the activities mediated by IFN-γ.

The Th1-Th2 profile in transplantation immunity

It has been suggested that tolerance to an allograft may be achieved by immune deviation of CD4⁺ T cells to a polarized Th2 phenotype. In this scenario, allograft rejection is associated with immune deviation toward a Th1 phenotype. Indeed, classical tolerance induction by intraperitoneal injection of an antigenic protein in incomplete Freund’s adjuvant into mice within 24 h of birth triggers a vigorous Th2 immune response [6]. Treatment of neonatal mice with anti-IL-4 mAB during the induction phase reversed tolerance [7]. On the other hand, there is evidence that tolerance in murine transplant models can be mediated by T suppressor cells [8]. This combined suggests that transplantation...
tolerance could be due to specific suppressor T cells that might migrate into the target tissue and release Th2 regulatory cytokines into the local environment.

Variability of intragraft cytokine gene expression associated with allograft rejection

If one assumes that a Th1-dominated immune response is responsible for allograft rejection, a pattern of Th1 cytokines should be detectable in the rejecting graft in the absence of typical Th2-associated cytokines. Indeed, it was reported that rejection of murine pancreatic islet allografts was characterized by intragraft IL-2 and IFN-γ expression, whereas IL-4 mRNA was not detected [9]. However, rejection of human renal allografts was found not to be associated with enhanced expression of intragraft IL-2 [10]. Another group detected IL-4 in rejecting and rejected renal allografts [11]. Upregulation of both Th1 (IL-2, IFN-γ) and Th2 (IL-4 and IL-10) cytokines have been detected in spontaneously accepted mouse liver allografts [12]. In another study, however, these cytokines (IL-2, IL-4 and lymphotoxin) were reported to be expressed only in rejecting allografts [13].

There are several problems that might lead to misinterpretations of intragraft cytokine expression pattern. Immunohistochemistry analysis and detection of cytokine mRNA do not take into account that the majority of cytokine producing, graft infiltrating cells are not antigen-specific [14]. Cytokines which are detected by immunohistochemistry can bind to receptor-positive cells in addition to cells that actively produce the cytokines. Although IL-2 mRNA was detectable in renal allografts of rats made tolerant by donor-specific transfusion, graft infiltrating cells failed to produce IL-2 protein upon restimulation [15]. Recently, expression of some chemokine receptors was found to be specific for CD4+ T cell subsets: Th2 lymphocytes preferentially express CCR3, whereas CCR5 is expressed at high levels on Th1 and is virtually absent on Th2 cells [16,17]. These cell surface markers may allow more accurate analysis of Th1- or Th2-dominance on the basis of individual cells.

Manipulation of the Th1 : Th2 balance in experimental transplantation

The hypothesis that preferential induction of Th2 response would promote allograft survival is based on the ability of Th2 cytokines to down-regulate Th1 polarization and function [5]. IL-10 is one of the Th2 cytokines which has been intensively investigated in transplantation models. Indeed, allograft survival of non-vascularized murine neonatal cardiac transplants was prolonged after transduction with viral IL-10 gene [18]. However, mice treated with chimeric proteins
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T cells and enhances IL-2-induced cytotoxicity by these cells. The other cytokine supporting a Th2 polarized immune response is IL-4. However, transfection of tumours with the IL-4 gene resulted in a T cell-dependent tumor rejection, even after a syngeneic tumor transplantation [20]. Again, IL-4 can also elicit certain proinflammatory effects including increases in MHC class II expression, expression of B7 on B cells, chemoattraction of macrophages and expression of intercellular adhesion molecule-1 on endothelial cells. Moreover, it has been suggested that immune deviation to a Th2-like pattern may support chronic vascular rejection [21].

Is a deficiency of typical Th1 cytokines associated with prolongation of allograft survival? When allogeneic islets were transplanted into IL-2 knockout mice, all IL-2 knockout mice rejected their allografts at a speed that was only modestly delayed in comparison to normal mice [22]. In addition, cardiac, skin or islet allografts were vigorously rejected in IFN-γ receptor knockout recipient mice [23,24].

In contrast, acceptance of allografts has been achieved after blockade of co-stimulatory signals. CD28-B7 interactions provide co-stimulatory signals necessary for optimal T cell activation, whereas CD40-CD40 ligand signals co-stimulate B-cells, macrophages, endothelial cells and T cells [25,26]. Simultaneous blockade of both the CD28- and the CD40-pathway effectively aborted T-cell clonal expansion, which was associated with long-term acceptance of murine skin or cardiac allograft [27]. Moreover, this treatment prevented and reversed acute renal allograft rejection in primates [28]. Interestingly, blocking both co-stimulatory pathways inhibited expression of Th1 (IL-2 and IFN-γ); as well as of Th2 cytokines (IL-4 and IL-10) [27].

Concluding remarks

The Th1-Th2 paradigm has been very useful to understand and to describe several immunological phenomena with a particular set of cytokines. However, typical Th1 or Th2 responses represent an extreme of a continuum of cytokine potency profiles. Each cytokine mediates a wide range of biological activities, which may be either proinflammatory or anti-inflammatory, depending on the concentration, on the responding cell type and on the time point of action during the course of an immune response. In addition, there are factors other than cytokines environment which play important roles in influencing the type of immune response such as antigen-presenting cells and the co-stimulatory signals they deliver. Recent data suggest that induction of long-term acceptance of allografts by immunotherapy relies on the blockade of both Th1 and Th2 responses rather then a modulation of the immune response toward a polarized Th2 type and this may be achieved for example by blocking co-stimulation pathways.

The complex role of osteopontin in renal disease

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Introduction

Osteopontin is a multifunctional protein which is produced not only in bone and cartilage as its name implies, but also in the kidney, hence its alternative name uropontin [1,2]. Osteopontin is encoded by a single gene which contains seven exons and six introns, and it maps to human chromosome 4q22 and mouse chromosome 5. Several splice variants have been described. The 5' flanking region of the osteopontin gene contains numerous consensus sequences for transcription factors, including a vitamin D-response element (VDRE), a glucocorticoid response element (GRE), a ras-responsive element (RRE) and several AP-1 (c-jun–c-fos heterodimer) binding sites [3]. These transcription factor recognition sites explain the complex regulation of osteopontin expression by vitamin D, growth factors, cytokines and phorbol esters. Transcription of the osteopontin gene results in a protein with ~300 amino acids in most species. Osteopontin is a secreted phosphoprotein which contains two calcium- and two heparin-binding sites, and an Arg–Gly–Asp (RGD) cell adhesion motif. The RGD sequence is required for binding of osteopontin to integrin receptors. The principal integrin which binds osteopontin is the vitronectin receptor zvβ3. Additional receptors include the integrins zvβ1 and zvβ5 and the hyaluronan receptor CD44 [4,5].

Osteopontin expression in cells and in the normal kidney

Osteopontin is expressed by many cell types in vivo and in vitro, including epithelial and mesenchymal cells and cells of haematopoietic origin such as T cells and macrophages. Cultured renal tubular epithelial and mesangial cells have been shown to produce osteopontin in vitro, particularly when stimulated with growth factors, cytokines or 1,25(OH)2-vitamin D [6–8]. In the normal kidney osteopontin is constitutively expressed by segments of the loop of Henle, the distal tubule and by the papillary and pelvic epithelium of the renal fornix, with some differences in mouse, rat and human [9–12]. Being secreted by these distal nephron segments and the urothelium, osteopontin is also found in the urine [13].

The diverse roles of osteopontin

Osteopontin is a calcium-binding protein and plays an essential role in regulating bone mineralization [1]. Osteopontin inhibits calcium oxalate and hydroxyapatite growth in vitro and acts as an inhibitor of stone formation [14,15]. Calcium oxalate crystals can bind directly to kidney tubular epithelial cells and stimulate osteopontin synthesis, thereby possibly limiting further crystallization [16,17]. Being present in the urine, osteopontin could act as an inhibitor of kidney stone formation in vivo [13,18,19]. Indeed, osteopontin has been found in calcium oxalate kidney stones.

It has been suggested that osteopontin could also be an inhibitor of tissue calcification through its ability to bind calcium at high capacity and low affinity [2]. Osteopontin is found at sites of calcification in atherosclerotic plaques and calcified aortic valves where it possibly could limit further calcium deposition. Osteopontin has also been found to be associated with intrarenal calcifications, for example in a rat nephrolithiasis model (ethylene glycol intoxication) [20].

Apart from playing an important role as an inhibitor of stone formation, it has been demonstrated that osteopontin is important in cell adhesion and migration. In vitro studies have shown that osteopontin is capable of stimulating macrophage chemotaxis [5,21] and vascular smooth muscle cell (VSMC) migration [22]. Macrophage recruitment in tubulointerstitial...
renal disease has been linked to chemotaxis by osteopontin [23], and VSMC migration in response to osteopontin could be important in the pathogenesis of atherosclerotic plaque formation [2]. Subcutaneous injection of purified osteopontin results in a macrophage-rich infiltrate [24,25]. Furthermore, osteopontin is found abundantly in granulomatous lesions such as tuberculosis and silicosis, which also suggests a role for osteopontin in macrophage infiltration and granuloma formation [26].

Recent studies have pointed to yet another role for osteopontin, namely its antagonism of nitric oxide (NO) synthesis. In studies examining inducible NO synthase (iNOS) expression in mouse and human kidney tubular epithelial cells, osteopontin was found to inhibit iNOS and subsequent NO production [27,28]. Osteopontin could thereby influence the various functions of NO in the kidney, including the regulation of vascular tone, glomerular haemodynamics and salt and water balance. Osteopontin is also capable of suppressing NO production by macrophages, suggesting a role in antagonizing the NO-mediated cytotoxic action of macrophages [29].

