

RENAL AND UROLOGIC DISORDERS

RENAL FAILURE

PREVENTION,
CAUSES AND
TREATMENT

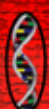
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COLIN ANDREW HUTCHISON
EDITOR



New York

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Contents

Preface		vii
Chapter I	Progressive Interstitial Fibrosis in Chronic Kidney Disease <i>Stuart W. Smith</i>	1
Chapter II	Cardiovascular Disease in the Chronic Kidney Disease Population – Burden, Pathophysiology and End-organ Manifestations <i>Magid A. Fahim and Carmel M. Hawley</i>	17
Chapter III	Protective Effect of Ozone Therapy in Renal Damage <i>José Luis Calunga and Silvia Menéndez</i>	37
Chapter IV	South Asian Ethnicity and Renal Replacement Therapy <i>Adnan Sharif</i>	55
Chapter V	Progress in Home Dialysis <i>Sandip Mitra and Anuradha Jayanti</i>	67
Chapter VI	Planning and Maintaining Functional Vascular Access in a Haemodialysis Population <i>Kevan R. Polkinghorne, Magid A. Fahim, Nirosha Gunatillake and Carmel M. Hawley</i>	89
Chapter VII	Cardiac Swinging Calcified Amorphous Tumors (SCAT) and Stroke in End-Stage Renal Failure <i>Hiroshi Kubota</i>	117
Chapter VIII	Assessment of Monoclonal Proteins in Patients with Renal Diseases: New Methods and Their Clinical Utility <i>Ellen Jenner and Colin Hutchison</i>	127
Chapter IX	Prevention of Acute Kidney Injury in Critically Ill Patients <i>Marlies Ostermann</i>	143
Chapter X	Renal Failure: Causes <i>Christos Paliouras</i>	159

Chapter XI	Renal Failure: Prevention <i>Georgios Aperis</i>	189
Chapter XII	Acute Renal Failure: Treatment <i>Polichronis Alivannis and Eirini Tsampikaki</i>	221
Index		277

Preface

Kidney failure represents a major health economic burden for all people and all nations. Despite the immense number of factors which can cause the initial injury to the kidneys, common response pathways are triggered which, unless broken, will ultimately lead to irreversible fibrosis within the kidneys. Unfortunately, early injuries to the kidneys can frequently be asymptomatic and chronic kidney disease has often developed before the patient has become aware there is a problem. Once established, chronic kidney disease is associated with a high morbidity and mortality for those affected. There has been a large amount of work in recent years focused on the early diagnosis and management of kidney disease to prevent its progression. The purpose of this book is to review the mechanisms which underlie both acute and chronic kidney injury, discuss their diagnosis, complications and management. The first section of this book covers the causes and complications of chronic kidney disease. Initially the author review the mechanisms which underlie the progressive fibrosis by which chronic kidney disease progresses. There are then detailed discussions of the cardiovascular complications of chronic kidney disease. The second section of the book focuses on established end stage renal disease. Reviewing access to renal replacement therapies across ethnicities, the role of home therapies and how their use can be increased and finally the author discuss the preparation and maintenance of access for dialysis. The third and final section of the book provides an update for the clinician into the diagnosis and management of acute kidney injury. Specifically the diagnosis and management of renal impairment in patients with plasma cell dyscrasias is reviewed and the prevention of acute kidney injury in the critically ill patient is discussed in detail.

Chapter I

Progressive Interstitial Fibrosis in Chronic Kidney Disease

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Abstract

Chronic kidney disease is a significant cause of premature morbidity and mortality. The dominant processes that promote progressive kidney disease, irrespective of the trigger, occur in the renal interstitial compartment where fibrosis is considered the hallmark of progressive disease. In this chapter the cellular and non-cellular mediators of this process will be reviewed with an emphasis on the emerging importance of the role the vasculature and stromal cells play in this process.

1. Introduction

Chronic kidney disease (CKD) affects 10-13% of the population and contributes considerably to premature morbidity and mortality [1]. The dominant processes that promote progressive kidney disease, irrespective of the trigger, occur in the renal tubulointerstitial compartment where fibrosis is considered the hallmark of progressive disease [2]. The extent of tubulointerstitial fibrosis seen at kidney biopsy has been repeatedly demonstrated to be a rigorous predictor of renal progression [3].

Fibrosis is the formation of excess amounts of fibrous connective tissue resulting from chronic inflammation of the tissue. This causes the destruction of functioning renal parenchyma [2].

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This process is driven by a complex interplay of cellular and non-cellular mediators. In this chapter the key mediators of progressive interstitial fibrosis will be outlined and current challenges and controversies within the field highlighted. Where space limits discussion readers will be directed to detailed recent reviews published within the literature to support the framework provided here.

2. Epidemiology

CKD is a major public health problem [1]. The number of patients with CKD is rising and this is mirrored by the increase of end stage renal failure (ESRF) patients requiring renal replacement therapy (RRT) globally [4]. In the UK the annual incidence of ESRF doubled in the last decade [4]. Figures taken from the UK renal registry show that in 2008 there were 47,525 adult patients receiving RRT equating to a UK prevalence of 774 per million population, an annual increase in prevalence of 4.4% [5].

The UK increase in prevalence, as in other countries, is projected to continue at a rate of 5-8% per year [6]. Quantifying the number of patients with ESRF alone probably underestimates the population burden of CKD as only a small proportion of patients with stage 3 to 4 CKD progress to RRT [7]. Despite this even the early stages of CKD are associated with an increased risk of developing vascular and cardiovascular disease [8-9].

3. Determinants of Progressive Interstitial Fibrosis

Not everyone with renal impairment will develop progressive fibrosis leading to ESRF requiring RRT. Multiple determinants that place patients at an increased risk and facilitate the development of progressive fibrosis are now recognized [10]. The determinants highlighted here, through their ability to generate pro-fibrotic mediators, are pivotal in driving the processes described in this chapter.

A detailed discussion of individual factors is beyond the scope that can be covered here. Several excellent reviews have addressed these factors in detail including population demographics [11], proteinuria [12-13], hypertension [14], anaemia [15] and the role of calcium-phosphate metabolism and vitamin D [11]. Increasingly genetic [16] and epigenetic factors [17-18] are also emerging as promising areas of research in respect of interstitial fibrosis.

4. Pathogenesis of Progressive Interstitial Fibrosis

It is perhaps simplest to consider interstitial fibrosis as a form of wound healing [19] that most likely begins as a beneficial response to acute injury. Regardless of the underlying

mechanism of injury, the ultimate aim of wound healing is restoration of tissue architecture and function.

The renal response to injury resembles that seen elsewhere in the body [20]. Following injury, leukocytes infiltrate wounded tissue and epithelial cells proliferate [19].

Infiltrating leukocytes are supported by resident interstitial fibroblasts and dendritic cells [2, 20]. Fibroblasts proliferate and become activated myofibroblasts that deposit pathological amounts of matrix and facilitate wound contraction and scar formation (fibrosis) [21]. Adult tissue healing is often only partially successful and acute inflammation may evolve into persistent chronic fibrosis associated with the deposition of excessive extracellular matrix (ECM) and the development of fibrosis.

Here attention is focused predominantly on the interstitium but it is important to remember that the glomeruli are also involved in the initiation of interstitial fibrosis as discussed by other authors [22-23]. Glomerulosclerosis is also an important component of CKD progression [22].

To simplify discussion individual mediators are described in isolation. While greater emphasis has been placed on the role fibroblasts and myofibroblasts play in this process, ultimately interstitial fibrosis is a complex interplay between all the factors described.

5. Cellular Mediators

5.1. Infiltrating Cells

5.1.1. Macrophages

The non-inflamed kidney has relatively few tissue macrophages [24]. Infiltration of renal tissue by monocyte/macrophages following injury is described in both human disease and animal experimental models [25-27]. In human disease macrophage infiltration is negatively correlated with renal outcome [26] and fibrosis can be ameliorated in animal models following the systemic depletion of macrophages [28-30]. Recruitment of circulating monocytes to the injured kidney is in response to the upregulation and *de novo* expression of selectins and integrins by endothelial cells of the post capillary venules and by chemokine release from the kidney itself [23].

These factors orchestrate rolling, adhesion and transmigration of activated monocytes into the kidney where they are involved in tissue repair, sterilising and debriding injured tissue through the release of cytotoxic substances and phagocytosis [31].

Repetitive injury or chronic inflammation drives aberrant macrophage activation that initiates fibrosis through the dysregulated release of reactive oxygen species that are directly damaging to tissue and through the generation of pro-fibrotic cytokines such as transforming growth factor beta (TGF β), fibroblast growth factor (FGF) and platelet derived growth factor (PDGF) that promote leukocyte recruitment and extracellular matrix deposition (ECM) by activated fibroblasts [23]. Macrophages can also directly remodel renal architecture through the release of metalloproteinases [32].

In vivo macrophages are a heterogeneous population of cells that can be divided into two polarised activation states [33]. The classically activated or M1 macrophages and the alternatively activated or M2 macrophages that are thought to promote tissue repair [34].

Evidence is accumulating to suggest that early in the development of injury macrophages adopt an M1 phenotype, but at later stages of disease an M2 phenotype predominates.

Depletion studies performed in murine models of both liver and kidney fibrosis have demonstrated that macrophage depletion in the context of advanced fibrosis resulted in reduced tissue scarring, but in contrast depletion during the recovery phase of injury led to a failure of matrix removal [34-35]. These observations have recently been reviewed in detail in the context of renal disease and readers are directed to the following literature [27, 33, 36].

5.1.2. *T Cells*

T cells are rarely found in non-inflamed renal tissue [24] and until relatively recently the idea that T cells play a direct role in the pathogenesis of interstitial fibrosis has received scant attention.

Renal immune mediated T cells injury is well described within the literature [37] and it has long been assumed that T cells generate injury to which fibrosis is the response. An argument supported by early reports suggesting lymphocytes do not contribute to interstitial fibrosis [38]. There is now mounting evidence that T cells directly promote interstitial fibrosis. Kalluri *et al* used a murine model of Alport renal disease to demonstrate that T cells are not required for the induction of glomerulonephritis but are required for the development of interstitial fibrosis [39].[40]. Tapmeier *et al* adoptively transferred either CD8⁺ or CD4⁺ T cells into Rag^{-/-} mice following renal injury [41]. CD4⁺ but not CD8⁺ T cells were found to increase fibrogenesis.

5.1.3. *Mast cells*

An increased number of mast cells is a consistent feature of interstitial fibrosis, whatever the underlying pathology [42-45]; these cells have also been implicated in the pathogenesis of chronic inflammation in non-renal organs [46]. Mast cells increase in number in areas of scarring of the renal cortex and have been shown to inversely correlate with renal function [47]. Animal studies on the role of mast cells in the development of interstitial fibrosis have proved inconclusive [48-51] and the functional role by which mast cells mediate fibrosis remains unclear.

5.2. Resident Cell Populations

5.2.1. *Dendritic Cells*

Dendritic cells (DCs) are found throughout the renal stroma where they have a role in immune surveillance and antigen presentation [52]. Murine proteinuric renal disease models have demonstrated that albumin fragments filtered at the glomerulus can be taken up by proximal tubular cells and presented in draining lymph nodes by renal DCs thus priming CD8⁺ T cells [53]

Further Heyman *et al* have demonstrated that DCs are intimately involved in the progression of proteinuric renal disease [54-55]; and that DCs depletion in a murine model of glomerular injury lead to the rapid resolution of immune cell infiltration and damage.