Osteopontin in experimental renal disease states

Osteopontin has been examined in various experimental models of renal injury. In contrast, much less information is available regarding osteopontin in human renal disease states. Using immunofluorescence staining and in situ hybridization, we found a marked up-regulation of osteopontin mRNA and protein in the proximal tubules of CBA/CaH-kdkd mice with interstitial renal disease and also in MRL-Fas+ mice with lupus nephritis [30,31]. In the rat, several renal injury models have been examined for osteopontin expression, including renal ischaemia [32–34], ureteral obstruction [35,36], protein overload proteinuria [37], angiotensin II-induced tubulointerstitial nephritis [38], cyclosporin nephropathy [39,40], puromycin nephrosis [41,42], anti-Thy-1 nephritis [41], passive Heymann nephritis [43] and anti-GBM nephritis [44,44]. The common pattern in these renal disease models is that osteopontin is markedly induced and overexpressed by proximal tubules, both at the mRNA and protein level. The factors that promote the expression of osteopontin at these sites have not been determined but could involve cytokines and growth factors. In most of the studies, a correlation exists between the magnitude of osteopontin expression in areas of tubulointerstitial injury and the infiltration with mononuclear cells, suggesting that osteopontin could participate directly in the renal macrophage infiltration in vivo.

Direct evidence that osteopontin plays a role in renal interstitial macrophage infiltration comes from a study in a rat model of anti-GBM nephritis where an anti-osteopontin antibody led to a significant reduction in glomerular injury and recovery of renal function [44]. Using an osteopontin knockout (KO) mouse, it was shown in a preliminary report that the early macrophage influx after unilateral ureteral obstruction was significantly reduced in the osteopontin KO mice compared with control mice [45]. Osteopontin is certainly not the only chemotactic protein involved in macrophage accumulation, and additional proteins such as the chemokines do play a significant role as well.

Whether osteopontin is important in human tubulointerstitial inflammation and whether it functions as a macrophage chemoattractant in man will need to be determined in future studies.

References

The antiproliferative effect of glucocorticoids: is it related to induction of TGF-β?

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Introduction

Glucocorticoids (GCs) are used in treating disorders of heightened immunity such as transplant rejection, owing to their capacity to prevent T cell activation by a multitude of mechanisms, including induction of the expression of the immunosuppressive cytokine, transforming growth factor (TGF)-β. Similar to GCs, TGF-β is a pleiotropic mediator that modulates several aspects of the inflammatory response, and is a potent suppressor of T cell activation and cytokine expression. Because of their similar scope of action, it is of interest to examine the available evidence to resolve the issue.

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Introduction

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whether GCs mediate their effects, at least in part, via TGF-β.

**Mode of action of glucocorticoids**

Despite their wide-spread use, the mechanism by which GCs exert their anti-inflammatory and immunosuppressive effects is not completely understood. It is well appreciated that these effects involve both direct and indirect events [1]. In this regard, GCs reportedly act directly by: (i) blocking proximal events of T cell receptor (TcR) signal transduction; (ii) inhibiting the expression of leukocyte adhesion molecules and; (iii) suppressing cytokine production and action [1,2]. In addition to these direct effects, GCs act indirectly by: (i) inducing synthesis of lipocortin which inhibits phospholipase A2 activity, and hence the release of arachidonic acid from membrane-bound stores and the ensuing production of eicosanoids, (ii) promoting a Th2 cell activity through preferential blockade of Th1 cytokines, thus precipitating a long-lasting state of tolerance and, (iii) inducing the expression of TGF-β, an immunosuppressing cytokine which blocks cytokine synthesis and hence T cell activation [1,3]. Depending on the target cell and the specific conditions of activation, GCs may utilize more than one of the aforementioned mechanisms in exerting their effects.

**TGF-β as an immunosuppressant**

TGF-β is a highly conserved 25 kDa protein produced by mitogen-activated T cells, B cells, monocytes, and fibroblasts [3], and exerts predominantly immunosuppressive effects on the growth and function of T cells, B cells, and other mononuclear leukocytes [4]. Its production by activated T cells was suggested as one mechanism by which T cells limit their response to a particular stimulation [5].

Although the mechanism by which TGF-β exerts its immunosuppressive effects remains elusive, recent evidence suggests that the site of action of TGF-β is distal to IL-2 production [5], involving inhibition of the expression of high-affinity cytokine receptors and signalling through cytokine receptors largely as a result of blockade of Jak-Stat signal transduction pathway [5]. Furthermore, by preferentially suppressing Th1 but not Th2 cytokine production and stimulating IL-10 accumulation [4], TGF/β converts the immune response from a Th1 to a Th2-like phenotype [4], hence alleviating Th1-mediated disorders such as allograft rejection and autoimmunity. It remains to be determined whether promotion of Th2 activity by TGF-β is the resultant of its co-expression with Th2 cytokines (and hence its mis-classification as a Th2 cytokine), as was suggested, or due to frank transcriptional repression of Th1 cytokines.

**Mediation of the effects of glucocorticoids by TGF-β: supporting views**

In view of the inducibility of TGF-β expression by GCs, and the similarities between GCs inhibitory effects on cytokine expression and T cell activation and those induced by TGF-β, it was speculated that GCs indirectly mediate their anti-proliferative effect by inducing TGF-β expression [3,6,7]. This conclusion was based on the findings that: (i) the synthetic GC, dexamethasone (DEX), up-regulated TGF-β mRNA expression in non-stimulated [3] and mitogen-activated T cells [3], fibroblasts [8], osteoblasts [9], macrophages [1], and other cells [6,7] in a concentration and time dependent manner and, (ii) GCs anti-proliferative effect was abrogated by neutralizing anti-TGF-β antibodies [3,7].

GCs upregulation of TGF-β expression was a rapid event, being detected as early as 1 h after GCs addition, peaking at 4–6 h, and persisting for up to 24 h post-GCs addition. Induction of TGF-β expression by GCs occurred at the transcriptional [7,8] and post-transcriptional [6,9] levels; the latter involving stabilization of TGF-β mRNA, largely as a result of antagonism of TGF-β specific RNases [3]. In addition, upregulation of TGF-β expression potentiated GCs transcriptional repression at the level of GCs receptor complex interaction with the GCs responsive elements (GRE) DNA sites, thereby constituting a feedback system between TGF-β and GCs and resulting in profound immunosuppression.

**Mediation of the effects of glucocorticoids by TGF-β: opposing views**

In spite of evidence implicating induction of TGF-β as a mechanism by which GCs mediate their anti-proliferative effects, other reports provided arguments against direct involvement of TGF-β in GCs anti-proliferative effects. This was based on the findings that GCs did not upregulate TGF-β mRNA expression or protein secretion [1], but rather suppressed its expression. In addition, GCs reportedly antagonized a number of TGF-β effects, such as induction of prostaglandin synthesis and expression of the procollagen gene [10]. Furthermore, the mechanism of action of GCs was distinct from that of TGF-β, as revealed by the opposing effect of TGF-β and GCs (DEX) on induced nitric oxide synthetase mRNA expression stimulated by IL-1 [11], procollagen synthesis (inhibited by GCs but stimulated with TGF-β) [12] and EGF-induced c-fos mRNA expression (inhibited by GCs but resistant to TGF-β). It is noteworthy that, while GCs anti-proliferative effect required continued GCs presence since removal of GCs results in enhanced cytokine secretion and augmented T cell proliferation, that induced by TGF-β did not require its continued presence, as removal of TGF-β did not restore T cell proliferation. Thus, induction of TGF-β by GCs and,
accordingly, any role TGF-β play in mediating GCs effects must be addressed in the context of the cell type studied, stimulation conditions, and biological readout system utilized.

Conclusion

Both TGF-β and GCs are pleiotropic mediators that affect many aspects of cell growth, differentiation, and function. It is clear that the effects of GCs on TGF-β are not uniform, and that induction, suppression, or lack of effect of GCs on TGF-β transcription are dependent on the tissue studied and the state of cellular activation. Furthermore, conclusions drawn on GCs effect on TGF-β expression were largely based on in vitro studies, thereby questioning the physiological role of TGF-β in mediating GCs effects, since TGF-β may act as anti-inflammatory or pro-inflammatory cytokine depending on the micro-environment and its local tissue concentration. It remains to be determined whether induction of TGF-β expression is the principal or just a secondary mechanism by which GCs exert their anti-proliferative effects.

References


Renal biopsy in lupus nephritis—what for, when and how often?

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Introduction

Renal biopsy is being used extensively in systemic lupus erythematosus (SLE). However, there is not complete agreement about the need for renal biopsy at presentation. Some physicians argue that the clinical diagnosis of lupus nephritis is easy and that the prognosis and treatment may be assessed without the support of histological features. Even more controversial are the indications to repeat biopsy in patients with established lupus nephritis.

The diagnostic utility of biopsy

There are few doubts that the clinical and biological data are generally sufficient for diagnosing SLE nephritis. However, renal biopsy is the only tool that permits the correct classification of lupus nephritis. An SLE patient with haematuria, proteinuria and normal or subnormal renal function may have any class of underlying glomerular lesions and unpredictable severity of histological lesions. This may imply a different prognostic and different therapeutic approaches. Moreover, there are instances in which the diagnosis can be difficult. A few patients may present initially with renal disease and only exhibit systemic and biological manifestations of SLE later in their course. This is relatively frequent for patients with an underlying
membranous nephritis. In some cases, the biological markers of SLE may be absent for years and the differential diagnosis between idiopathic and SLE membranous nephritis can be established only by biopsy, which may show mesangial immune deposits, endothelial tubuloreticular inclusions, the typical virus-like particles, and sometimes subendothelial deposits. A different situation is represented by those patients who have no clinical evidence of renal involvement despite underlying glomerular lesions at biopsy. Usually, this silent nephritis is characterized by mesangial or mild focal proliferative lesions but, exceptionally, it may be associated with a diffuse proliferative glomerulonephritis.