5.2.2. Renal Tubular Epithelial Cells

Renal tubular epithelial cells (TEC) act as a conduit between the glomerular and interstitial compartments and thus play a key role in the pathogenesis of interstitial fibrosis. TEC can be damaged directly for example through toxic or ischemic mechanisms [56] and indirectly by glomerular proteinuria or cytokine and reactive oxygen species (ROS) release from leukocytes [23, 26]. *In vitro* TEC express leukocyte directed chemokines, such as the macrophage chemokine monocyte chemoattractant protein 1 (MCP-1), in response to high concentrations of intermediate weight proteinuria, for example albumin [57]. Interventions that decrease proteinuria in human clinical trials [23] are protective and in animal models of disease are associated with reduced chemokine expression and inflammation [23]. Proteinuria has also been demonstrated to activate complement within the tubular lumen [58] and blockade of this process may be protective against fibrosis [59]. TEC injury is reported to lead to cell cycle growth arrest [60], autophagy [61-62] and apoptosis [63], processes that culminate in tubular atrophy, loss of functional parenchyma and fibrosis. TEC may even, through epithelial mesenchymal transformation (EMT), become matrix depositing myofibroblasts [64-66].

5.2.3. Fibroblasts and Myofibroblasts

Fibroblasts at renal and non-renal sites are a heterogeneous and functionally diverse cell population [21] which exhibit topographic differentiation, displaying distinct functional identities based on their tissue of origin [67-68]. In addition to site-specific differences fibroblasts are also heterogeneous, with distinct functional properties, within individual tissues [69-70]. In the kidney resident stromal fibroblast heterogeneity has not been addressed in detail although subpopulations have been reported [71-72].

In normal human kidney, 'quiescent' stromal fibroblasts represent a small population with a low turnover rate [73] that play a homeostatic role maintaining and regulating the deposition and organisation of ECM. Fibroblasts have multiple functions beyond simply maintaining normal tissue architecture [24] and can also secrete prostaglandins and cytokines in a paracrine manner [73]. Additionally Zeisberg *et al* have also demonstrated that they have an endocytic and antigen presenting capacity [74]. The transformation from a quiescent to an activated population of fibroblasts is dependent on a combination of growth factors, cytokines, extracellular matrix and environmental stimuli. Aside from the activated form of the fibroblast, known as a myofibroblast, there is no formal nomenclature or markers to classify fibroblast heterogeneity. The myofibroblast is therefore the prototypical activated stromal fibroblast described within the renal literature.

In contrast to fibroblasts, myofibroblasts are larger, exhibit long processes with bundles of microfilaments which stain positive for alpha smooth muscle actin (α SMA) [73]. α SMA is therefore classically used to define myofibroblasts *in vitro* and *in vivo* [21]. *In vitro* α SMA molecules incorporate into actin filaments and function to produce the contraction of collagen gels [75]. They also limit cell migration and motility by increasing cell adherence to extracellular matrix [76]. Intriguingly experimentally induced tubulointerstitial fibrosis in the α SMA^{-/-} mouse showed that α SMA^{-/-} developed more severe fibrosis compared to controls and fibroblasts isolated from α SMA^{-/-} mice produced more type collagen 1 compared to wildtype controls [77]. Reflecting the heterogeneity of the fibroblast response α SMA⁻

fibroblasts are also described elsewhere in the renal literature and are known to contain and express interstitial collagens *in vivo* [72, 78].

5.2.4. Origin of Activated Myofibroblasts in CKD

The origin of activated renal fibroblasts, the primary cell responsible for the deposition of matrix that destroys renal architecture, is both controversial [65-66, 79] and complex [80-81]. Recruitment has been proposed to occur from resident stromal cell populations [82] (peritubular fibroblasts and pericytes), from circulating bone marrow derived precursors (fibrocytes) [83] and through the process of epithelial mesenchymal transformation [2]. Iwanoet *al* attempted to describe the relative importance of the various potential sources of activated fibroblasts. Using bone marrow chimeras and transgenic reporter mice, the authors suggested that resident fibroblasts, EMT and circulating precursors contribute 52%, 38% and 9%, respectively [84].

The concept that activated stromal fibroblasts are derived from resident renal fibroblasts is intuitive, widely accepted by most authors and long standing [85]. Other potential sources are contentious and here EMT and fibrocytes will be discussed.

Fibrocytes, first reported in 1994, are a circulating CD34⁺ bone marrow derived population of fibroblast like cells [86]. These cells constitute less than 1% of circulating leukocytes and are defined by their co-expression of both leukocyte and of mesenchymal cell markers such as collagen I [83]. Fibrocytes are proposed to infiltrate inflamed and fibrotic tissue and become activated fibroblast-like cells [87]. In kidney fibrosis infiltrating fibrocytes probably represent a small population of cells [84, 87-88]. More recent studies have called the presence of fibrocytes in fibrotic kidney into question [82, 89]. Although these latter observations from animal models should be tempered by reports of fibrocytes in human disease states [90].

For the last 15 years the predominant theory for the origin of activated stromal fibroblast populations, aside from recruitment of resident stromal cells, has been through the process of epithelial mesenchymal transformation (EMT) [21]. A concept well established in the literature on cancer [91]. This ideain the kidney is based on pioneering work by Strutz and colleagues [92-93] who first suggested that tubular epithelial cells can de-differentiate to express fibroblast markers in various renal disease states [64, 94-96] raising the possibility that EMT is a potent source for myofibroblasts in CKD. More recently endothelial mesenchymal transformation (EndMT) has also been suggested as a source of activated stromal fibroblasts at least in animal models of CKD [71].

The fibroblast marker most associated with EMT is fibroblast specific protein-1(FSP-1). Although it should be highlighted that this marker is also expressed on some leukocyte populations [97]. Using *In vitro* studies and *in vivo* animal models TECsare reported to acquire amyofibroblast phenotype and express FSP-1, a process driven by TGFβ(reviewed in detail recently [98]). In one study of human IgA nephropathy there was a negative correlation between the number of FSP-1 positive cells on renal biopsy specimens and subsequent renal survival [99]. However these observations are confounded by FSP-1 expression on infiltrating leukocytes which by themselves are known determinants of progressive CKD [26, 100-101]. Further, despite the extensive literature on EMT in the kidney, as noted by Krizet *al*, there is no experimental evidence to demonstrate *in vivo* tubular derived cells are capable of

depositing type I collagen or that they can migrate across the tubular basement membrane [65].

The concept of EMT in the kidney has been further drawn into question in recent years by elegant studies by Lin *et al* that have highlighted the importance of injury to the vasculature in driving fibrosis and a role for the renal pericyte [82]. Using a transgenic reporter mouse, which expresses Green Fluorescent Protein (GFP) under regulation of the collagen promoter, they demonstrated that activation of pericytes and peritubular fibroblasts contributed significantly to interstitial αSMA^+ activated stromal fibroblast (myofibroblast) populations in experimental interstitial fibrosis. Crucially in these studies EMT was not seen *in vivo* but TECs isolated from the same mice could be induced to express FSP-1 *in vitro* in response to stimulation with TGF β . An observation repeated by the same group [81] and by others [62].

6. Pericytes and the Renal Microvasculature

Renal tubulointerstitial pericytes have been relatively neglected in the renal literature of the last 30 years, with few publications focusing on their structure, function and involvement in renal pathology. The last few years, however, has seen an increase of interest in the role pericytes play in the development of renal disease [81-82, 88, 102-104]. Pericytes are not only a major contributor to the activated, matrix depositing, myofibroblast populations seen in progressive fibrosis, but perhaps even more importantly, detachment of renal pericytes from the vasculature may drive the microvasculature rarefaction and subsequent hypoxia associated with CKD [105-106].

Pericyte detachment from the vasculature in order to become myofibroblast exacerbates renal injury by destabilising the vasculature [102] a process mediated by vascular endothelial growth factor (VEGF) and PDGF signalling.

Endothelial cell damage and microvascular rarefaction are seen in pathological studies of human renal disease [25, 106] and in numerous animal models [102, 107-108] of interstitial fibrosis. Cell damage and failure of repair mechanisms compromise renal perfusion and drive tubular atrophy [109]. Intuitively the loss of the microvasculature suggests the generation of a hypoxic microenvironment and a 'chronic hypoxia hypothesis' [110] has been suggested as an underlying mechanism of interstitial fibrosis.

7. Non-Cellular Mediators

7.1. Extracellular Matrix and Tissue Proteases

The extracellular matrix (ECM) together with the tissue proteases are involved in supporting and fine tuning the fibrotic response to injury [111]. In the kidney as injury evolves the expanded interstitial space as a consequence of tubular atrophy, is filled with fibrillary matrix, predominately collagens type I and III together with fibronectin [112]. This matrix is organised and refined by tissue proteases.

Proteases are important modifiers of extracellular matrix that can attenuate interstitial fibrosis by facilitating matrix degradation, but can equally be detrimental through their cleavage of matrix and non-matrix substrates leading to the release of fibrotic growth factors and the induction of EMT [113]. Two main families of molecules are described in the literature. The matrix metalloproteinases (MMPs) and their antagonists the tissue inhibitors of matrix metalloproteinases (TIMPs) [114]; and the plasminogen-plasmin proteases [115]. Reviewed in detail in [114, 116].

7.2. Chemokines and Growth Factors

Chemokines are a group of chemotatic cytokines that attract leukocytes in response to inflammation through binding to G protein coupled receptors [117]. They are thought to play a pivotal role in the development of chronic renal injury [118-119] and have been reviewed in detail by Chung *et al* [117]. Chemokines are divided into four families (CCL, CXCL, CX3CL and CL) based on the distribution of cysteine residues within their molecular structure [120]. Endothelial cells, podocytes, TEC, fibroblasts and mesangial cells of the kidney are all capable of producing chemokines in response to injury [121], although chemokines are also secreted as part of normal homeostasis. A switch from the expression of CXCL chemokines such as IL-8, to CCL chemokines such as MCP-1, is thought to accompany the transition from acute to chronic renal inflammation [117, 122]. Similarly growth factors, recently reviewed by Boor *et al* [123], are released by infiltrating and resident cells, and as their name suggests, are capable of stimulating cellular growth, proliferation and differentiation and thus represent a promising treatment target for interstitial fibrosis.

Conclusion

An improved understanding of interstitial fibrosis may lead to novel therapies for slowing CKD progression. Indeed advances in this area are being made using animal models (reviewed in detail by Boor *et al* recently [124]).

The development of progressive interstitial fibrosis in CKD is a consequence of a complex interplay of cellular and non-cellular factors. These orchestrate the deposition of pathological matrix that destroys functional renal parenchyma; a process driven in part by clinically measurable determinants of disease progression. Despite significant advance in our understanding of progressive interstitial fibrosis in the last 15 years a detailed unifying hypothesis of how this process evolves is lacking and progressive interstitial fibrosis is one of the greatest challenges facing clinical nephrology today.

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Chapter II

Cardiovascular Disease in the Chronic Kidney Disease Population – Burden, Pathophysiology and End-organ Manifestations

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Abstract

Individuals with chronic kidney disease have a disproportionate risk of cardiovascular disease which accounts for the majority of the morbidity and mortality in this population. While traditional cardiovascular risk factors are overrepresented in the chronic kidney disease population, this alone is not sufficient to explain the excess risk observed. Chronic kidney disease is also associated with a number of novel pathophysiological mechanisms including salt and water retention, bone and mineral disorders, sympathetic overactivity and oxidative stress which combine to cause a number of pathological cardiovascular changes unique to chronic kidney disease. A greater understanding of these mechanisms is the first step to developing effective cardiac risk monitoring strategies and therapies.

This chapter reviews the pathophysiology of cardiovascular disease in the chronic kidney disease population with a particular focus on those mechanisms unique to chronic kidney disease, their physiological consequences and end-organ effects.

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Introduction

The Burden of Cardiovascular Disease in Chronic Kidney Disease

Cardiovascular disease encompassing cardiomyopathy, arrhythmia, coronary and peripheral vascular ischaemia is the leading cause of death in chronic kidney disease. Compared with the general population individuals with chronic kidney disease have a 1.5–30 fold increased risk of cardiovascular mortality depending on age and stage of chronic kidney disease in both crude and multivariate analyses from large cohort studies and registry analyses [1-5]. The risk is particularly heightened in individuals with end-stage renal disease on dialysis in whom cardiovascular mortality rates are reported to be between 6.6-9.6 deaths per 100 patient years; representing 43% of all deaths in this group [4, 6]. Indeed, it is likely that these figures underestimate the true mortal burden of cardiovascular disease in dialysis, as over a third of all withdrawals from dialysis therapy have also been attributed to this entity [4]. Cardiovascular disease is also a major source of morbidity and the leading cause of hospitalization in patients on haemodialysis irrespective of age, accounting for 34.7-56 hospitalizations per 100 patient years [6, 7]. Cardiovascular disease assumes even greater precedence in light of the fact that there has been little [5] or no improvement [8] in cardiovascular mortality of the end-stage renal disease population over the last decade while cardiovascular mortality in the general population has fallen by 33% over the same period [9].

Among the various causes of cardiovascular mortality, sudden cardiac death accounts for 15-30% of all deaths in the dialysis population making it the single leading cause of death in this group [4, 5, 7, 10]. In contrast to the general population, cardiomyopathy and not coronary artery disease is reported to be the primary pathology underlying sudden cardiac death in the dialysis population [4, 5, 11-13]. This fact combined with the high prevalence of cardiomyopathy in the dialysis population (61.8 – 84.5%) [12, 14] have made it the focus of efforts aimed at improving current poor outcomes in dialysis.

The excess burden of cardiovascular disease in populations with renal disease is explained by the fact that cardiovascular disease is both an important cause *and* consequence of chronic kidney disease. Compared with the general population, individuals with chronic kidney disease have a higher incidence and prevalence of cardiovascular risk factors especially diabetes and hypertension [15, 16], as well as established end-organ disease [7, 12, 15-17] which may be partly or wholly implicated in the aetiology and/or progression of their renal disease. Indeed over 80% of incident and prevalent chronic kidney disease patients treated with dialysis have at least one cardiovascular diagnosis [7, 12]. In addition, end-stage kidney disease is itself an independent risk factor for cardiovascular disease [18, 19], mediated through a variety of pathophysiological mechanisms including volume overload, sympathetic overactivity, hyperphosphataemia, hyperparathyroidism, oxidative stress, and anaemia. This chapter reviews the pathophysiology of cardiovascular disease in the chronic kidney disease population with a particular focus on those mechanisms unique to chronic kidney disease. The physiological derangements and end-organ pathologies that characterize cardiovascular disease in chronic kidney disease result from a confluence of multiple inciting mechanisms (Figure 1). The physiological aberrations and their end-organ consequences will be discussed first before detailing the novel mechanisms that combine to produce these changes.

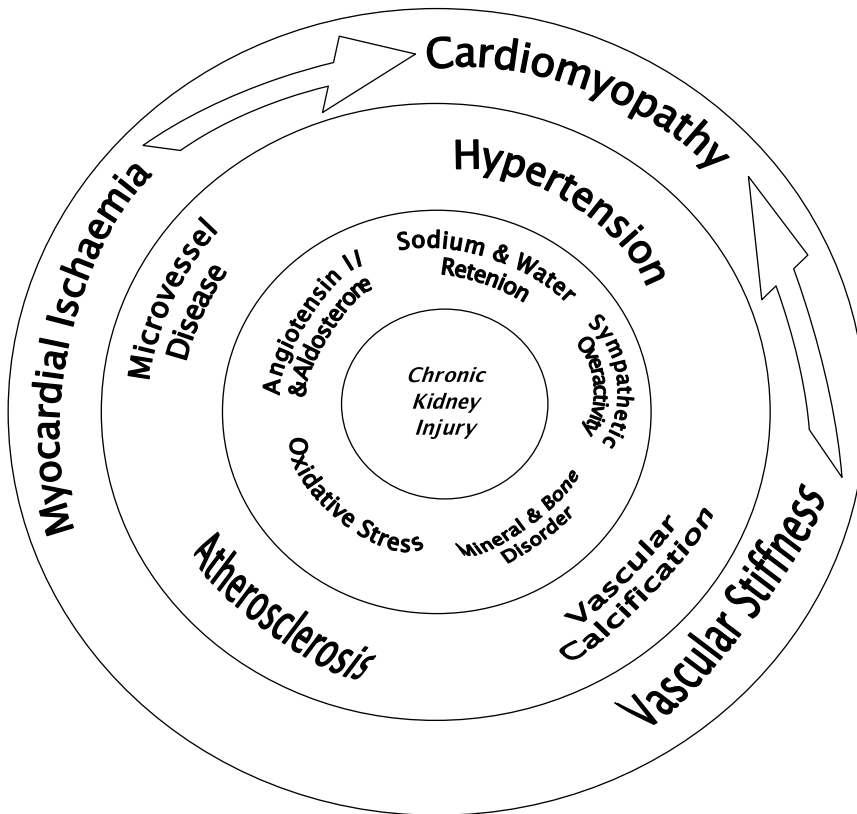


Figure 1. The pathophysiology of cardiovascular disease in association with chronic kidney disease. Chronic renal injury incites several pathological mechanisms including sodium and water retention, sympathetic overactivity, mineral and bone disorders, oxidative stress and activation of the renin-angiotensin-aldosterone axis. An interplay between these pathological mechanisms produces a number of adverse physiological changes including hypertension, volume overload, vascular calcification and stiffness, coronary and peripheral atherosclerosis, and coronary microvessel disease which result in cardiomyopathy, and cardiac and peripheral ischaemia.

End-organ Pathology

Cardiomyopathy

Cardiomyopathy encompassing left ventricular hypertrophy, dilatation, systolic and/or diastolic dysfunction is highly prevalent in the dialysis population (61.8 - 84.5%) [12, 20-22] and carries a poor prognosis. A prospective cohort study of 433 incident dialysis patients followed for 41-months found that the only independent predictors of overall mortality at ≥ 2 -years were a diagnosis of cardiac failure and cardiomyopathic indices after adjusting for demographic, comorbid, traditional and non-traditional vascular risk factors [12]. These results were echoed by a prospective cohort study of 220 prevalent peritoneal-dialysis patients followed for 5-years which found that the only independent predictors of sudden cardiac death were left ventricular systolic dysfunction, systolic and diastolic blood pressure [23].

Heart failure is the most common non-fatal manifestation of cardiomyopathy in dialysis; is highly prevalent (30-40%) and portends an increased risk of overall mortality of 80-100% [12, 14]. A prospective cohort study of 230 prevalent peritoneal dialysis patients followed for 4-years [14], found that the only independent predictors of new-onset heart failure were cardiomyopathy and diabetes mellitus, while cardiomyopathy and low serum albumin (possibly reflecting fluid overload) were the only independent predictors of recurrent heart failure.

Left ventricular hypertrophy may be classified morphologically into either concentric or eccentric hypertrophy, although the two types may also co-exist. Concentric hypertrophy is characterized by the addition of new sarcomeres in a parallel formation leading to an increase in ventricular wall thickness without an increase in ventricular luminal diameter and usually occurs in response to pressure overload. In contrast, eccentric hypertrophy represents an adaptive response to volume overload in which sarcomeres are added in a serial formation leading to an increase in both ventricular luminal diameter and wall thickness [24, 25]. In individuals with non-dialysis dependent chronic kidney disease eccentric hypertrophy is the predominant pattern observed [26], while both patterns are equally represented among the dialysis population [12].

Cardiomyocyte hypertrophy is the histological hallmark of left ventricular hypertrophy irrespective of renal disease; however, the cardiomyopathy of chronic kidney disease is additionally characterized by excessive intermyocardial fibrosis. This was illustrated in a post-mortem series with a case-control design comparing the cardiac fibrosis scores between individuals with renal disease and matched individuals with normal renal function. The myocardium of individuals with renal disease demonstrated the highest fibrosis scores and renal disease was found to be an independent predictor of intermyocardial fibrosis even after adjusting for demographic factors and co-morbid conditions. Furthermore dialysis duration was found to be strongly correlated with the severity of fibrosis [27]. The fibrosis observed in these cases is due to the deposition of type I collagen fibres in between cardiomyocytes at the expense of myocardial capillaries resulting in impaired myocardial perfusion, reduced ventricular compliance and variances in electrical conduction and resistance which in turn predisposes to arrhythmia [28].

A number of factors contribute to the genesis and evolution of cardiomyopathy in dialysis including hypertension, volume overload, vascular stiffness, sympathetic overactivity, cardiotoxic steroids, direct fibrotic effects of angiotensin II and aldosterone, hyperparathyroidism and cardiac ischaemia. These factors are discussed in detail in subsequent sections of this chapter.

Coronary Atherosclerosis and Microvessel Disease

Individuals with chronic kidney disease have an increased incidence and prevalence of coronary artery disease compared to matched individuals in the general population [7, 15, 17, 29]. Coronary atherosclerosis associated with chronic kidney disease is characterized histologically by plaque calcification, and concurrent medial hypertrophy and calcification [30].

While myocardial ischaemia is more prevalent among the dialysis population, a disproportionate number of individuals on dialysis present with either symptomatic

myocardial ischaemia or myocardial infarction but do not have a significant coronary artery stenosis on angiography [31]. This finding is thought to be related to reduced myocardial capillary density caused by cardiac fibrosis, and to thickening of the walls of post-epicardial intramyocardial vessels – so called microvessel disease. Such vessel wall thickening has been documented in animal models [32] and in post-mortem myocardial biopsies from individuals with end-stage renal disease but not in biopsies taken from hypertensive individuals with normal renal function [27]. Post-epicardial vessel wall thickening occurs in the absence of an increase in luminal area reducing myocardial perfusion and impairing oxygen diffusion into the surrounding myocardium.

Vascular Calcification

Vascular calcification refers to ectopic accumulation of calcium-phosphate mineral in the arterial vasculature, myocardium and cardiac valves. This pathological phenomenon is frequently observed among individuals with chronic kidney disease and has been associated with an increased risk of cardiovascular mortality. A prospective cohort study of 439 individuals with a mean estimated glomerular filtration rate (MDRD eGFR) of 50.6 ml/min reported that the prevalence of any calcification in the coronary arteries, descending thoracic aorta, aortic valve, and mitral valve was 67, 49, 25, and 20% respectively [33]. The prevalence of vascular calcification is even greater among individuals with end-stage renal disease on dialysis; a randomised controlled trial of 360 haemodialysis patients investigating the impact of two therapies on vascular calcification progression reported that the prevalence of calcification in the thoracic aorta, mitral valve and aortic valve at enrollment was 91, 50, and 46% respectively [34].

The poor prognosis portended by vascular calcification is highlighted by the findings of a prospective cohort study of 110 haemodialysis patients followed for a mean duration of 53 ± 21 months assessing the association between the presence and severity of vascular calcification, and all-cause and cardiovascular mortality. The study reported a significant, graded increase in the risk of all-cause mortality with an increase in the number of vascular sites involved with calcification (Risk of all-cause mortality for 0 to 4 sites involved was 3, 17, 31, 50 and 73% respectively). Furthermore, a multivariate analysis adjusting for demographic factors, co-morbidities and vascular functional indices found that vascular calcification severity assessed using a calcification score was an independent predictor of both all-cause mortality (HR = 1.9 per unit increase in calcification score) and cardiovascular mortality (HR = 2.6 per unit increase in calcification score) [35].

The mortality risk conveyed by vascular calcification is thought to be mediated by increased vascular stiffness which acts to promote left ventricular hypertrophy and reduce myocardial perfusion. This hypothesis is supported by findings of a prospective longitudinal study of 134 dialysis and non-dialysis dependent chronic kidney disease patients assessing the association between change in vascular calcification severity and (1) vascular stiffness assessed using pulse wave velocity and pulse pressure, and (2) all-cause mortality. The study demonstrated a significant correlation between progressive vascular calcification and increasing pulse pressure and pulse wave velocity, in addition to a significant association between increasing vascular calcification and the risk of all-cause mortality [36]. These findings were echoed by a prospective cohort study of 110 haemodialysis patients which

demonstrated a significant association between measures of increasing vascular stiffness and increasing severity of vascular calcification [35].