The prognostic role of renal biopsy

In the past, it has been well documented that glomerular pathology is a reliable prognostic indicator in SLE. Older studies found a good correlation between the WHO classification and the short-term renal outcome. Of the five classes devised in the 1970s, patients with minimal changes (class I), pure mesangial lesions (class II) or focal proliferation limited to few glomeruli (class III) were found to have little probability of progression, independently of the type of treatment. More controversial was the prognosis for membranous glomerulonephritis (class V) which was usually considered to be an indolent disease although a review of the literature reported that 50 of 136 patients (36.7%) either died or developed renal failure [1]. There was consensus that patients with extended focal proliferation and those with diffuse proliferative glomerulonephritis (class IV) had the worst prognosis, but with marked variability in the clinical course. Because of this, efforts have been made to better define the histological features associated with a poor renal prognosis in patients with SLE nephritis. The original WHO classification was expanded by adding several sub-classes which took into account the extension of active and sclerosing lesions. This reinforced the prognostic significance of renal biopsy. A further contribution was made by the introduction of the so-called activity and chronicity indices which summed the semi-quantitative scores of certain histological features. The Bethesda group [2] reported that the semi-quantitative index of activity (which considered florid, potentially reversible, lesions such as fibrinoid necrosis, cell proliferation, interstitial inflammation, etc.) and the index of chronicity (which considered irreversible lesions such as glomerular sclerosis, interstitial fibrosis, etc.) could predict the risk of renal failure and orientate the therapy better than the WHO classification alone.

Recently, a number of studies reported an excellent long-term renal survival in patients with class IV nephritis, no different to that seen in patients with class II or III [3,4]. Other investigators were unable to duplicate the results of the Bethesda group with the use of activity and chronicity indices [5]. Does this mean that renal biopsy is useless in patients with lupus nephritis? We feel exactly the opposite. The fact that the different classes of SLE nephritis may now have a similar outcome is not due to the lack of prognostic differences but rather is caused by the choice of treating patients showing a severe histological pattern with appropriately aggressive therapies tailored on the basis of biopsy. In the early 1960, Pollak et al. [6] provided evidence that low-dose corticosteroids were unable to stop the downhill course of type IV nephritis while high-dose corticosteroids could improve the outcome of this disease. Since then, several therapeutical approaches have been suggested, but the principle has been the same: patients with diffuse proliferative glomerulonephritis should be treated aggressively in order to reach a clinical and histological quiescence of lupus activity. This approach has allowed excellent results to be achieved. While in the past most patients died or developed renal failure within 2 years of clinical onset (mainly because of undertreatment), more recent data reported a 10 year renal survival of ~90% in patients with class IV nephritis, at least in some series [3,4]. One of the main reasons for this dramatic improvement is that physicians realized how important adequate treatment is in patients with a biopsy-proven diffuse proliferative nephritis and elevated activity index, even when the clinical presentation is not too severe. However, in several cases, it can be difficult to assess the severity of the underlying renal lesions on clinical grounds only. An SLE patient with moderate urine signs may have a class IV lupus nephritis and active histological lesions. Inadequate treatment may favour the transformation of active lesions into sclerotic irreversible lesions. On the other hand, SLE patients with increased plasma creatinine may have important non-glomerular lesions but only mild glomerular lesions that do not necessitate aggressive therapy [7]. Thus, if the clinical assessment remains the cornerstone for planning therapy, renal biopsy can add vital information. A cautious approach may be justified in patients with class II and mild class III nephritis, although these patients must be followed carefully to catch possible transformations into more severe renal disease. Conversely, patients with extensive focal proliferation or with class IV nephritis should be treated aggressively in order to prevent irreversible lesions.

The same considerations are valid for the so-called activity and chronicity indices. The fact that several groups, including ourselves [3], could not find any correlation between the activity index at initial biopsy and renal outcome is not an argument against the prognostic significance of this parameter. Rather it is a further proof of how much an appropriate treatment can stop the natural progression to renal failure in patients with an active form of lupus nephritis. On the other hand, the lack of correlation between chronicity index and renal outcome in some series may be explained by the fact that the mean chronicity index had low values so that it was unlikely that mild chronic lesions could influence the outcome. In other series, the follow-ups were too short to see the unfavourable
impact of an elevated chronicity index, which may occur in the long-term.

**Should renal biopsy be repeated?**

With the prolonged survival of patients with lupus nephritis, the potential of histological findings at initial renal biopsy to predict long-term renal prognosis has diminished. It is well known that transformations from one class to another can be observed in up to 50% of repeat biopsies. Moreover, the signs of activity or chronicity may vary considerably over time as a consequence of the disease and its treatment [8]. Thus, it is difficult to know whether the histological presentation at initial renal biopsy remains or not the same over the time in a particular patient.

Unfortunately, little attention has been paid in the literature to the prognostic value of serial renal biopsies in patients with lupus nephritis. This is due in part to reluctance to repeat an invasive procedure which is not without potential complications. We feel that there are at least three main clinical settings, in which a repeat renal biopsy may provide useful information for the clinician. Group A: improvement in renal disease with persistent proteinuria. In this case, biopsy may help in deciding whether or not to reduce or even discontinue therapy. Group B: persistent or relapsing nephrotic syndrome. Here biopsy may allow one to see whether or not there has been a transformation and whether or not immunosuppression should be increased. Group C: slow worsening of renal function. Renal biopsy is the only investigation that is able to predict whether it may be worth administering aggressive therapy to reverse renal dysfunction.

Together with the group of Professor Zucchelli, we recently evaluated the significance of repeated biopsy in these three groups [9]. We found that ~50% of renal biopsies showed a transformation from the original class to another one. In group A there was a good correlation between improved clinical and histological features. Most patients showed a transformation towards less proliferative forms and the activity index was significantly reduced at repeat biopsy. In group B, histological lesions tended to remain unchanged, but there was a mild increase in the chronicity index. In group C, the worsening of renal function was associated with a variable and clinically unpredictable mixture of active and chronic lesions, justifying a rescue treatment in some, but not all, cases. Particularly in these instances there is no substitute for renal biopsy if one has to make decisions about therapy. In the same study, it was found that repeat renal biopsy was useful in providing prognostic clues for the long-term. Crescents in >30% of glomeruli and a chronicity index >5 at control renal biopsy were significantly associated with an increased risk of doubling plasma creatinine after a median follow-up of 10.5 years. It is of interest that no histological parameter found at initial renal biopsy had predictive value in the long-term.

**Conclusions**

Renal biopsy has a paramount role in the management of patients with lupus nephritis. No clinical or biological feature at onset uniformly predicts renal morphology, particularly the extent of renal lesions. In contrast, kidney biopsy can allow a correct diagnostic framing and can orientate the most appropriate treatment. This has certainly contributed to the considerably improved prognosis of SLE nephritis.

Whether and when renal biopsy should be repeated in SLE patients are still far from being established. Excellent results can be obtained by intensive clinical monitoring which allows prompt and aggressive treatment of renal flares, characterized either by an increase in plasma creatinine or by an increase in urine protein excretion [10]. However, only repeat renal biopsy allows the establishment of the long-term prognosis and the taking of important therapeutic decisions in particular cases. A good correlation between clinical signs and histology is usually found in patients with clinical improvement. Stable histological features are usually seen in patients with persistent nephrotic syndrome. Conversely, the histological picture in patients with impaired renal function is unpredictable. In these particular patients who are those at the highest risk of irreversible uraemia, repeat renal biopsy is not only fully justified, but is almost mandatory in order to evaluate whether or not to subject them to further aggressive treatments.

**References**

Cyst infection in polycystic kidney disease: a clinical challenge

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Introduction

With a prevalence of 1:500–1:1000, autosomal dominant polycystic kidney disease (ADPKD) accounts for 4–10% of patients on dialysis. Significant advances in the genetics and pathophysiology of ADPKD have been made over the years, and its complications are well documented. Infection remains one of the commonest of these.

Lower urinary tract infection and pyocystis

Symptomatic lower urinary tract infection affects 50–75% of all polycystic patients at some time. Treatment is simple and the condition is usually uncomplicated. Infection of the upper urinary tract is different, however. An autopsy study by McNamara in 1965 showed evidence of pyelonephritis in 56% of patients with ADPKD, even though clinical sepsis was not considered to be significant in many of these cases [1]. The infection of a single cyst within a polycystic kidney—pyocystis—is a well-recognized and potentially serious complication of ADPKD.

Cyst infection probably originates from the lower urinary tract, a theory that is supported by the observation that up to 92% of upper tract infections occur in females [2]. The infecting organisms are very similar to those causing lower urinary tract infections—the enterobacteriaceae. Treatment can be difficult, and significant morbidity, mortality and complications, notably the development of perinephric abscesses, have been described [3]. Diagnosis is not always simple, and supportive diagnostic aids such as imaging modalities are lacking. The choice of antibiotic for use in cyst infection can be difficult because of uncertainty over the diagnosis, penetration of antibiotics into cysts and fluid, and potentially resistant organisms. Sporadic research on the topic was reported from 1981 to the early 1990s, but interest in the topic has waned. It is therefore timely to re-examine this work.

The microbes

Microbiological results from small case series and anecdotal reports confirm that the commonest organisms involved in cyst infections are *Escherichia coli*, *Klebsiella*, *Pseudomonas* and *Proteus* species [4]. Infections with staphylococci [5] and streptococci [2] are rare, tuberculous and fungal disease even more so. The potential for haematogenous infection is supported by occasional reports, for example, of staphylococcal infection of a cyst in an intravenous drug abuser [5]. Anaerobic infection is uncommon, but perinephric abscesses [3] and aspirated cyst fluid have grown anaerobes [6]; the finding of low oxygen tensions within some cysts would support the potential for anaerobic infections [4].

Clinical presentation

Infection of the lower urinary tract and acute pyelonephritis in a patient with polycystic kidney disease are not usually diagnostic dilemmas; the same cannot be said for pyocystis. The clinical presentation is classically that of a discrete area of tenderness relating to one kidney. Torsion of or haemorrhage into a cyst may, however, present similarly. A more difficult challenge is the assessment of the significance of bacteremia in an ADPKD patient with only equivocal clinical signs. Many cysts do not communicate with the rest of the urinary tract and, therefore, associated lower urinary tract symptoms and bacteriuria may be absent. In a series of 15 such patients investigated by Schwab [2], however, attempts to isolate an organism from blood and urine were always successful. Furthermore, four patients from this group required nephrectomy which confirmed that cyst infection was caused by the same organism as that in blood or urine. If necessary, puncture of a suspicious cyst under ultrasonographic guidance may also be diagnostic.