Vascular calcification associated with chronic kidney disease is characterized by accumulation of calcium phosphate mineral in the medial rather than the intimal layer of arterial vessels. Ultrastructural examination of vessels from patients end-stage renal disease undergoing renal transplantation reveals calcium-phosphate mineral in extracellular loci as either hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6\text{OH}_2$] and/or whitlockite [$(\text{CaMg})_3(\text{PO}_4)_2$] crystals co-localizing to areas of damaged vascular smooth muscle cells, extracellular vesicles, and bone proteins including Type I collagen fibrils, osteopontin, bone sialoprotein and alkaline phosphatase [37-39]. There is also inconclusive evidence that arterial elastin fibrils may be disrupted and/or calcified as part of the vascular calcification process [40]. The pathogenesis of vascular calcification is discussed in the subsequent section entitled 'Mineral and Bone Disorders and The Pathophysiology of Vascular Calcification'.

Physiological Derangements

Hypertension

Hypertension is highly prevalent in the dialysis population (75–86 %) [16, 41, 42], is principally related to volume overload and can be remedied in over 90% of cases by ultrafiltration [43, 44]. Other contributing factors include sympathetic overactivity, activation of the renin-angiotensin axis, and vascular stiffness which are discussed in more detail below.

Early studies examining the association between blood pressure and survival in the dialysis population suggested a 'U' shaped relationship whereby mortality risk was increased not only with extremely high post-dialysis blood pressures (systolic >180 mmHg or diastolic >90 mmHg), but also with blood pressures targets often prescribed in dialysis units (pre- or post- dialysis blood pressure <110 mmHg) [45,46]. These findings contrast with those of a longitudinal cohort study demonstrating that baseline hypertension at dialysis inception and residual hypertension at 1 year post-dialysis commencement were associated with a significantly increased risk of mortality without any survival disadvantage associated with low blood pressure [47]. These findings were echoed by a prospective cohort study of 692 haemodialysis patients in whom a mean arterial blood pressure > 110 mm Hg was associated with an increased risk of all-cause and cardiovascular death after adjusting for demographic factors and co-morbid conditions [48].

Finally, a recent meta-analysis of 8 randomised controlled trials of antihypertensive therapy in dialysis found significant reductions in the risks of fatal and non-fatal cardiovascular events and all-cause mortality in actively treated patients compared with controls supporting the hypothesis that hypertension portends an adverse prognosis in the dialysis population [49].

The discrepancy between early and contemporary studies regarding the association between hypertension and mortality is likely explained by a lack of adjustment for important confounding factors, particularly cardiac systolic dysfunction in which low blood pressure increases the risk of mortality [50].

Vascular Stiffness

Vascular stiffness refers to a reduction in the compliance and elastic properties of central arteries such as the thoracic aorta. The reduced compliance of these vessels impairs propagation of the cardiac pressure wave generated during systole, necessitating an increase in systolic blood pressure in order to maintain systemic perfusion. This increased myocardial work stimulates myocardial hypertrophy and increases myocardial oxygen demand. Furthermore, increased vascular stiffness accelerates the propagation of the pulse wave and earlier return of the reflected wave towards the myocardium which reduces diastolic blood pressure compromising coronary perfusion which occurs predominantly during diastole [51, 52].

Vascular stiffness is most often measured as central pulse pressure and pulse wave velocity. This latter technique measures the rate of propagation of the pulse wave from the heart to a central artery using tonometry and oscillometric pulse recognition algorithms; increasing pulse wave velocity reflects worsening vascular stiffness [52].

The adverse prognosis conveyed by vascular stiffness was demonstrated in a prospective cohort study of 265 haemodialysis patients followed for 63 ± 23 months investigating the association between pulse wave velocity, and all-cause and cardiovascular mortality. When stratified around the cohort's median value, increasing pulse wave velocity was shown to be an independent predictor both all-cause and cardiovascular mortality after adjusting for demographic and co-morbid conditions including diabetes and hypertension [53].

Vascular stiffness observed in chronic kidney disease populations results from an interplay between several pathologic mechanisms including vascular calcification [54], reduction in the elastin content of central vessels [40], and vascular smooth muscle hypertrophy secondary to hypertension and the trophic effects of catecholamines, angiotensin II and aldosterone [55].

Myocardial Ischaemia

Ischaemic heart disease has a prevalence of 30–40% in the dialysis population [7, 22] and is related to accelerated atherosclerosis of epicardial coronary arteries due to a higher prevalence of traditional ischaemic risk factors [15] and novel mechanisms including oxidative stress, sympathetic overactivity, and mineral and bone disorder. However, approximately 30% of dialysis patients presenting with symptomatic ischaemic heart disease (myocardial infarction or angina) do not have evidence of epicardial coronary stenosis [31].

Myocardial ischaemia in these individuals is thought to be due to reduced myocardial oxygen reserve secondary to the reduction in myocardial capillary density that accompanies myocardial fibrosis and thickening of the vessel wall of post-epicardial arterioles [27, 32]. Cardiac hypoperfusion may also be exacerbated by vascular stiffness which impairs coronary and myocardial perfusion during diastole as has been discussed previously.

Inciting Pathological Mechanisms

Sodium and Water Excess

Extracellular volume expansion as a result of sodium and water retention is common both among individuals with early stage chronic kidney disease [56] and those with end-stage renal disease on dialysis therapy [57, 58]. Several studies have identified volume overload as a critical risk factor for both morbidity and mortality in the dialysis population. A cohort study of 269 prevalent haemodialysis patients followed for 3.5-years found that overhydration assessed by bioimpedance spectroscopy (an instrument to objectively assess volume state) was associated with an independent relative risk of all-cause mortality of 2.1 in a multivariate analysis [58]. Similarly, a cohort study of 3009 prevalent haemodialysis patients followed for 1-year demonstrated that increasing volume state conveyed a significant, graded increase in the risk of death. Indeed, the relative risk of death was as high as 2.83 for the most overhydrated patients following adjustment for demographic factors, co-morbid conditions and novel cardiovascular risk factors [28]. A number of cohort studies have also demonstrated a significant association between clinical and surrogate biochemical measures of overhydration, and cardiovascular mortality [57-61] and sudden cardiac death [23, 62].

Sodium and water accumulation in chronic kidney disease results from hormonally induced adaptations to renal injury, a progressive overwhelming of tubular solute reabsorptive capacity, and excessive sodium intake. Glomerular injury and subsequent nephron loss from any aetiology induces a compensatory response whereby the single nephron glomerular filtration rate (GFR) of remaining functioning nephrons increases to compensate for the reduction in absolute numbers of nephrons. This glomerular hyperfiltration is effected by an increase in renal perfusion due to extracellular fluid volume expansion, and concurrent dilatation of the afferent arteriole and relative vasoconstriction of the efferent arteriole which have the net effect of increasing glomerular transcapillary pressure and single nephron GFR. These adaptations are mediated in large part by activation of the intra-renal renin-angiotensin-aldosterone axis in response to the renal hypoperfusion caused by any aetiology. Angiotensin II plays a critical role in inducing the changes in arteriolar caliber described above, while aldosterone stimulates an increase in tubular sodium and hence water reabsorption producing extracellular volume expansion [63-65].

Progressive chronic kidney disease is accompanied by tubular adaptations which increase fractional sodium excretion per nephron in order to maintain sodium homeostasis despite a reduction in functional nephron mass. However, despite this increase in relative sodium excretion per nephron, *absolute* sodium excretion is reduced contributing to excess sodium and water retention particularly in the latter stages of chronic kidney disease [56, 64].

Extracellular volume expansion induced by sodium and water retention plays an important role in the genesis of hypertension in chronic kidney disease. This is particularly true of the end-stage renal disease population in whom hypertension can be attributed to volume overload in over 90% of cases [43, 66] and can be effectively remedied using ultrafiltration [44]. Volume expansion has been shown to be an independent predictor of cardiomyopathic changes including left ventricular hypertrophy, left atrial dilatation, and left ventricular systolic dysfunction in all stages of chronic kidney disease [12, 14, 20, 56], while control of volume state in dialysis has been shown to improve echocardiographic indices [67].

In addition to its role in volume expansion, sodium excess has a number of independent adverse physiological effects including the direct stimulation of angiotensin II by vascular tissue [68] and stimulating the secretion of the cardiotonic steroid marinobufagenin by adrenal cortical cells [69, 70]. This latter hormone has been implicated in the genesis of cardiomyopathy and cardiac fibrosis in animal models of chronic kidney disease [71, 72].

Mineral and Bone Disorders and the Pathophysiology of Vascular Calcification

Progressive chronic kidney disease and the consequent fall in GFR reduces the filtered phosphate load and increases plasma phosphate concentrations [73]. The resulting hyperphosphataemia has a number of important consequences including (1) antagonizing 1α -hydroxylase activity; reducing circulating concentrations of $1,25(\text{OH})_2$ Vitamin D (calcitriol) [74] (2) inducing hypocalcaemia due to its effect on reducing circulating calcitriol concentrations and to a much lesser degree by directly binding ionized calcium to form calcium hydroxyphosphate [75] (3) inducing secondary hyperparathyroidism by directly upregulating parathyroid hormone synthesis [76, 77], its hypocalcaemic effects and through reducing calcitriol concentrations both of which also directly upregulate parathyroid hormone synthesis.

The association between bone mineral disturbances and mortality is highlighted by a recent systematic review of 35 prospective, observational and interventional studies which examined the association between all-cause and cardiovascular mortality, and hyperphosphataemia, hypercalcaemia and hyperparathyroidism. Heterogeneity between studies with respect to participant characteristics, method of mineral parameter assessment (continuous vs. dichotomous vs. categorical) and control for confounding precluded meta-analysis of the studies' findings, however, the studies were consistent in finding a significant association between hyperphosphataemia and both all-cause and cardiovascular mortality albeit of varying magnitudes. In addition, the majority of studies demonstrated a significant increase in the risk of all-cause mortality in association with hypercalcaemia and hyperparathyroidism [78]. The increased risk of mortality conveyed by these mineral disturbances is thought to be mediated through their role in initiating and promoting vascular calcification and subsequent vascular stiffness. This is particularly true of hyperphosphataemia which has been shown to be an independent predictor of vascular calcification even after adjustment for CKD severity, demographic factors, co-morbidities, parathyroid hormone and $1,25(\text{OH})_2$ Vitamin-D concentrations [33].

Vascular calcification represents an interplay between a number of pathological processes including the (1) osteogenic / chondrogenic differentiation of vascular smooth muscle cells (VSMC), (2) extracellular release of calcium-phosphate rich vesicles by VSMC (3) a reduction in circulating factors that inhibit calcification, and (4) apoptosis of vascular smooth muscle cells. Two receptors – Pit-1 and Pit-2 – located on VSMC play differing but complimentary roles in vascular calcification. In the presence of hyperphosphataemia, the Pit-1 receptor increases intracellular phosphate concentrations in VSMC and induces osteogenic / chondrogenic differentiation through the upregulation of the osteogenic transcription factor Runx2. This transcription factor induces the synthesis of extracellular matrix bone proteins such collagen type I, osteopontin, and bone sialoprotein which are able to undergo

calcification [79, 80]. In contrast, the Pit-2 receptor plays a critical role in loading intracellular VSMC vesicles with calcium and phosphate [54]. These vesicles are subsequently secreted and act as nidus for extracellular medial calcification [38]. Vascular calcification is also promoted by a reduction in concentration of circulating calcification inhibitors such as fetuin-A and pyrophosphate which are reduced in chronic kidney disease its associated chronic inflammatory state [79, 81, 82]. In addition to its metaplastic effect, phosphate is also able to induce apoptosis of VSMC with the resulting apoptotic bodies acting as nuclei for calcification [54].

Sympathetic Overactivity

Sympathetic activity measured in the form of circulating norepinephrine concentrations or using microneurography of the peroneal nerve (muscle sympathetic nerve activity) has been shown to be markedly elevated in patients with dialysis- [83, 84] and non-dialysis [85, 86] dependent chronic kidney disease and correlates with the severity of renal impairment [86] suggesting that chronic renal injury may stimulate sympathetic hyperactivity. This hypothesis is supported by the observations that patients with end-stage renal disease on dialysis who have undergone bilateral, but not unilateral, nephrectomy have sympathetic activity in keeping with that of healthy controls [84].