Diagnostic problems

Diagnostic imaging is often less helpful than might be expected. Despite advances in available modalities, imaging of polycystic kidneys remains a problem, and attempts to find a single infected cyst therein is a ‘radiologist’s nightmare’. Polycystic kidneys often contain multiple cysts with very different contents, and pus and organizing haematomas can look very similar when scanned. Ultrasound, computed tomography and magnetic resonance imaging scanning image cystic kidneys well, but the confident identification of an infected cyst is often impossible. Radioisotope studies

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Penetration of antibiotics into cysts

Antibiotic treatment of infected cysts has variable effects; cure can be rapid, but resistant infection requiring radical intervention has been described. The reason for this is thought to relate to the transport characteristics of individual cysts and was first studied in detail by Muther and Bennett, who aspirated and analysed the contents of individual cysts from polycystic kidneys removed at nephrectomy or autopsy [7]. In each case, antibiotics had been given for 36–48 h before operation, but in only two cases was there thought to be an infected cyst. By calculating the cyst:serum sodium ratio, all cysts were divided into proximal (ratio > 0.9) or distal (< 0.2). Analyses of antibiotic concentrations in these cysts demonstrated that gentamicin, tobramycin and ticarcillin were undetectable in distal cysts, and only cephapirin was found in these cysts. Tobramycin was not found in proximal cysts either, whilst gentamicin and ticarcillin were. These findings bring into question the mechanism by which antibiotics might enter cysts.

Microdissection reveals that cysts of tubular origin communicate with the glomerulus proximally. One might suspect, therefore, that an antibiotic that is filtered at the glomerulus might accumulate in a cyst to the concentrations seen; quantitative studies, however, do not support this. Several authors previously have noted that even a single healthy nephron filtering at 1 × 10^{-6} ml/h would take a week or so to deliver 1 ml of filtrate to a cyst, and this is not enough to explain the antibiotic accumulation seen [7,8]. The inevitable conclusion is that much movement of antibiotics into cysts is transepithelial.

Whilst the exact mechanism of cyst development remains unknown, it is recognized that cysts retain some of the histological and physiological characteristics of the epithelium from which they seem to develop. Most cysts are ‘non-gradient’, and are thought to be derived from proximal tubular epithelial cells, between which are only loose apical junctions and leaky paracellular channels. Solute access to these cysts is by diffusion, and cyst contents are similar in composition to plasma. Active mechanisms to transport organic anions are found in some non-gradient cysts, but are not invariable.

Distal cysts, by contrast, are able to sustain considerable solute gradients. These cysts are composed of distal tubular cells which are joined by tight intercellular junctions, across which diffusion is severely limited. Hydrophilic lipid-insoluble antibiotics penetrate these cysts poorly, as might be expected; the transport of lipophilic antibiotics is not uniform, however, as the mechanisms for this are influenced by cyst fluid pH and the diffusion constant (pK_a) of the antibiotic used.

In a study of clindamycin accumulation in cysts, Schwab demonstrated that concentrations of the drug rose as cyst fluid pH fell, and related this to a relatively alkaline pK_a of 7.45 [8]. At a physiological pH, unbound drug will be almost one half ionized and one half not; being a lipophilic antibiotic, the non-ionized half will move relatively freely into cysts. Once inside a cyst, an acidic environment would result in ionization of the previously non-ionized half, thus making back-diffusion out of the cyst difficult (ion trapping). Extrapolation of this concept would also suggest that anionic antibiotics, notably the ß-lactams (which are also lipophobic), would not enter an acidic cyst. The conclusion from this work was that drugs with an alkaline pK_a should be used for cyst infections but, with cyst pH varying from 5 to 7.6, it is hard to be dogmatic with regards to this. Clindamycin levels in cysts of neutral pH approached very low levels comparable with the lipophobic antibiotic gentamicin; the benefit of the higher pK_a is obviously lost in this situation.

Practical guidelines for the selection of antibiotics

What, therefore, are the ideal characteristics of an antibiotic for use in cyst infection? In the absence of microbiological sensitivities, activity against Gram-negative bacteria is essential. High bioavailability, widespread distribution throughout body fluids and lipid solubility would be desirable. This simple set of requirements is actually surprisingly difficult to achieve, as illustrated in Table 1.

A final caveat to this is that much of the above comes from work on uninfected cysts. The pharmacokinetics of infected cysts may well be very different, and indeed one study has demonstrated that the normally non-penetrating aminoglycoside amikacin can be found inside infected cysts [10].

The choice of antibiotic to use in treating an infected polycystic kidney therefore remains an issue of debate. Current guidance suggests that systemic sepsis be

### Table 1. Antibiotic characteristics relating to cyst infection

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Lipid soluble?</th>
<th>Active against Gram-negative enteric pathogens?</th>
<th>Shown to accumulate in cyst fluid, or documented as curing cyst infection?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
</tbody>
</table>

Adapted from Sklar et al. [4] and Elzinga and Bennett [9].
treated with intravenous ampicillin and an aminoglycoside, whilst recognizing that the failure of aminoglycosides in particular to penetrate cysts be used almost as a diagnostic tool. Failure to respond to these antibiotics would, therefore, suggest cyst infection, and therapy should be adjusted appropriately. With their potential for toxicity, however, aminoglycosides may be withheld, particularly when renal function is compromised; ciprofloxacin would appear to be a reasonable alternative.

One case report has demonstrated its efficacy where other antibiotics have failed [11], and local experience has found it to be useful in at least two cases. Where a cure seems impossible, intervention may be required, by surgical or radiological drainage, or the release of obstruction. In severe cases, or in those with persistent recurrent infection, nephrectomy may be required.

The changing pattern of cyst infection

Within our practice, the need for drastic measures in controlling pyocystis has declined considerably over the years; indeed the incidence of serious infection complicating ADPKD seems to be decreasing. A 1983 study of polycystic patients identified an infection rate of 26%, nephrectomy being needed in 45% and death occurring in 7% [12]. A similar study in 1996 suggested rates of 16, 12 and 0%, respectively [13]. The reasons for this are not known, but can be speculated. The knowledge gained from reported studies and the use of newer antibiotics may have had its impact, as will have improved microbiological services. The rapid treatment of lower urinary tract infection by primary care services in the community, and the widespread use of antibiotics as part of the treatment of acute episodes of loin pain may well have been a major influence.

Control of serum phosphate in patients with renal failure—new approaches

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Introduction

Impaired phosphate excretion with resulting hyperphosphataemia is one of the earliest consequences of chronic renal failure. Hyperphosphataemia plays an important role in the development of secondary hyperparathyroidism. Both secondary hyperparathyroidism and high serum phosphate levels (in association with hypercalcaemia in some cases) are associated with significant morbidity. Consequently, prevention and treatment of hyperphosphataemia is one of the major treatment goals of chronic renal failure.

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**Dietary interventions**

The first modality of therapy is restriction of dietary phosphate intake. The usual Western diet contains 800–2000 mg/day (26–67 mmol/day) of phosphate, depending mainly on the protein content of the diet [1]. The major sources of dietary phosphate include meat, fish, dairy products, certain vegetables, and soft drinks. Processed foods usually contain significantly more phosphate than natural products.

The phosphate content of the different diets prescribed to patients with renal failure varies between 550 and 1100 mg/day (18–36 mmol/day) [2,3]. Decreasing dietary phosphate is very difficult to achieve without significant reduction in protein intake. Consequently, a diet that may help to maintain phosphate balance and normal serum phosphate levels for a prolonged period carries the risk of malnutrition in patients with progressive renal failure. Based on the evidence available, severe protein restriction cannot be advised in the treatment of progressive renal disease.

In patients with mild to moderate renal failure, a protein intake of 0.8–1.0 g/kg/day may be a reasonable target that is both safe and acceptable for the patients. In patients on maintenance dialysis, who are usually catabolic, a diet containing more protein, 1.0–1.2 g/kg/day, is needed to achieve neutral nitrogen balance [4]. However, the above diets may contain approximately 800–1200 mg (26–40 mmol) of phosphate. As the intestinal absorption ranges between 40 and 80% of the ingested phosphate, the amount of absorbed phosphate varies between 10 and 30 mmol/day or 70–210 mmol/week and usually cannot be matched by the decreasing phosphate excretion of the failing kidney or by the dialytic phosphate removal in patients on maintenance dialysis (see below).

**Phosphate binders**

As dietary restrictions are usually insufficient in maintaining phosphate balance and normal serum phosphate levels, phosphate absorption from the gut needs to be reduced. This can be achieved by the use of phosphate binders taken with meals. After recognition of the severe toxic effects caused by chronic administration of aluminium-containing medications, the use of these has declined markedly. There seems to be no safe dose of aluminium that is not associated with progressive aluminium accumulation in patients with renal failure. However, in approximately 15–25% of patients on maintenance dialysis, their application cannot be avoided completely [5].

Magnesium-containing antacids can reduce phosphate absorption effectively, but their use has generally been avoided because of the risk of hypermagnesaemia and the frequent development of diarrhoea.

Currently calcium carbonate and acetate have been used more extensively as phosphate binders. The dose of calcium carbonate can be increased gradually up to 15–20 g/day, until serum phosphorus concentration is decreased to normal or close to normal levels, or hypercalcaemia ensues. Recent reports suggest that calcium acetate is a more effective phosphate binder than is calcium carbonate [6]. It is known that its effect does not depend on the gastric acid secretion. This is an advantage as many patients with advanced renal failure are taking H2 blockers or have achlorhydria. The incidence of hypercalcaemia, however, appears to be the same with both [6]. Although calcium salts are effective phosphate binders, they are not without side-effects, including frequent development of hypercalcaemia and gastrointestinal symptoms. The combination of hypercalcaemia and hyperphosphataemia may lead to extraosseous calcifications and possibly calciphylaxis. As well, patient compliance is frequently difficult to achieve.