The adverse prognosis portended by sympathetic hyperactivity was highlighted by a prospective cohort study of 228 haemodialysis patients followed for 34±15 months, 45% of whom had elevated circulating norepinephrine concentrations. After adjusting for demographic features, co-morbidities and concurrent medication use, the authors reported a significant, graded association between plasma norepinephrine concentrations and the risk of fatal and non-fatal cardiovascular events, and all-cause mortality [87]. These findings are also circumstantially supported by the results of two pilot randomised controlled trials in dialysis demonstrating a reduction in mortality [88] and improvement in cardiac diastolic function with the use of the beta-blocker carvedilol [89], however the beneficial effects observed may be partly or wholly related to concurrent improvements in blood pressure.

Sympathetic overactivity associated with renal injury is explained both by an increase in sympathetic outflow and reduced catecholamine breakdown. Animal studies have demonstrated that acute and chronic renal injury stimulate autonomic centers in the hypothalamus via afferent nerves in the spinothalamic tract resulting in increased sympathetic outflow [90] and that this sympathetic hyperactivity can be abolished by denervation of the injured kidney [91].

Angiotensin II and adenosine have been implicated as potential mediators between the kidney and the autonomic nervous system. As discussed previously both acute and chronic renal injury are characterized by upregulation of the renin-angiotensin axis. The increase in circulating concentrations of angiotensin II stimulates angiotensin receptors in the medulla oblongata which in turn stimulate the posterior hypothalamic nuclei leading to an increase in sympathetic efferent activity [92]. The importance of this pathway in promoting sympathetic hyperactivity was elegantly demonstrated in animal models in which sympathetic overactivity associated with renal injury could be abolished by either intravenous or targeted intracranial injection of an angiotensin receptor blocker [93]. Angiotensin II is able to upregulate sympathetic nervous activity through direct peripheral, pre-synaptic binding which increases

the secretion and reduces the reuptake of norepinephrine [92]. Adenosine is released from the injured kidney following minor ischaemic insults and has also been implicated as an important mediator of sympathetic excitation. This was illustrated by experiments in 1-clip, 2-kidney dogs in which intrarenal adenosine infusion increased sympathetic activity and circulating norepinephrine concentrations which could be abolished by renal denervation or ganglionic blockade [94].

In addition to increased stimulation of efferent activity, it is now also recognized that sympathetic hyperactivity associated with chronic kidney disease is related to reduced clearance of circulating catecholamines [95]. The kidney has been identified as the synthetic site of the proenzyme prorenalase [96, 97], which in the presence of high circulating concentrations of catecholamines is activated to renalase which in turn metabolizes and inactivates catecholamines including dopamine, epinephrine and norepinephrine [98]. Renalase synthesis and activity are reduced in individuals with chronic kidney disease [96] which contributes to the increase in circulating catecholamine concentrations.

Sympathetic hyperactivity has a number of direct and indirect adverse cardiovascular consequences. It contributes significantly to hypertension associated with chronic renal disease as is illustrated by the correlation between blood pressure and sympathetic nerve activity [99] and the profound blood pressure response to sympatholytic agents in haemodialysis [100]. Norepinephrine is able to induce left ventricular hypertrophy directly through a trophic effect on cardiac myocytes [101, 102], contributes to increased vascular stiffness by promoting hypertrophy of vascular smooth muscle in the peripheral vasculature [103], and may play a role in triggering arrhythmias [104].

Oxidative Stress and Inflammation

Oxidative stress is defined as tissue injury caused by excess circulating anionic free radicals called reactive oxygen species (ROS). The increased concentration of these injurious free radicals is caused both by the increased generation of ROS and reduced synthesis of neutralizing anti-oxidant molecules [105]. ROS cause cellular injury both directly and indirectly through the activation of cellular and humoral inflammatory processes. Increased concentrations of ROS and inflammatory cytokines, and reduced levels of antioxidants have been documented in the chronic kidney disease population and are associated with a poor prognosis. A prospective cohort study of 19 patients with stage 5 CKD, 15 of whom were on dialysis, reported significantly higher concentrations of two oxidative species (Carbonyls and F₂-isoprostanes) and numerous inflammatory markers in the end-stage renal disease group compared to healthy controls. In addition, there was a significant positive correlation between the concentrations of F₂-isoprostanes and C-reactive protein [106]. The adverse prognosis associated with oxidative species and inflammation is illustrated by a cohort study of 94 prevalent haemodialysis patients followed for 2-years which reported a significant direct association between the concentrations of both C-reactive protein and anti-oxidized LDL antibody (a marker of oxidative stress) and the risk of all-cause mortality in a multivariate analysis [107]. These findings were echoed by a retrospective cohort study of 105 haemodialysis patients followed for 9-years which reported a significant inverse association between concentrations of anti-oxidant proteins and the risk of cardiovascular mortality [108]. The possible role of renal dysfunction per se in promoting oxidative stress is supported by the

finding that concentrations of oxidative species and inflammatory markers fall following successful renal transplantation and approximate those of healthy controls [106].

The mechanisms underlying the association between oxidative stress and heightened cardiovascular risk have not been fully elucidated but may include accelerated atherosclerosis related to oxidized LDL, carbonyl proteins and advanced glycation end-products [109, 110] or endothelial injury and dysfunction leading to hypertension, vascular stiffness and promoting atherosclerosis [111].

Increased concentrations of oxidant species in chronic kidney disease may be due to an increase in the generation of ROS through reactions involving nitrogenous waste products including urea [112], derangements of the mitochondrial respiratory chain [113], and exposure to artificial dialysis membranes. In addition, chronic kidney disease is associated with reduction in concentration of antioxidant molecules such as thiols [114] and antioxidant enzymes such as superoxide dismutase which is normally expressed in renal tubules [115].

Conclusion

Individuals with chronic kidney disease have a disproportionate risk of cardiovascular disease which accounts for the majority of the morbidity and mortality in this population. While traditional cardiovascular risk factors are overrepresented in the chronic kidney disease population, this alone is not sufficient to explain the excess risk observed. Chronic kidney disease is also associated with a number of novel pathophysiological mechanisms including salt and water retention, bone and mineral disorders, sympathetic overactivity and oxidative stress which combine to cause a number of pathological cardiovascular changes unique to chronic kidney disease. A greater understanding of these mechanisms is the first step to developing effective cardiac risk monitoring strategies and therapies.

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Chapter III

Protective Effect of Ozone Therapy in Renal Damage

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Abstract

This is a review of all our research about the protective effect of ozone therapy in renal damage due to ozone's immunomodulator effect and its capacity to increase the antioxidant defense system and enhance oxygen metabolism. We developed preclinical studies in renal ischemia-reperfusion (I/R) model, indicative of an acute renal damage, and toxic glomerulonephritis produced by adriamycin, one of the causes of chronic renal failure (CRF) syndrome. Likewise, we carried out preclinical studies in a model of CRF by total nephrectomy of the right kidney and vascular ablation of the renal mass of the left kidney. Also, a clinical assay with patients suffering from CRF was studied. CRF has become one of the diseases that have attracted an increasing attention as a health priority problem at world wide. CRF can be presented in multiple pathological processes, where there is a compromise in blood flow of the renal artery, as it is present in the shock of different causes: in severe burn patients, in renal transplantation and in patients with hypovolemia of any etiology. For that reason, CRF is considered as one of the causes of renal complications. The most frequent complication of renal failure reported is the acute tubular necrosis. It appears in a greater frequency when the time of ischemia is over 30 min; therefore, it can be considered that this time is decisive in kidney viability at the moment of reoxygenation. Taking into account the high morbimortality of renal diseases worldwide, mediated mainly by reactive oxygen species that produce cell damage compromising renal function and even the patient's life, we propose to study ozone as a possible kidney protective agent since it is capable to modulate the oxidative stress and the immune system without side effects. In preclinical and clinical assays, ozone

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protective effect was demonstrated in the preservation of renal function and morphological integrity of the nephron, glomerules and proximal convoluted tubules of the kidneys, analyzed in the preclinical models; in the achievement of a REDOX (reduction-oxidation) homeostasis by the stimulation of the antioxidant defense system; and in the modulation of pro-inflammatory cytokines. All these effects contribute the delay of the progression of the disease, with an important improvement in the quality of life of patients who have CRF. Also, ozone therapy can be considered as an important therapeutic strategy to minimize the renal damage after transplantation.

Keywords: Ozone therapy, renal protection, reactive oxygen species, oxidative stress, reperfusion, warm ischemia, chronic renal failure

Introduction

During ischemia, changes which affect the cell and provide the biochemical and physiological basis for a damage increase during reperfusion [1] occur. Renal vasoconstriction and tubular dysfunction have been clearly defined as the most important mechanisms that affect the nephron functioning, reducing glomerular filtration rate (GFR), after I/R phenomenon [2].

Ischaemia provokes endothelial damage and, therefore, endothelial dysfunction, creating an unbalance between vasodilators agents [nitric oxide (NO^*), adenosine, prostaglandine E_2 (PGE_2), decreasing their values] and vasoconstrictors agents [endothelin 1 (ET-1), angiotensin AII, thromboxane A_2 (TBxA_2), leukotrienes, increasing their values], displacing the equilibrium to the production of the latter, achieving an uncontrolled vasoconstriction. All this produces a decrease of the glomerular filtration coefficient (kf) and the glomerular filtration rate (GFR), increase of the vascular resistance at the level of the afferent and efferent arterioles, with the subsequent decrease of the renal blood flux (RBF) [2]. During tissue reoxygenation, after an ischemia, a turbulent blood flux is produced, which increases the shearing force in the endothelium. All these effects increase endothelial damage, favoring the release of vasoconstrictors, responsible for the maintenance of vasoconstriction during the reperfusion and, therefore, decreasing GFR in the post ischemic kidney [2].

Tubular dysfunction occurs due to the decrease of adenosine triphosphate (ATP) and the lack of oxygen, leading to cell dysfunction, sublethal damage and cell death. All these events, at the level of the tubular epithelium, culminate with epithelial cell desquamation, provoking tubule obstruction with increase of the hydrostatic pressure of the Bowman capsule and a decrease of GFR [1-3].

At present, in the physiopathology of the ischemia/reperfusion (I/R), a leading role has been appointed to reactive oxygen species (ROS), as superoxide anion ($\text{O}_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical (HO^*), singlet oxygen ($^1\text{O}_2$), nitric oxide (NO^*), peroxynitrite ($\text{O}=\text{NOO}^*$), hypochlorous acid (HOCL), among others. By increasing chronically, they originate an unbalance between the activity of the prooxidant and the antioxidant systems, with a predominance of the first, generating an oxidative stress [4].

When ROS are increased and not neutralized with antioxidant substances, they are capable to induce lipid peroxidation in the membranes. They can react with unsaturated fatty acids provoking their structure and function modification. Also, they produce the lateral chain

oxidation of amino acid residues and the formation of protein-protein cross bonds, as well as the oxidation of the protein skeleton producing its fragmentation (for example the Na^+/K^+ ATPase and Ca^{++} ATPase). Also, ROS are able to react with the thymine of the nuclear and mitochondrial DNA, inhibiting cell repair and proliferation [5].

Some researches have tried to neutralize ROS damage using antioxidant enzymes as SOD, CAT and glutathione peroxidase or allopurinol (xanthine oxidase inhibitor) and deferoxamine (inhibitor of Fenton reaction). They have obtained a reduction in cell damage and in the organ dysfunction caused by I/R, proving the role of the oxidative stress in I/R process [2, 6].

CRF represents a world health problem; once established it goes irreversible far to a final stage, provoking the patient death. It is known that the first leading causes of CRF are diabetes mellitus, arterial hypertension and glomerulonephritis [7].