Recently a significant phosphate- and parathyroid hormone-lowering effect of calcium-alpha-ketoglutarate was demonstrated both in animals and in patients on chronic dialysis therapy. In a randomized crossover study it caused fewer hypercalcaemic episodes than did calcium carbonate [7]. However, as it is very expensive, it is unlikely to become first-line therapy for hyperphosphataemia.

Recently several reports were published on the use of a novel agent, poly (allylamine hydrochloride) (RenaGel), which contains neither aluminium nor calcium. It also seems to modulate serum lipid levels favourably, lowering total cholesterol concentration. This agent is equally efficacious in phosphate binding as the calcium salts are [8]. Further studies, however, on the safety and efficacy of RenaGel are needed to find its final place in the treatment of hyperphosphataemia.

Another agent, phosphonophosphoric acid (PFA) was shown to inhibit sodium-dependent phosphate transport in the proximal tubule of the rat and thereby increase the fractional excretion of phosphate [9]. PFA is nephrotoxic; therefore it cannot be used in humans for the treatment of hyperphosphataemia. Similar drugs, however, might prove to be useful in patients with mild to moderate renal failure.

**Dialytic phosphate removal**

The last modality of treatment of hyperphosphataemia is enhanced removal of phosphate by dialysis therapy. The average dialytic phosphate removal is 20–40 mmol/session with haemodialysis, i.e. 60–120 mmol/week, and 70–85 mmol/week with CAPD. This means that many patients on dialysis are in net positive phosphate balance, even with optimal dietary compliance.

Although it had been suggested that altering the buffer in the dialysate may increase the amount of phosphate removed, several papers later demonstrated that modification of the buffer does not lead to increased phosphate removal [10]. Haemofiltration or haemodialfiltration, by increasing the ultrafiltration
rate and thereby taking advantage of convective transfer, seem to be somewhat more effective than conventional haemodialysis [10], although the amounts removed were still inadequate to maintain normal serum phosphate levels. Several reports have shown that the dialyser surface area and the predialysis serum phosphate level were the major determinants of dialytic phosphate removal. Also it has been shown repeatedly that the type of dialyser membrane used did not affect the amount of phosphate removed [10,11].

From kinetic studies we know that during haemodialysis the serum phosphate level drops rapidly in the first 1–2 h of treatment, and then reaches a plateau. The amount of phosphate removed decreases significantly in the second half of dialysis. It has also been well documented that serum phosphate concentration rises relatively quickly in the first few hours after termination of dialysis (rebound phenomenon) [12]. Accordingly, it was suggested that prolonging the duration of dialysis or using larger, higher efficiency dialysers would not increase phosphate removal further.

As a result, there has been a search for increasing the efficacy of dialysis therapy to achieve better control of hyperphosphataemia. In Italy, Buoncristiani and co-workers have extensive experience with the use of daily short dialysis sessions. They were able to achieve remarkable blood purification and showed that many of the complications of uraemia have been ameliorated by this new method [13]. In one of their early reports they suggested that daily short dialysis is effective in controlling serum phosphorus as well [13]. However, currently the data published on this method is inadequate to assess its effect on serum phosphate fully.

A different approach to altering conventional dialysis prescription has been taken in France. Charra et al. have been treating patients with end-stage renal failure with prolonged dialysis prescription (8 h three times weekly). This group has achieved superb results in terms of blood-pressure control and patient survival [14]. However, detailed discussions of metabolic consequences of prolonged dialysis (such as control of hyperphosphataemia) have not yet been published.

We have recently summarized our results with a novel dialysis modality, nocturnal home haemodialysis (NHD). In this setting patients dialyse themselves at home, 8–10 h per night, 6 nights a week [15,16].

We found that the net dialytic phosphate removal during one session with conventional haemodialysis (CHD), as compared to NHD, was almost identical, at about 25 mmol/session. Consequently, the cumulative weekly phosphate removal, due to the more frequent dialysis sessions, was twice as much with NHD as with CHD. The removal of 25 mmol/day phosphate with dialysis alone would allow for our patients to consume an average ‘western diet’ containing 40–50 mmol phosphate/day and still remain in phosphate balance (assuming that about 50% of the dietary phosphate is absorbed).

The long-term efficacy of NHD in controlling serum phosphate was also demonstrated. We showed that within 5 months all patients changed to NHD became almost normophosphataemic. In fact they were able to maintain acceptable serum phosphate levels (serum phosphate < 1.8 mmol), while increasing their phosphate intake significantly, as well as discontinuing all their phosphate binders. During the study period the mean phosphate intake rose from 25 to almost 40 mmol/day with serum phosphate levels < 1.8 mmol. This was achieved by dialysis therapy alone.

Conclusions

In spite of advances in the therapy of renal failure, the problem of controlling serum phosphate has not yet been solved. One important method is to find new phosphate binders that have fewer side-effects so that patient compliance may be maintained. An alternative approach is to find novel dialysis prescriptions by which dialytic phosphate removal could be enhanced to meet the phosphate content of a fairly liberal diet containing more than 1 g/kg protein daily. Recent results utilizing daily dialysis protocols show promise in meeting some of these goals.

References

Anorexia in patients with chronic renal failure—progress towards understanding the molecular basis

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Introduction

Among the commonest symptoms in patients suffering from uraemic intoxication are anorexia, nausea and vomiting, which typically develop when the glomerular filtration rate is <10–15% of normal and increase in severity with progression towards end-stage renal failure. Data from the MDRD study (Modification of Diet in Renal Disease) in the US [1] show that an adaptive reduction in the intake of protein may start early during the development of renal failure (glomerular filtration rate 25–30 ml/min), associated with reduction in energy intake and various nutritional parameters. More recently, a prospective analysis of protein intake by patients with chronic renal disease was reported, showing that patients tended to restrict their protein intake spontaneously (evaluated from 24 h urea excretion) with the progression of renal failure, to <0.6 g/kg body weight/day, when creatinine clearance fell below 10 ml/min [2].

A plausible explanation of this is that inhibition of appetite is caused by retention in body fluids of one or more toxic substances as a consequence of reduced renal function. Conservative treatment of renal failure with a low protein diet may alleviate temporarily or forestall uraemic symptoms in the form of anorexia, nausea and vomiting, suggesting that one or more of these toxins are generated by breakdown of dietary protein. Signs of malnutrition are common in end-stage renal disease patients at the start of maintenance dialysis treatment and appear to be prognostically unfavourable [3,4].

After dialysis therapy is started, these symptoms are partly relieved or they disappear within a few days. Such observations indicate that one or more uraemic toxins causing these symptoms have a molecular size which permits their diffusive transport through conventional cellulosic dialysis membranes, i.e. a molecular weight <10000 Da.

Nutritional requirements in uraemia

The requirements for protein appear to be higher in dialysis patients than in healthy persons. This has been attributed, inter alia, to dialytic losses of amino acids and, in peritoneal dialysis, also protein. Other factors which may enhance net protein catabolism and increase protein requirements are low energy supply, metabolic acidosis and co-morbid conditions (peritonitis, other infections, systemic disease, etc.) [5,6]. Generally, a protein intake of 1.2 g/kg body weight/day is recommended for dialysis patients, i.e. much higher than the level of protein intake (0.75 g/kg body weight/day) which is considered safe for healthy adults.

Energy requirements depend on the level of physical activity, an intake of 35–40 kcal/kg of body weight/day being recommended for adults not performing heavy physical exercise. Ikizler and Hakim recently have reported that resting energy expenditure (REE) is actually higher in haemodialysis (HD) patients, even on non-dialysis days, compared with age-, sex- and body mass index-matched normal controls [7]. However, other studies in HD and continuous ambulatory peritoneal dialysis (CAPD) patients do not show that energy expenditure for a given physical activity differs from that in normal subjects [8].

Nutritional intakes in dialysis patients

The mean intake of protein is <1 g/kg of body weight/day in a large proportion of patients on maintenance HD [9], which suggests that requirements for optimal protein intake are not met. A large proportion of CAPD patients also ingest considerably lower amounts of protein than the recommended intake [10].
The energy intake, like the protein intake, is often also low in groups of HD patients, i.e. the mean intake has been reported to be 26–29 kcal/kg of body weight/day [11]. The total energy intake may also be low in CAPD patients, despite the continuous supply of energy by glucose absorbed from the dialysis fluid [11].

**Anorexia, dose of dialysis and residual renal function**

Several studies in HD and CAPD patients report a correlation between the dose of dialysis for small-molecule removal (Kt/Vurea) and the protein intake, especially in the lowest dose intervals [12]. It has been found that the relationship between Kt/Vurea and protein intake in CAPD patients, estimated from the urea appearance rate, differed from that in HD patients [12]. At the same low Kt/Vurea levels, the estimated protein intake was higher in CAPD patients than in HD patients and the protein intake increased more for the same increase in Kt/Vurea in CAPD than in HD patients. In small groups of dialysis patients, it has been shown in prospective studies that an increase in the dose of dialysis results in a significant increase in the estimated protein intake [13].

The intake of protein was assessed by urea kinetic modelling, based on the concept that the amount of urea generated reflects the net amount of protein catabolized which gives an estimate of the protein intake, at least when patients are in metabolic steady state and not markedly catabolic or anabolic. It has been argued [14] that the relationship between Kt/Vurea and protein intake (urea appearance) reflects mathematical coupling rather than a biological relationship, since the two variables are, to some extent, independent: both are normalized to body size and both are dependent on urea determination in plasma pre- and post-dialysis. However, some data show a relationship between the quantity of urea removed and protein intake, calculated from the dietary records and interviews. In CAPD patients, this relationship could be demonstrated even when the quantity of urea or creatinine removed was not normalized to body size [10].

An attractive hypothesis has been proposed to explain the difference in the relationship between Kt/Vurea and protein intake (estimated from urea appearance) in CAPD patients compared with HD patients, i.e. that molecules of a molecular size larger than urea—so-called middle molecules—cause anorexia. Such hypothetical molecules would be dialysed more efficiently by the peritoneal membrane than by an HD membrane. The hypothesis that middle-molecule compounds cause anorexia is also in keeping with the observation in HD patients by Lindsay and Spanner [12]. These authors found that protein intake, estimated from the urea appearance, increased proportionally more for a given increase in Kt/Vurea in patients treated with high-flux than with low-flux membranes.