In Cuba, the mean incidence of new cases that start a dialysis is 120 by millions of habitants per year (with a prevalence in the general population of 350 cases and with a death per year in 130 cases per million of inhabitants), for the United States and Japan is near 300 cases. World population under dialysis is greater than half a million and increases, at an annual rate of 10 %. In 1995, in the United States, the cost of dialysis and transplantation program was 13.3 billion dollars; in Cuba it surpasses the 3.5 millions per year. Due to its progressive increase and high costs, some epidemiologists have named it the "catastrophic disease". [National Program for the Attention of Chronic Renal Patient (2005). "Dr. Abelardo Buch López" Nephrology Institute, Havana, Cuba]. Today, the international and Cuban strategy for the renal patient is to guide all the efforts, mainly to delay the progression of the CRF, diminishing the dialysis processes and the terminal CRF, as well as to increase the quality of life of these patients.

In contrast with the capacity of the kidneys to regain function, following acute renal injury, renal injury of a more prolonged nature often leads to progressive and irreversible destruction of nephron mass [8]. Such reduction of renal mass, in turn, causes structural and functional hypertrophy of surviving nephrons. This compensatory hypertrophy is due to an adaptive hyper filtration mediated by an increase in the glomerular capillary pressures and flows. Eventually, these adaptations prove maladaptive, predisposing to sclerosis of the residual glomerular population [8-11]. The intrarenal vasculature is the most affected structure, preventing an appropriate blood flow, favoring the glomerular sclerosis [8-12]. Therefore, improvement of the rheological properties of blood could delay the progression of CRF.

Glomerular damage caused by a toxic agent is mediated by different molecular mechanisms where the ROS are also involved. It is known that the action of this toxic agent in renal tissue releases a great quantity of free radicals as superoxide anion and hydroxyl radical, among others [13]. In spite of that, the kidneys have a potent antioxidant capacity (enzymatic and non enzymatic), but in the development of glomerulonephritis this capacity is disabled due to the high levels of ROS in renal tissue [14]. ROS have been demonstrated to be capable of degrading glomerular basement membrane and inducing glomerular injury, characterized by impaired glomerular filtration and sieving function [15, 16].

In general, all the cells that form the renal structure, at vascular level (endothelial and smooth muscles) or at glomerular (endothelial and mesangial) or tubular level (proximal, distal and collecting) are able to produce and release ROS before a certain stimulus, such as drugs, acute hypertension, radiation or high oxygen pressure [17]. Also, granulocytes,

monocytes-macrophages and platelets, that are present in several renal inflammatory processes (glomerulonephritis, vasculitis, pyelonephritis), produce high quantity of ROS, being impossible to separate the ROS that become from these infiltrate cells from the other ones produced by the resident cells at the time to evaluate their action in the renal pathology [14-19].

At glomerular level, in some glomerulonephritis, micro thrombotic and microangiopathic processes and in damage due to toxics (drugs, radiation), the ROS induce the production of edema, endothelial detachment and basement membrane denudation, thrombi, mesangiolysis, epithelial vacuolization and pedicle fusion. From the functional point of view, all these effects produce an increase in permeability and proteinuria, as well as intraglomerular hemodynamic changes. In the tubule, , edema, basal membrane denudation and lyses can be seen [20, 21].

Studies performed in patients with different degrees of CRF suggest that renal patients are in an oxidative stress condition if they are compared with healthy persons and that the degree of oxidative stress directly correlates with the degree of CRF [14-19].

In order to eliminate toxic ROS, cells are equipped with various antioxidant defense systems. Therefore, the development of tissue injury depends on the balance between ROS generation and tissue antioxidant defense mechanism [22]. It has been demonstrated the role of the antioxidant enzymes [superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx)] against the oxidative renal damage. These enzymes distributed in cytosol and/or mitochondria can abase primary ROS, such as superoxide anion (by SOD) and hydrogen peroxide (by GPx and CAT) before they can interact to form more reactive cytotoxic metabolites (hydroxyl radical or hypochlorous acid, among others). Thus, we suggest that the glomerular antioxidant enzymes play an important role in the functional derangement induced by ROS [23]. A protective effect in renal function and morphology against the ROS is obtained by increasing the level of these antioxidant enzymes in the glomerule [24, 25]. Therefore, by modulating the levels of these enzymes, a potent mechanism of resistance against the acute renal damage is possible to achieve.

Ozone (O₃) has been used for medical purposes for more than 100 years. Its mechanism of action is related to the generation of secondary products in its reaction with: double bonds present in lipids, bisulphide bonds and -SH groups of protein (albumin) present in cell membranes. Formation of hydroxyhydroperoxides, hydrogen peroxide, aldehydes and ozonides have been described as intermediate compounds capable to activate biochemical mechanisms and gene expression, being involved in several cell processes [26-29]. The application of this gas, at controlled doses, produces a slight and transient oxidative stress that stimulates the endogenous antioxidant mechanisms, preparing the host to face physiological conditions mediated by ROS [30].

It is reported, at renal level, a protective effect of the ozone oxidative preconditioning (OzoPre) in some biomarkers of renal function in kidneys submitted to ischemia of 30 min and reperfusion of 180 min [13]. In this case, ozone is applied before the ischemia. Also, at hepatic level, it was demonstrated that OzoPre protected the liver from tissue damage mediated by I/R, with time of ischemia and reperfusion of 90 min [31]. Both studies proved the cytoprotective effect of OzoPre in the preparation of the tissues to face the I/R. In these studies and in other animal models developed by the Ozone Research Center (Havana, Cuba), as well as in clinical assays performed, it has been demonstrated the effect of ozone in the stimulation of the antioxidant defense systems achieving the REDOX (reduction-oxidation) homeostasis [32-51].¹

Nowadays, there are different strategies to face I/R, but most of them are in study or in clinical trial phase, therefore, their use is limited in medical practice. In CRF, not much can be done to delay the progression of the disease. Therefore, it is necessary to find new therapeutical procedures, able to preserve the kidneys without side effects during the I/R present in several clinical situations and to increase the quality of life of CRF still present in patients.

Taking into account that the oxidative stress play an important role in renal impairment and ozone is capable to modulate the oxidative stress and the immune system without side effects, as well as to increase oxygen metabolism by means of a better transportation, absorption and use of oxygen, resulting in an improved tissue oxygenation and blood rheological properties, with the correspondence cell function recovery, among other effects, the aim of this review is to discuss the ozone protective effect in renal damage based in some acute and chronic studies [13,38,42,50,52-56] by means of functional, biochemical, immunological and histological parameters measured in preclinical and clinical experiences.

Results and Discussion

There are clinical situations in daily medical practice such as: renal transplantation, nephrolithiasis and in conservative surgery of renal tumors, among others, in which it is necessary to produce a temporal renal ischemia, but it can produce morphological and functional lesions. Then, the timing of warm and cold ischemia is determinant for kidney's viability [57]. To this, a number of nosological entities are added where renal ischemia occurs, such as: peripheral vasodilatation in the course of a bacteriemia, hypovolemia during a hemorrhage, renal vascular obstruction during an embolism at the level of the renal artery, congestive cardiopathy and acute myocardium infarction [58-60]. From the preclinical and clinical point of view, renal I/R phenomenon is the main role player of the acute renal failure, then, all the strategies employed for the management of the acute renal insufficiency must be addressed mainly to diminish, by different ways, the molecular events that occur during the I/R.

Also, it has been taken into account the high prevalence of patients with CRF, whose quality of life is severely affected and once established it goes irreversible to a final stage, provoking the patient's death. For that reason, any prophylactic approach aiming at preserving the kidney and relieving these patients is of great clinical importance.

In both, acute and chronic renal failure, an excess of ROS is present, increasing the damage [14,18]. ROS have been increasingly recognized as potential mediators of cell inflammatory cells injury during glomerulonephritis [61].

There are different studies on the use of ozone to prevent renal cell damage which includes renal ischemia-reperfusion (I/R) model, indicative of an acute renal damage, toxic glomerulonephritis produced by adriamycin, one of the causes of chronic renal failure (CRF) syndrome and a model of CRF by total nephrectomy of the right kidney and vascular ablation of the renal mass of the left kidney, as well as a clinical assay with patients suffering of CRF. In all it had been demonstrated that ozone therapy was able to revert the damage, by means of different mechanisms, where the activation of the endogenous antioxidant defense system had an important role in renal protection.

Nowadays, it is postulated that other mechanisms associated to signal transduction for the activation or repression of specific gene transcription are the cornerstone in the mechanism of action for the oxidative stress modulation [26]. It had been demonstrated that the administration of SOD and CAT are very effective in diminishing functional and structural abnormalities (proteinuria and glomerular lesions) in rats submitted to a damage induced by puromycin amino nucleoside [62,63]. Therefore, an increase in the activity of antioxidant enzymes produced by the ozone treatment could protect the nephrons against the toxic effect of ROS. By this way, ozone therapy can generate a dynamic regulation between the prooxidant and antioxidant defense activities produced by the organism.

With respect to the parameters related to oxidative stress, studies have revealed similar results as reported by other authors [31, 34, 64], where the OzoPre was able to stimulate, at the level of the damage tissue, the activity of the antioxidant enzymes. However, in the positive control group (without ozone) it was observed a decrease of the antioxidant capacity of the enzymes: SOD, CAT y GPx, as well as the decrease of GSH and the increase of lipid peroxidation (measured by means of TBARS). GPX is an enzyme Se-dependent or Se-independent, being one of the most important antioxidant systems of the cell. The main role of GPx is to protect the "internal milieu" from possible damage due to excess H_2O_2 or lipid hydro peroxides [5, 65]. The behavior of this enzyme, at the level of renal tissue submitted to I/R without previous treatment, is similar to that reported by other authors [66], a decrease of the activity of this enzyme in both phases (ischemia and reperfusion). However, in I/R and partial nephrectomy models, an increase of GPx in post ischemic renal tissue was observed, contributing to the cell antioxidant defense against the H_2O_2 . In a study using transgenic mice submitted to I/R, an overproduction of GPx (intra and extra cellular) with a subsequent decrease of chemokine expression, macrophage inflammatory protein 1 α and 1 β and neutrophil infiltration, resulting in a less damage to renal function after the ischemia has been reported [67]. These results showed the importance of this enzyme activation in diminishing inflammation, during the ischemia and also when the CRF is established. When ozone stimulates the GPx activity, could have a delay effect in H_2O_2 increase and therefore, in the amplification of the inflammatory process achieving the protection of the kidney submitted to I/R phenomenon.

Hui Chen et al. [64], showed some of the mechanisms associated to the effects of ozone therapy in the prevention of renal injury during the I/R phenomenon. OzoPre was able to inhibit inflammation and apoptosis in kidneys of rats submitted to ischemia (45 min) and reperfusion (24 h). Inhibition of caspase activity and reduction of lipid peroxidation and proinflammatory interleukins (TNF α and IL-1) were demonstrated. In this study an ozone dose of 1 mg/kg, by rectal insufflation during 10 sessions, before the ischemic damage was used. This study clarified some of the mechanism of action of the OzoPre in the protection against the renal I/R, though the time of ischemia was only of 45 min and only one ozone dose was used. However, in our study, one hour of ischemia is applied and three different ozone doses are applied, demonstrating, by the results achieved by microscopy of high resolution, morphometric study, interleukin 6 immunoreactivity in renal tissue, evaluation of REDOX state and protein attack, that the optimum dose was 0.5 mg/kg, with 10 sessions of ozone application.

There are other studies that reported about the effect of OzoPre and ozone oxidative post conditioning (OzoPost, when the ozone is applied after the ischemia during the reperfusion) in renal damage [44, 45]. In a model of acute renal nephrotoxicity mediated by cisplatin, it

was demonstrated that both preconditionings were able to protect renal tissue against the oxidative damage induced by this drug in kidneys [44, 45].

With respect to SOD, only the enzyme that acts upon a radical (catalyzes the dismutation of $O_2^{\bullet-}$ to H_2O_2), has an important role in kidney protection against free radical release during the I/R and in CRF [66, 68]. In our experiments, OzoPre produced the stimulation of the SOD activity, in the injured renal tissue, similar to those reported about the tissue stimulation of SOD activity in organs submitted to I/R [13, 51, and 52]. In our conditions, the kidneys of the positive control group showed a significant decrease of renal SOD activity with the subsequent damage to renal function and structure, due to the lack of protection against oxidative stress. The significant stimulation of SOD in the O_3 group suggests that cellular protection is most likely achieved through the reduction in the availability of superoxide anion ($O_2^{\bullet-}$). The interaction between hypoxanthine and xanthine oxidase results in generation of superoxide. Once formed, $O_2^{\bullet-}$ is rapidly converted to hydrogen peroxide (H_2O_2) by SOD and then H_2O_2 is converted to water (by glutathione peroxidase) or to water and oxygen (by catalase). However, in the presence of various transition metals, H_2O_2 is rapidly converted to hydroxyl free radical (Fenton reaction). A delicate balance must, therefore, be maintained among the availability of superoxide, hydrogen peroxide and reduced iron (Fe^{2+}) to minimize the highly toxic hydroxyl radical formation. Superoxide acts as a chemotactic agent of inflammatory cells such as neutrophils and when they reach the damaged tissue, they release great quantities of ROS and proinflammatory interleukins, expanding even more the tissue injury. Superoxide can also react with nitric oxide (NO^{\bullet}) producing peroxynitrite, a highly toxic product and chimiotactic agent of inflammatory cells. Nitric oxide acts as a potent vasodilator readily degraded by superoxide anion, therefore, antioxidants, particularly SOD (through their ability to scavenge superoxide anion) can maximize the renal protective action of NO^{\bullet} (guarantees the blood flow to damaged renal tissue protecting it from vasoconstriction and hypoperfusion phenomenon) [69,70].

Also, SOD is one of the few antioxidant enzymes that is filtered by the glomerule, protecting it and the tubules from the attack of $O_2^{\bullet-}$ [66]. It is reported that the administration of SOD prolongs the NO^{\bullet} muscular relaxation action, corroborating the protective role of this enzyme upon the intra-renal hemodynamics, when the kidneys are submitted to I/R or presented CRF [70, 71]. Others authors referred that the administration of SOD, during the reoxygenation, protects the renal function and organ structure during this event [66].

In studies performed in kidneys, reperfusion followed the ischemic damage, provoked the loss of peroxisome matrix proteins, with drastic compromise of their functions, as well as a significant decrease of CAT activity [72]. In our studies using ozone [13, 38, 42, 50, 52-56] in the positive control group of all the animal models studied, a significant decrease of CAT was observed. An increase of H_2O_2 peroxide is demonstrated during I/R occupying the active centers of the enzyme. For that reason, a CAT enzyme saturation is produced and the enzyme can not respond to the excess of substrate (H_2O_2) being, therefore, inactivated. This phenomenon is named enzymatic inactivation by excess of substrate [73, 74] and it can be the reason for the reduced figures obtained in CAT activity in the positive control group. However, ozone stimulates the tissue activity of CAT, with the highest values in comparison with the other groups. Then, CAT activation diminished H_2O_2 levels in renal tissue (glomerule, tubule epithelial cells, and endothelial cells) in comparison with the renal tissue submitted to damage (positive control). A significant decrease was achieved in the positive control group in comparison with all the groups. This effect has a favorable repercussion in

renal tissue, because all the ways of renal damage provoked by a pathological increase of H_2O_2 (lipid peroxidation at the level of basal and epithelial glomerular membrane, activation of nuclear transcription factors for the synthesis of proinflammatory interleukins, proinflammatory cell recruitment) will be inhibited or at least delayed, giving a protective effect upon the viability of the post ischemic kidney. The results of this study agree with that already reported about CAT stimulation in the protection of kidneys submitted to acute or chronic pathological events [75].

Reduced glutathione (GSH), a tripeptide (L- γ -glutamyl-L-cysteinyl-glycine) member of the antioxidant system, is localized mainly in the mitochondria and cytoplasm, but it is also present in the nuclear matrix. Although GSH is ubiquitous, the liver is the major source of synthesis but high concentrations are present in the kidneys, erythrocytes, CNS, crystalline and in the bile. The main role of SGH and GPx is to protect the "internal milieu" from possible damage due to excess H_2O_2 , but it also detoxifies peroxides, protects DNA and neutralizes 4-hydroxyaldehydes by means of the enzyme glutathione-S-transferase. This last enzyme plays an important role in the inactivation of the most toxic aldehydes of lipid peroxidation, in the metabolism of xenobiotics and in the production of leukotriene B_4 [76]. Moreover, by preserving the $-\text{SH}$ (thiol) group of several proteins (Ca^{2+} -ATPases, hormonal receptors), GSH maintains calcium homeostasis, thus preventing the triggering of apoptosis. GSH also plays a role in signal transduction and in gene expression. Therefore, GSH has a great importance in cell protection against oxidative stress [77]. In our studies, in the positive control and oxygen groups (using oxygen instead of ozone), a significant decrease of GSH at the level of damaged renal tissue was observed. However, ozone preserved GSH figures with values significant similar to those of the negative control, beneficial aspect for renal protection. The increase of the antioxidant enzyme activity could avoid GSH consumption. We can postulate the possibility of a stimulatory mechanism that promotes the resynthesis of this tripeptide as of its enzymatic mechanisms located in the cytosol. The process of GSH synthesis occurs in two steps where ATP is required. On the other hand, it is known that ozone improves oxygen metabolism and ATP contribution to cells [65, 78]. Previous studies have demonstrated that one of the metabolites produced during ozone therapy, the 4-hydroxyalkenals [79], induce the expression of antioxidant proteins of the oxidative stress, by means of the activation of the transcription factor Nrf2 in macrophage cultures [67]. It can be thought that ozone produces transitory figures of 4-hydroxyalkenals, which in our experimental conditions could preserve GSH synthesis avoiding its consumption.

With respect to lipid peroxidation, measured by means of TBARS [80], a significant increase was observed in all the positive control groups of the different animal models studied, producing a ROS increase, with the subsequent damage of the cell lipid membrane integrity. This effect is potentiated by the increase in the arachidonic acid metabolism, that after an hour of reoxygenation and with the entrance of oxygen to a dysfunctional mitochondria, release more toxic radicals that are converted in chemotactic neutrophil agents resulting in a maintained ROS release [81]. In the I/R model, with the OzoPre at the doses of 0.3 and 0.5 mg/kg, there is a lipid peroxidation decrease with respect to the positive control and oxygen groups, demonstrating once more the role of OzoPre to maintain REDOX balance in organs submitted to I/R [47]. However, OzoPre at the highest dose (1.1 mg/kg) showed an increased TBARS. Similar results were achieved in the models of I/R applying OzoPost and in CRF. Although this significant increase of TBARS exists, the antioxidant enzymes are so increase that they compensate this effect and achieve the cell REDOX balance. In fact, no

renal damages were observed by the histological studies performed. It must be emphasized that the oxygen group showed a lipid peroxidation increase similar to those of the positive control group; this could be related with the non activation of the endogenous antioxidant enzyme activity demonstrated in both groups, in our experimental conditions.

Arachidonic acid pathway represents an important aspect in the mechanism of renal injury. It is well documented that by the increase of cytosolic Ca^{2+} and other factors, an activation of phospholipases is produced. Among them, phospholipase A_2 (PLA_2) [2], plays a basic role in the damage of cell functions, mediated by the degradation of membrane phospholipids. Analyzing our results, an increase of PLA_2 was observed in the positive control and oxygen groups. However, in OzoPre (at the three levels of ozone doses applied) and in OzoPost, PLA_2 activity decrease significantly in renal tissue submitted to I/R, another important fact that demonstrates the effect of ozone in the preservation of renal structure integrity (cell membranes, tubular epithelium, etc). These results are similar to those described by other authors, that using PLA_2 inhibitors, achieved a protective effect against the ischemic damage in heart, renal cell cultures and convoluted proximal tubules [2]. Stimulation of the antioxidant enzyme activity, at the level of the injured tissue, contributed in some way to PLA_2 activity regulation. In the organ protected against ROS, free fatty acid release is smaller, suggesting a lesser PLA_2 activation. Other authors obtained similar results as ours, when they performed in rats' pancreas transplantation and submitted this organ to I/R. A significant increase of PLA_2 activity and lipid peroxides concentration, in pancreatic tissue, was found, in addition to thromboxane A_2 and prostaglandin $\text{F}_{1\alpha}$ increases. In this study, an antioxidant substance was applied before the revascularization. It was observed a decrease in PLA_2 activity and lipid peroxides and thromboxane A_2 concentrations. It was concluded that ROS are mediators of PLA_2 action and the subsequent formation of arachidonic acid derivatives in the transplanted tissue [82]. Therefore, it can be thought that the effect of ozone in the stimulation of the antioxidant enzyme activity in renal tissue, produced the regulation of PLA_2 tissue activity in our experimental conditions, demonstrated by the significant decrease of this enzyme in the animals that received ozone with respect to those submitted to I/R without ozone treatment.

During I/R, advanced glycation end products (AGEs) are increase in the injured tissue. Fructosamine is an advanced glycation protein product highly related with protein damage and with blockade of the nitric oxide vasodilator response. AGEs are stable and their formation is irreversible as that of fructosamine. Our experiences demonstrated, as previous studies [13], the reduction of AGEs in post ischemic kidney, now achieved at three levels of ozone doses and with a longer time of ischemia. The doses of 0.5 and 1.1 mg/L were the most effective, with similar and lesser renal values of fructosamine with respect to the negative control and positive control groups, respectively. Non-protection was found in the positive control and oxygen groups. In I/R and CRF, the AGEs are placed on the walls of blood vessels affecting lipoproteins, coagulation factors, enzyme activity and also being capable to activate mechanisms that produce proinflammatory interleukins (IL-1, IL-6 y $\text{TNF}\alpha$) [83]. All these events damage the structure and functions of the organ submitted to the injury. The effect of ozone preserving the values of fructosamine demonstrated the protection of the structure and renal function conferred by this gas. It can be thought that due to the effect of ozone in the control of AGEs, the protein damage, the activation of proinflammatory interleukins, the generation of ROS will not be produced [83].

During I/R, IL-6 amplified inflammation, as well as the number and size of platelets in systemic inflammatory lesions [84]. In our model of I/R using OzoPre, positive control group showed an extend expression of IL-6, at the level of the post ischemic renal tissue, with respect to the other groups. This is because the I/R behaves as an inflammatory process [3], where the recruitment and release of inflammatory cells (neutrophils, monocytes, macrophages), which are activated releasing proinflammatory interleukins (IL-1, IL-6 y $\text{TNF}\alpha$), with the subsequent damage of the post ischemic kidney, are present. In our study, OzoPre diminishes IL-6 expression in kidneys submitted to ischemia (60 min) and reperfusion (180 min), obtaining the best results with the ozone dose of 0.5 mg/kg. The effect of OzoPre in IL-6 expression in renal tissue could be mediated also by the role of OzoPre in the stimulation of the antioxidant endogenous enzymes. It has been demonstrated, that during the systemic inflammatory response in its late phase, there is an increase in IL-6 values, which contribute to other organ damage, as with the lungs [85]. As the best result was achieved with the dose of 0.5 mg/kg, in respect to IL-6 and other parameters of oxidative stress, is why we emphasized in and recommended this dose in the other animal model studied.

In the injured renal tissue, ROS behave as chemotactic agents, with the recruitment of neutrophils and macrophages and the subsequent release of great quantities of proinflammatory interleukins. It has been also reported that ROS induces proinflammatory interleukin gene expression at the level of the inflamed tubular epithelium [86]. It has also been demonstrated that the superoxide radical participates in glomerular cell apoptosis, induced by the tumor necrosis factor ($\text{TNF}\alpha$) [87, 88]. Therefore, it can be assumed that when ozone stimulates the enzymatic antioxidant activity in renal tissue, it diminishes the effect of ROS increase in the release of proinflammatory interleukin (IL-6), contributing to its lesser expression at renal level (glomerule, proximal tubule). It is stated that agents able to diminish the values of proinflammatory interleukins, as $\text{TNF}\alpha$ and IL-6, protect the kidney against the ischemic damage [89].