At the start of maintenance dialysis, most patients have some residual renal function which seems to be better preserved on CAPD than on HD. After the start of CAPD, the patients generally experience increased well-being and improvement in appetite. However, some patients may become underdialysed and fail to thrive, along with a reduction in residual renal function. In most studies showing a correlation between Kt/V (or creatinine clearance) and protein intake, the sum of peritoneal and renal Kt/V or creatinine clearance was used in the calculation. However, multiple regression analysis of data in CAPD patients from our unit showed that the residual renal function correlated with the protein intake, whereas the dose of peritoneal dialysis had no significant effect [10]. These results suggest that the residual renal function is more important for appetite than the dose of peritoneal dialysis. The pivotal role of residual renal function is supported further by longitudinal studies showing that total body nitrogen decreases during the first 2 years of CAPD treatment, concomitantly with a decrease in protein and energy intake [15] and that protein intake (estimated from urea appearance) decreases, along with the loss of residual renal function [16]. An international cross-sectional multicentre study showed that lack of renal function is associated with anorexia and symptoms of severe malnutrition [17].

These findings are in line with our hypothesis that one or more compounds that cause anorexia in uremic patients are normally excreted by the kidneys. This hypothesis is supported by our observation [18] that food intake in the rat is inhibited after intraperitoneal injection of a 1000–5000 Da middle-molecule fraction, isolated from normal urine and corresponding to the fraction from uremic plasma ultrafiltrate, which has a similar effect.

**Anorexia and the middle molecules**

We assessed food intake quantitatively by measuring the consumption of intragastrically infused nutritional solutions in conscious, free-moving rats. This model has been used earlier in neuropharmacological studies of food intake, and has proved to be accurate and highly reproducible, especially because the same group of animals can be studied repeatedly on consecutive days and can serve as their own controls.

Using this new method as a bioassay, we have started to isolate and characterize factors in uremic plasma and normal urine which suppress appetite. We collected and pooled ultrafiltrate obtained from end-stage renal failure patients at the beginning of their first dialysis treatment. Ultrafiltrate from pooled normal plasma and normal urine was obtained in vitro by filtration through the same type of dialyser used in the patients. Uraemic ultrafiltrate and normal urine, which had not been concentrated or otherwise modified, injected into rats with normal renal function, inhibited the ingestion of carbohydrate and protein. The absence of an effect on food intake of the non-uraemic ultrafiltrate and normal saline supports the
conclusion that the inhibition of the uraemic ultrafiltrate is a feature of uraemic intoxication and that the test system is appropriately reliable. This implies that one or more toxic factors that normally are eliminated from the body by excretion of urine accumulated in the body fluid of patients with renal failure and suppressed food intake. However, we do not know if the effect of normal urine and uraemic ultrafiltrate is mediated by the same substance or by various substances.

Fractions of the pooled ultrafiltrates of various molecular sizes (0.1–0.5, 0.5–1, 1–5 and 5–10 kDa) were isolated and concentrated by serial filtration, using membranes with known cut-offs. The subfractions of uraemic ultrafiltrate, having a molecular weight ranging from 1 to 5 kDa and 5 to 10 kDa, inhibit ingestion in a dose-dependent manner, whereas fractions having molecular weights <1 kDa are inactive. An ultrafiltrate of normal urine also inhibited appetite, an effect entirely confined to a fraction with a molecular weight of 1–5 kDa. These results support the hypothesis that middle-molecule compounds, some of which normally are eliminated by urinary excretion, accumulate in the plasma of uraemic patients and suppress food intake [18].

Role of splanchnic–brain signalling in anorexia of uraemia

Injections of plasma ultrafiltrate, which had not been concentrated or otherwise modified, in rats weighing ~300 g with an estimated total body water volume of ~180 g (60% of body weight) and an extracellular fluid volume of ~60 g (20% of body weight) inhibit food intake. This implies that any active factor in the ultrafiltrate is diluted in the body fluid of the rat, so that the concentration becomes much lower than the original concentration in uraemic plasma. One may therefore assume that the inhibitory effect on food intake of the original uraemic plasma is considerably larger than that recorded in our experiments. On the other hand, we do not know where the effect is triggered.

Seeking a mechanism of action that inhibits food intake in uraemia, we used the previously mentioned bioassay in rats which had been fed a carbohydrate solution by mouth. Intraperitoneal injection of a middle-molecule fraction of uraemic ultrafiltrate (1–5 kDa), isolated and concentrated by molecular filtration (25:1), significantly inhibited carbohydrate intake, but intravenous injections of the same concentrations did not influence the intake. However, higher doses of intravenous injections inhibited food intake as well. The middle-molecule fraction (10:1) isolated from urine, like uraemic ultrafiltrate, inhibited food intake when injected i.p., but higher doses were required to inhibit intake when injected i.v. This suggests that the inhibitory effect of the middle molecules is triggered locally in the splanchnic region, possibly by stimulation of the intra-abdominal receptor site or by activation of the hepatic membrane potential that inhibits food intake by signalling to the brain via the hepatic vagus nerve. However, to be effective i.v., these middle-molecule fractions must be given in higher doses to reach their site(s) of action, because they are diluted in the general circulation.

We observed that fractions in the middle-molecule weight range, isolated from uraemic plasma and urine ultrafiltrates, inhibit food intake in a dose-dependent manner when injected into the lateral brain ventricle. However, the effect of the middle molecules on the brain-feeding centre remains unclear, and our limited knowledge of their molecular weight, transport through the blood–brain barrier and their availability to the brain warrant further investigations. Nevertheless, these results suggest that middle molecules directly inhibited food intake via a central mechanism, as documented by direct injection into the lateral brain ventricle. This mechanism may be complementary to the splanchnic pathway described above.

Conclusion

Anorexia is common in end-stage renal failure patients and contributes to the development of protein–energy malnutrition, which is strongly associated with increased morbidity and mortality. One or more dialysable uraemic toxins accumulate when renal function is reduced and inhibit nutritional intake. This effect is mediated via specific receptors in the splanchnic region and/or in the brain. The compounds have until now been poorly defined. Their characterization with regard to chemical composition and mechanisms of action may open up new possibilities for treating malnutrition.

References


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**Peritoneal fluid eosinophilia**

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The occurrence of irregular and intermittent peritoneal fluid eosinophilia during the course of peritoneal dialysis has intrigued clinicians and researchers since its first report in 1967 by Lee and Schoen [1]. This self-limiting process has not been demonstrated to cause permanent adverse effects on the peritoneal membrane function, and treatment usually is not required. It has been described under various terminologies, but the term ‘peritoneal fluid eosinophilia’ should be preferred to distinguish it as a clinical entity with diagnostic considerations separate from those of known infectious aetiological processes.

The significance of peritoneal fluid eosinophilia is uncertain. In general, the stimulatory and inhibitory effects of eosinophils in various allergic and inflammatory disease states is now well established. They have been implicated in, amongst others, progressive morphological changes occurring in glomerulosclerosis, arterial obliteration, interstitial nephritis and chronic vascular rejection of renal allografts [2,3]. The percentage of hypodense eosinophils, i.e. activated eosinophils with increased metabolic activity, has been shown to increase in peritoneal fluid eosinophilia and decrease with resolution of the entity [4]. These observations and newer understanding of the physiology of eosinophils suggest that peritoneal fluid eosinophils may not be mere innocent bystanders in peritoneal dialysis, but may have a pathophysiological function such as a host defence function in inactivating inflammatory mediators in the peritoneum.

The recruitment of eosinophils into the peritoneum during peritoneal dialysis is not explained solely by hypersensitivity reactions to constituents of the peritoneal dialysis systems and medications [5], because mechanical and chemical irritants, introduction of air into the peritoneal cavity, uraemia and fungal infections have been demonstrated to induce this phenomenon. A variety of other materials, even inert materials, induce eosinophilia when introduced into the peritoneum of mice by activating the coagulation mechanism to produce the eosinophilic fibrin. A growing body of evidence suggests that peritoneal fluid eosinophilia may be due to the chronic inflammatory process that persists in the peritoneum of peritoneal dialysis patients [6,7]. Cytokines, chemokines, chemottractants and other inflammatory mediators released into this inflammatory site up-regulate pre-formed molecules and de novo synthesis of adhesion molecules [8]. These adhesion molecules are important for immune regulatory mechanisms concerning antigen presentation, intercommunication and activation of immune cells, localization and migration as well as effector–target cell interactions in inflammatory processes. The incidence and intensity of the peritoneal eosinophil accumulation may be due to the local balance of pro- and anti-inflammatory mediators, the up-regulation of the quantity and avidity of adhesive receptors and their ligands by systemic and peritoneal cytokines, the organ specificity to adhesion molecule pathways and the differential cell surface distribution of adhesion molecules expressed constitutively [9,10].

The concept of adhesion molecules brings a new perspective to our understanding of peritoneal fluid eosinophilia. While it may not explain all of our dilemmas, it probably signals a paradigm shift in our approach to this intriguing phenomenon.

**References**

Renal failure and bone marrow transplantation

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Introduction

Acute renal failure (ARF) after bone marrow transplantation (BMT) is a frequent event, with a 30–80% occurrence rate [1–4], and a constant worry to the clinicians because of its management difficulties and its ominous prognosis. Chronic renal failure is less usual, because it is often the consequence of severe ARF, a complication associated with a high mortality rate in the first 3 months post-BMT. Furthermore, chronic cyclosporin nephrotoxicity is rarely encountered because cyclosporin (CsA) is withdrawn at 6 months. Whichever the renal dysfunction mechanism, the aetiological and therapeutic approaches have to take into account the haematological context: allogeneic or autologous BMT, conditioning therapy, haematological risk factors, graft-versus-host-disease (GVHD), underlying diseases recurrence-risk, age, veno-occlusive disease.

During the first year post graft, four periods evolve from the classical haematological complications intricated with ARF

Period 1

The first 2 weeks are a crucial period, when aplasia is an obligatory event with a major risk of sepsis. The prognosis has improved through isolation in laminar airflow rooms. However, the risk of tubular necrosis persists during sepsis, and the large use of antibiotics and antifungal agents increases the risk of drug nephrotoxicity. Patient selection and the prophylactic use of volume expansion, urinary alkalinization, and allopurinol therapy explain the low incidence of tumour lysis syndrome. Likewise, the improvement of cryopreservation and marrow infusion modalities permitted to largely avoid today the uncommon cases of ARF during the first 3 days [3]. Veno-occlusive disease of the liver is now the main complication of this initial period, because of the inevitable endothelial injury resulting from pretransplant chemoradiation therapy. Most cases of veno-occlusive disease are clinically obvious with jaundice, liver pain, oedema, and ascites. They are sometimes followed by ARF mimicking the chronic cyclosporin nephrotoxicity, with a 75% mortality rate. Many treatments have been tried to prevent veno-occlusive disease, but none of them have proved to be effective. Haemodialysis is rarely required, but if it is the risk of hypovolaemia should be borne in mind [5].

Period 2

After 2 weeks, the early complications can still be observed (veno-occlusive disease or delayed graft function and their infectious consequences), but acute GVHD is the main risk in recipients of an allogeneic graft. While acute GVHD of low grade could contribute to prevention/treatment of leukaemic relapse, GVHD of grade >1 may cause serious lesions of skin, liver, and gut. Renal dysfunction is caused by several mechanisms. (i) Hypovolaemia: skin and gut lesions may cause hypovolaemia, which is often difficult to manage in the context of malnutrition. (ii) Infection: high-grade GVHD often requires prolonged, high-dose corticosteroid therapy, and sometimes antilymphocyte globulin, frequently giving rise to severe infections (CMV disease, bacterial and fungal sepsis). (iii) Nephrotoxic drugs: the risk of ARF is further increased when septic patients are exposed to nephrotoxic drugs such as aminoglycosides and amphotericin B. (iv) Haemolytic–uraemic syndrome: severe acute GVHD leads to TNF-α release [6], which contributes to endo-
thelial injury, and which in turn may account for HUS [7]. Because haemolysis and thrombocytopenia are frequently encountered for many reasons other than HUS, schizontocytes, indices of haemolysis, and occurrence of hypertension are valuable signs pointing to the presence of HUS. The incidence of HUS is underestimated, as kidney biopsy is not often performed because of the higher risk in this situation. Because the different pathomechanisms are often operative simultaneously, it is often difficult to ascribe renal impairment to one simple mechanism.

Period 3

From the third month onwards, persistence or appearance of clinical signs of GVHD indicate the development of chronic GVHD. This period is a turning point: the absence of chronic GVHD increases in the risk of relapse of the initial haematological illness. On the other hand, if severe chronic GVHD is not well under control the patient is exposed to a high risk of HUS. The diagnosis is easier at this point in time because the clinical context is less confounding than in the earlier periods.

Period 4

After 6 months, persistence or occurrence of renal failure carries a grave prognosis.

The presence or absence of chronic GVHD indicates whether or not HUS is a likely diagnosis in an allograft recipient with renal failure. When HUS occurs after more than 6 months in a recipient of an autologous BMT (with no risk of GVHD and no use of CsA), clearly the possibility of endothelial injury resulting from other mechanisms must be considered. Such cases of delayed renal failure, particularly a nephritic syndrome or HUS are often a sequel of radiation nephritis with mesangiolysis and arteriolonecrotic lesions. The diagnosis can be made by renal biopsy [8]. The long-term outcome of this renal complication seems to be the same as for classical radiation nephritis. A prophylactic measure is fractionation of doses during initial total body irradiation [9,10]. Finally, some forms of glomerulonephritis, e.g. minimal-change disease, have been described in patients experiencing a chronic GVHD [11].

What is the role of CsA for renal impairment after bone marrow transplantation?

The use of CsA contributes markedly to the occurrence of ARF. Its nephrotoxicity is well known. The great variations of the incidence of ARF between different teams may well be related to differences in the use of CsA. When a moderate increase in serum creatinine responds well to a decrease in the dose of CsA, the cause is obviously CsA and this is seen in up to 80% of cases. Reduction of the dose of CsA poses the risk of under-immunosuppression. This may trigger or aggravate GVHD [12].

The deleterious effects of CsA on renal haemodynamics could enhance the severity of other forms of renal dysfunction and render their management difficult. It is impossible to define a minimal effective CsA trough level. Pharmacological survey is essential, because drug interactions and interindividual variations are frequent. Under Neoral®, blood peak value can help to detect the patients who are most exposed to the acute haemodynamic effects of the drug on the kidney. Such patients may then be switched to three divided doses instead of two to be on the safe side.

Irrespective of its haemodynamic toxicity, the procoagulant effect of CsA facilitates the occurrence of HUS during GVHD. The procoagulant effect resulting from TNF-α release by GVHD may also be potentiated by CsA. CsA alone usually does not fully explain the occurrence of HUS. One should always look for an associated clinical cause, particularly haematological or infectious causes. No form of symptomatic treatment has proved its efficacy (this is also true for plasmapheresis). Clinical improvement will only be possible when the initial cause of endothelial injury can be controlled. It is necessary to decrease the dose of CsA, but it makes the control of GVHD difficult. In this case, one may consider the use of mycophenolate mofetil; this will be permit withdrawal of CsA and also avoid azathioprine, a drug classically prescribed, but with well-known bone marrow toxicity.

Contrary to what is seen after cardiac transplantation, chronic renal failure due to a direct chronic nephrotoxicity of CsA is uncommon, because CsA is withdrawn 6 months after BMT.

The conditioning chemoradiation therapy plays certainly a role in determining whether chronic renal failure occurs after an acute episode of HUS.

Does acute renal failure contribute to patient mortality?

After allogenic BMT, early mortality up to 6 months is 40%, and ARF is a major prognostic factor by univariate analysis, but hyperbilirubinaemia is also identified as a mortality risk factor. In fact ARF and hyperbilirubinaemia often accompany the main complications encountered after allogenic BMT (grade ≥2 acute GVHD, veno-occlusive disease, HUS, heavy sepsis) which are themselves significantly associated with a high mortality rate. Thus, performing a multivariate analysis to select stepwise variables that are significant and independent of each other, sepsis and hyperbilirubinaemia clearly appeared to persist as high risk factors for mortality in contrast to ARF that was no longer significantly associated with mortality. In the absence of hyperbilirubinaemia, ARF has no deleterious effect on the survival rate at 1 year. In fact, in multivariate analysis, hyperbilirubinaemia is highly predictive of the development of ARF and often precedes it. Thus the association of hyperbilirubinaemia and ARF has ominous implications for patient survival rate [13].
Pre-emptive kidney transplantation

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Introduction

Because of the better chances of maintaining a better quality of life, it is widely accepted that renal transplantation is the treatment of choice for a substantial proportion of patients with end-stage renal disease. In general, transplantation is performed after a varying period of chronic haemo- or peritoneal dialysis. The other option of transplanting patients not yet on renal replacement therapy, so-called pre-emptive transplantation, has been much less popular. A recent analysis of the ERA–EDTA Registry data showed that pre-emptive transplantation in Europe is rarely used in adults, but that its frequency differs remarkably among European countries [1]. In Sweden 70% of children entering renal replacement therapy receive renal transplantation prior to dialysis. In Norway almost 15% of adult patients receive a pre-emptive transplantation whilst in countries like Austria, Germany, and Ireland, pre-emptive transplantation is nonexistent.

The advantages of pre-emptive transplantation

The rationale for transplanting patients not yet on dialysis, is to optimize the benefits of transplantation over chronic dialysis. Pre-emptive transplantation lessens considerably the costs of treatment of end-stage renal disease, it avoids the inconvenience of frequent hospital visits and/or frequent peritoneal dialysate exchanges, it avoids dialysis associated morbidity and access surgery and perhaps most of all, it facilitates social and vocational rehabilitation. In a retrospective case-control study performed at the University of Texas Medical School in 85 cases of pre-emptive transplantation, it was found that, compared with the matched control patients transplanted after a minimum of 6 months’ chronic dialysis therapy, significantly more patients who had received a transplant before being on dialysis, were employed 6 months post-transplant [2].

Potential concerns

In the past some concern has been expressed towards worse results in patients transplanted prior to dialysis compared to patients transplanted after having been on dialysis for some time. On the one hand, this was based on the finding of depressed mixed lymphocyte stimulation, reduced skin test antigen reactivity, and prolonged skin graft survival both in uraemic animals and patients. Although it is well accepted that chronic renal failure impairs immunity, no clear correlation between the degree and duration of renal failure and
the degree of immunodeficiency could be demonstrated. In a study comparing the immune response of three groups of uraemic patients, patients in haemodialysis, patients with GFR <10 ml/min and patients with GFR of 10–20 ml/min, no significant differences between the three groups was found [3]. On the other hand, earlier clinical studies had suggested impaired patient and graft survival results in patients transplanted prior to dialysis [4]. More recent studies, however, were unable to confirm these findings [2,5,6]. On the contrary, an even better survival rate was recently found [1].

A further argument against pre-emptive transplantation is the possibility of a higher incidence of non-compliance in the patients transplanted prior to dialysis, as found in the abovementioned study from Texas [2]. Patients who have not experienced the inconvenience and morbidity of chronic dialysis may be less inclined to strictly adhere to the immunosuppressive therapy, especially in case of drug-related side effects. A higher incidence of non-compliance has however not been found in other studies [5]. Although it may be premature to conclude that pre-emptive transplantation indeed results in better survival rates, taken into account the retrospective character of the available studies and the possibility of major byasses in the selection of patients, it can at least be concluded that patients with pre-emptive renal transplantation are not at a higher risk of early and late graft loss. At present concerns about pre-emptive transplantation are therefore much more ethical than purely medical.

At which point to consider pre-emptive transplantation?

The unpredictability of the organ supply and the difficulty in predicting for an individual patient the progress to renal failure, may result in the transplantation of patients many months before renal replacement therapy is indeed really needed. Too early transplantation will of course increase the overall costs of renal replacement therapy as the same organ could be used in the meantime to transplant a patient who is already on an expensive form of renal replacement therapy. Considering pre-emptive transplantation is therefore only acceptable if the evolution of the underlying renal disease is well documented and a prognosis of the progression of the renal disease can be made with a high degree of accuracy. As most of the patients with a creatinine clearance <15 ml/min will become dialysis dependent within 1 year, it seems reasonable to put patients on the waiting list only when creatinine clearance has reached <15 ml/min. This policy however is also only possible if the overall mean waiting time for finding a suitable kidney is no longer than 1 year.

Ethical considerations

The latter relates to a second important ethical consideration. Indeed transplantation of a patient not yet on dialysis may deny the opportunity of a transplant to patients who are already on dialysis for months or even years. At present organ allocation in most western countries is based on a balance between utility and justice. In the present context utility means allocation of the available organ to the ‘best’ patient in order to get the best short- and long term results. This medical argument can rather easily be defined in terms of HLA-matching and ischaemia times. The criterion of justice means assuring equal access to the scarce donor organs for all waiting patients. The implementation of this criterion is however much more difficult. In the new kidney allocation system within the Eurotransplant organ exchange organization, this argument is handled by giving points to the waiting time. Although this may appear an acceptable method, the definition of waiting time remains a matter of dispute. It has been suggested to use the time since the start of renal replacement therapy as waiting time [8]. In this scenario, patients waiting for a pre-emptive transplantation will not receive points for the waiting time factor. By this it can be expected that these patients will only receive well matched kidneys which will improve the overall long term results (and thus the need for organs for retransplantation) and may compensate for the increased use of organs for early transplantation. On the other hand the chance to be transplanted within a reasonable time delay will decrease making pre-emptive transplantation only possible if the overall waiting time is not too long. In our transplant centre the mean waiting time for non-immunized patients in 1996 and 1997 was 9.6 ± 9.4 and 12.6 ± 12.9 months respectively with a median waiting time of 8.7 and 8.0 months, respectively. It has been suggested that for specific ‘medical’ categories of patients e.g. children and diabetics exceptions to the waiting time rule should be made [8]. Whereas it is generally accepted that in children growth is better preserved after a successful transplantation compared to chronic dialysis, the superior outcome of transplanted diabetics compared with those on dialysis is more in dispute. But also for a young father or mother who has the responsibility for a family, the maintenance of employment that would otherwise be lost may also be an equally compelling reason for avoiding dialysis.

Most of the abovementioned ethical considerations however only apply to the cadaveric kidney donor situation. If transplantation with a living donor kidney is considered, the pre-emptive approach is probably to be preferred over transplantation while the patients are already on dialysis.

Conclusions

In conclusion, pre-emptive transplantation is for medical as well as for socio-economical reasons the preferred mode of renal replacement therapy. In the context of the present organ shortage and the long waiting time for those patients already on dialysis, pre-emptive transplantation cannot be realised in most
countries. However in countries with a high donation rate, such as in Belgium and Austria, where the number of available cadaveric donor kidneys equals the yearly demand, pre-emptive transplantation is justifiable when either medical or socio-economical compelling reasons are present. In case of living donor transplantation, pre-emptive transplantation may be the treatment of choice.

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References


Another compartment syndrome for Nephrologists?

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Nephrologists who see patients with acute renal failure due to rhabdomyolysis are aware of the importance in such patients of acute muscle compartment syndrome. In this condition, muscle necrosis within a closed compartment leads to increased tissue pressure, followed by compromise of the local circulation and neuromuscular function. The diagnosis is usually suspected from the clinical circumstances and can be confirmed by measurement of intracompartment pressure with a wick catheter [1]. Treatment by emergency surgical decompression and debridement of non-viable tissue may help diminish or prevent the renal injury which occurs due to the combined effects of intratubular haem pigment casts, hypovolaemia, and proximal tubular cell injury [2].

Tan and Kua in this issue discuss the role of another compartment syndrome in critically ill patients who develop acute renal failure. The abdominal compartment syndrome refers to alterations in respiratory function, haemodynamic parameters and renal function that occur as a result of increased intrathoracic pressures causing functional obstruction to cerebral venous outflow via the jugular venous system. In addition to these features, the clinical and pathophysiological manifestations include a tense distended abdomen, carbon dioxide retention, and increased central venous pressure. Massive fluid resuscitation is an associated feature of many cases, and narrowing of the intrahepatic IVC on CT scan can be seen in some patients with increased intra-abdominal pressure [6].

Abdominal compartment syndrome is seen most often in patients with ruptured abdominal aortic aneurysm or intra-abdominal infection, or following laparotomy for severe abdominal trauma. The mechanism responsible for renal failure in abdominal compartment syndrome appears to be predominantly haemodynamic, in the form of decreased renal perfusion rather than ureteral compression. In individual patients, the increase in intra-abdominal pressure (IAP) may be caused by a variety of pathological processes, singly or in combination and these include intra-abdominal haemorrhage, ascites, bowel wall oedema, retroperitoneal/bowel haematoma, necrotising fasciitis or intra-abdominal abscess/peritonitis.

As in muscle compartment syndrome, diagnosis of abdominal compartment syndrome depends on recognising the clinical picture in at risk patients, followed by an objective measurement of intra-abdominal pressure, usually by the indirect method of urinary bladder
pressure measurement. The exact definitions used in published series show variation. Meldrum [7] identified 14% of 143 consecutive patients admitted to a surgical ICU developed abdominal compartment syndrome defined as an intra-abdominal pressure > 20 mmHg complicated by one of the following: peak airway pressure > 40 cm H₂O, oxygen delivery index < 600 ml O₂/min/m² or urine output < 0.5 ml/kg/h. Williams [8] in a series of five surgical ICU patients defined an elevated compartment pressure as greater than 25 mmHg. Fietsam [9] in a report of four patients in whom the condition occurred with abdominal aortic aneurysm suggested criteria which excluded abdominal distension due to bleeding, and included only those in whom the cause was massive interstitial and retroperitoneal swelling.

There is therefore an established relationship between abdominal compartment syndrome and renal dysfunction, but there are areas of uncertainty which render it difficult to make explicit recommendations on management of the syndrome. The variations in level of measured IAP taken to indicate a raised level meritting intervention are referred to above. In addition, the goals of treatment in abdominal compartment syndrome need to be clearly specified; is it improvement of cardiorespiratory function? Reduction in mortality? Prevention of renal failure and avoidance of dialysis? Diagnosis of acute intra-abdominal pathology? Where the latter is not a consideration, surgical decompression in patients with abdominal compartment syndrome is a daunting undertaking on account of the high death rate [10]; this reflects the severity of the underlying illness in such patients and the potential for intractable asystole and hypotension to occur during the decompression procedure. Some authors on the other hand believe it is invariably fatal not to intervene once the syndrome has developed [11]. In some cases of abdominal compartment syndrome, prompt reversal of anuria may not follow abdominal decompression; this can occur if, as is often the case in critically ill patients, the renal failure is multifactorial and not solely due to the effect of raised intra-abdominal pressure on renal haemodynamics. In other cases where rapid reversal of renal failure does occur, it may do so for reasons other than correction of raised intra-abdominal pressure alone, thus laparotomy may result in the removal of a source of intra-abdominal sepsis as well as lowering intra-abdominal pressure. This interpretation might apply to Tans second patient with fulminating pseudomembranous colitis whose renal function improved after laparotomy at which hemicolecotomy was also carried out.

What should be the clinical approach to the patient with abdominal compartment syndrome and acute anuria? It will obviously vary according to the overall clinical circumstances. The clinician should remember that abdominal compartment syndrome has diverse causes and that overall outcome is likely to be determined by the course of the underlying causative disorder rather than the relief of raised intra-abdominal pressure per se. Abdominal compartment syndrome may in some patients indicate an acute intra-abdominal surgical condition exists, and the primary purpose of laparotomy in such cases is not therefore decompression for relief of cardiorespiratory dysfunction and anuria, but instead confirmation or exclusion of causative treatable pathology—most commonly necrotic gut. In cases where the nature of the underlying intra-abdominal condition is already established, no additional pathology may be seen at laparotomy other than the ‘classical’ findings of abdominal compartment syndrome—ascites, bowel wall oedema, haematoma; it is likely in this setting that there is a causative relationship between the raised intra-abdominal pressure and renal failure, provided other treatable causes of cardiopulmonary and renal compromise such as cardiac tamponade, sepsis etc. have been excluded. Laparotomy for decompression in these circumstances may produce cardiorespiratory and renal functional improvement in the short term; this may not however prevent later development of renal failure as illustrated by Tans second case of the patient with acute pancreatitis.

Prevention of abdominal compartment syndrome may be possible when its likely occurrence can be foreseen, as in patients with ruptured abdominal aortic aneurysm or severe abdominal trauma. Measures which have been recommended to prevent development of abdominal compartment syndrome in these type of at risk patients include delayed laparotomy closure and use of absorbable mesh closure of laparotomy wounds. Delayed wound closure however is associated with established risks and policy on these issues remains unclear. Over-transfusion when attempting to maintain circulatory support may contribute an intravascular component to the excess of intra-abdominal fluid in some cases of abdominal compartment syndrome, highlighting the need for accurate methods of assessing intravascular volume in critically ill patients.

Tan’s Paper is a reminder that in certain circumscribed clinical situations, acute anuria may occur due to raised intra-abdominal pressure and that prompt reversal of renal failure, together with other physiological improvements may follow abdominal decompression. Identification of those patients in whom urgent laparotomy is indicated, not for diagnostic purposes but for relief of deranged cardiopulmonary and renal physiology may be difficult. It requires exclusion of alternative treatable causes for the observed physiological derangements, regular monitoring of intra-abdominal compartment pressure, judicious use of abdominal imaging (ultrasound, computed tomography) to detect ascites, retroperitoneal haematoma or other pathology, and a risk-benefit analysis in each individual patient. Dialogue between intensivist, surgeon and nephrologist may be helpful in arriving at a balanced decision in difficult cases.

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