With respect to the renal function, RPF and GFR, in the positive control and oxygen groups of all the models studied, achieved a significant decrease in comparison with the negative control and ozone groups. The ischemia produced damaged to the endothelial cells and when the blood flow decreases and then increases in the reperfusion phase, a turbulent flow is produced increasing the shearing forces and producing more ROS release, damaging the endothelium even more [1,90].

In the groups treated with O_3 , a preservation of renal function was present, with significant similar values of RPF and GFR with respect to those of the negative control group. OzoPre and OzoPost influences on tissue oxygenation, improving oxygen metabolism and increasing the levels of 2, 3 DPG, in its hemorheologic effect increasing erythrocyte pliability [29, 70], and the subsequent possibility to diminish blood viscosity and erythrocyte aggregation, allowing a lesser vascular resistance that permits an appropriate renal blood flow during reperfusion, in an organ previously submitted to a lack of blood flow [13, 29, 50, 78, 91].

The filtration fraction (FF), defined as the GFR/RPF ratio, can increase when GFR increases or RPF decreases. In our results, ozone application maintained the values of the filtration fraction similar to those of the negative control, preserving the RPF. This flow did not diminish and, thus, a lesser plasma fraction was filtered in the glomerular capillaries, in comparison with the animals that did not receive ozone (higher values of FF). This effect

causes a lesser raise in plasma colloid osmotic pressure of the glomerular capillaries and therefore, a lesser inhibitor effect on the GFR.

Creatinine is a substance that depends mainly for its excretion on the glomerular filtrate, because it is not reabsorbed and it is poorly secreted. Then, when the GFR diminishes, it also decreases creatinine excretion, provoking its accumulation in the organic liquids and the increase in plasma concentration. In the O₃ group, creatinine figures decreased in comparison with the positive control and oxygen groups, demonstrating an improvement of the renal function. No significant differences were obtained between the positive control and oxygen groups, demonstrating that the oxygen treatment did not help the renal function recovery. In our experimental conditions, ozone avoided the increase in plasma creatinine values, explaining the positive effect in renal function recovery. These results are similar to those obtained by other authors related to OzoPre in renal ischemia [13, 64].

All these ozone beneficial effects in renal function preservation are mainly mediated by the stimulation of the antioxidant enzymes in renal tissue. For example, NO[•] acts endogenously as a vasodilator [3] and was first described by Furchgott and Zawadzki as an "endothelial-derived relaxing factor" [92]. Until 1987 nobody believed that a toxic gas could be produced by cells and would perform crucial functions. During the ischemia, NO[•] is consumed by different reasons, one of them is that there is a great release of superoxide anion (O₂^{•-}), which has a big affinity with NO[•], reacting with it and forming the peroxyntirite radical, damaging the intra-renal hemodynamics and subsequently the function of the ischemic kidney [93, 94]. In our study, NO[•] was not measured, but it is demonstrated in several papers (liver I/R [40] and diabetic experimental models [33]) that OzoPre exerts a modulation in NO[•] tissue levels. In the animals, of the different experimental models studied, a stimulation of SOD activity was achieved; therefore, this effect produced a decrease of superoxide anion (considered as a vasoconstrictor) and a subsequent lesser reaction of this anion with NO[•], in comparison with the positive and oxygen groups. In this way, NO[•] level could be preserved, increasing its biodisponibility in the post ischemic renal tissue, contributing to the renal function protection. Therefore, the activation of the antioxidant defense system has a favorable repercussion on the preservation of renal function. These results are similar to those reported by other authors, where the administration of allopurinol (hydroxyl radical scavenger and also blockade the xantine oxidase pathway) and deferoxamine (inhibitor of Fenton reaction) produced a ROS decrease and the preservation of renal function in kidney submitted to ischemia [95].

With respect to the histological studies, similar results were achieved to those reported previously, about the effect of OzoPre in organs submitted to I/R [13, 31, 47, 64] though in this case the time of ischemia is bigger (60 min). Kidneys belonging to the positive control and oxygen groups showed a severe damage of their structure, with markers of renal injury, such as significant decrease in the percentage of damaged tubules that presented border brush loss, discontinuity and denudation of the tubular basal membrane, presence of peritubular inflammatory cells and necrotic cells. However, ozone was able to attenuate all these structural changes in conjunction with a renal morphology recovery. In the ozone group, the lesions were moderate, proving that the renal damage is minor in comparison with the positive control and oxygen groups. Therefore, the ozone treatment, by a structural point of view, favors kidney recovery.

During I/R or CRF, several deleterious events are present, such as cytoskeleton damage, cell polarity loss, microvillose damage, alterations of the different transportations at the level

of apical and basolateral membranes of tubular cells up to cell denudation with lumen obstruction. The beneficial effects that ozone offered to the integrity of the tubular cell contributed to the maintenance of the function equilibrium between the different parts of the nephron (tubule-glomerulus)

In the morphometric (quantitative) study [42,53], animals treated by OzoPre and OzoPost, showed a significant decrease in the quantity of nuclei in the tubular lumen, as well as a smaller area of the tubules and tubular perimeter in comparison with the positive control group. This correlates with the GFR in the animals of the positive control group, because the presence of nuclei in the tubular lumen increases the hydrostatic pressure in Bowman capsule decreasing the GFR, as it was demonstrated in this group.

Ozone by means of its different effects, such as stimulation of the antioxidant enzyme activity, preservation at physiological values the tissue levels of AGEs and PLA₂ and diminishing the IL-6 expression, produced a better preparation of the renal tissue to afford the damage in our experimental conditions. The ozone dose of 0.5 mg/kg resulted to be the optimum, achieving better REDOX balance and better effect in IL-6 expression, at the level of post ischemic renal tissue, in comparison with the dose of 1.1 mg/kg.

The clinical trial [96] deserves a separately discussion, due to its social and economic repercussion that can be achieved when renal function is preserved and then, hemodialysis, as the last possibility of patients with CRF, could be avoided, representing a better quality of life to those patients.

The OzoPost applied in the clinical assay demonstrated similar results of those found in the preclinical tests, referred to the effects of ozone therapy, by rectal insufflation, as a protective therapy of renal morphofunction in different types of physiological events. With respect to some oxidative stress biomarkers, in these patients with CRF submitted to ozone therapy, a significant decrease of lipid peroxidation in blood was obtained. This effect has positive repercussion in renal function, since it has been reported that lipid peroxidation increase is related to a worsen functioning of the nephron, as a structural and functional unit already damaged [2, 65]. In these patients, the increase of the antioxidant defense system was very important. For example, SOD is the only enzyme able to cross the glomerulus membrane; therefore, the proximal convoluted tubule can be protected against the deleterious effect of an uncontrolled increase of superoxide anion on the tubular epithelium. In this way, the ulterior deterioration of glomerulus/tubule balance will be avoided and the subsequent GFR decrease.

With respect to renal function tests (creatinine and GFR), applying OzoPost, a significant decrease of creatinine in serum, as well as the preservation of GFR values during the study were observed. However, in control group both markers diminished significantly at the end of the study. This positive effect of OzoPost could be mediated by all the ozone therapeutical properties referred previously.

Specifically, SOD and CAT stimulation at plasmatic level, antioxidant enzymes of first line that defend the renal system from superoxide anion and H₂O₂, respectively, protect different structures, such as glomeruli, tubules, renal interstitium, vascular endothelium, among others, from ROS attack thus contributing to delay the progression of CRF and offering a better quality of life to these patients.

Conclusion

Preclinical and clinical assays demonstrated the ozone protective effect in the preservation of renal function and morphological integrity of the nephron, glomerules and proximal convoluted tubules of the kidneys analyzed in the preclinical models, as well as an achievement of a REDOX (reduction-oxidation) homeostasis by the stimulation of the antioxidant defense system and in the modulation of pro-inflammatory cytokines. All these effects contributed to delay the progression of the disease, with an important improvement in the quality of life of patients with CRF. Also, ozone therapy can be considered as an important therapeutic strategy to minimize the renal damage after transplantation.

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Chapter IV

South Asian Ethnicity and Renal Replacement Therapy

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Abstract

South Asian populations have distinct healthcare requirements in comparison to other ethnic demographics. Epidemiologically they constitute a high-risk group for many public health diseases such as cardiovascular disease, chronic kidney disease and diabetes mellitus. From a renal perspective, there is a lack of ethnocentric-specific approach to meeting the health needs of the South Asian population. In addition there is increasing evidence of disparate outcomes for South Asians versus other ethnicities in the context of progression of chronic kidney disease, assessment and referral for kidney transplantation and outcomes post commencement of renal replacement therapy. The purpose of this article is to review the available literature and illustrate how an ethnocentric approach to meet the needs of a growing South Asian population with chronic kidney disease and end-stage renal disease is essential.

In the United Kingdom, the prevalence of individuals with end-stage kidney disease is approximately 0.05% yet it consumes a disproportionately large 1-2% of the National Health Service budget [1]. In a similar fashion ethnic minority groups make up 7.9% of the British population (4% comprising South Asian) based upon 2001 UK Census data, but they have a greater incidence of chronic kidney disease and are over-represented on renal replacement therapy programs (comprising 14.4% of patients with available ethnicity data) [2]. Due to the improved morbidity/mortality profile and cost effectiveness of kidney transplantation it is imperative to facilitate organ transplantation in ethnic minority populations, which in the UK is predominantly made up of the South Asian community (defined as individuals with either Pakistani, Indian or Bangladeshi heritage).

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Despite the growing South Asian population with advanced chronic kidney disease, the proportion of South Asians receiving kidney transplants is unduly low and results in burgeoning South Asian populations on dialysis and organ waiting lists, resulting in subsequent adverse outcomes. A myriad of factors interplay to explain the differences observed in the South Asian ethnic group with regards to epidemiology, access to transplantation and outcomes post-transplantation compared to other ethnic (especially white) groups. Understanding the complexity of renal replacement therapy requirements for South Asians is essential to facilitate targeted public health initiatives to tackle the rising population of South Asians who will commence dialysis but remain un-transplanted. The aim of this article is to highlight the problem facing South Asians with regards to dialysis and access to transplantation, explore the various factors at play in such health inequalities and propose strategies to tackle such disparities.

South Asians and End-stage Kidney Disease

It is widely acknowledged that South Asians have an increased risk of reaching end-stage kidney disease and subsequently requiring renal replacement therapy. This increased burden is partially explained by the increased prevalence of major culprits for progression of chronic kidney disease, such as diabetes and hypertension [3], within these communities. Not only is the incidence of chronic kidney disease higher but the severity of disease also appears more advanced in South Asians when compared to white groups. Dreyer et al. [4] performed a cross sectional study of 34,359 diabetic patients across three primary care trusts in the UK to investigate the effect of ethnicity on prevalence of diabetes and associated chronic kidney disease. Compared to white diabetics, South Asians demonstrated a three-fold increase in prevalence of diabetes, earlier onset of diabetes, worse proteinuria and poorer diabetic control. In a multivariate analysis adjusted to risk factors, South Asian ethnicity had a 54% higher risk of more advanced chronic kidney disease stages (stage 4 or 5) compared to whites. The high incidence of diabetes amongst South Asians, and earlier onset of the disease, is one explanation for the high incidence and severity of chronic kidney disease observed.

However, although South Asians are likely to have distinct pathological disease risks such as diabetes compared to other ethnic groups, there are also likely to be social, cultural and environmental factors that contribute to the observed increase in health burden [2]. The integration of the South Asian community into medical and public health programmes is not optimal and it is likely that factors such as late presentations (due to late self-referral), lack of awareness, inferior access to healthcare services and distrust of medical frameworks may all contribute to South Asians having a higher incidence of end-stage kidney disease.

Outcomes for South Asians on Dialysis

It is interesting to observe that South Asians appear to have better prognosis on prolonged dialysis compared to other ethnicities. Jain et al. [5] performed a prospective, observational study of a multiethnic population cohort group in four regional hospitals serving a population of four million UK residents. Other than transplantation, South Asian ethnicity was associated

with better survival for patients with end stage kidney disease with a relative risk compared to whites of 0.6 (95% CI [0.46 – 0.80], $p < 0.001$). Although it is difficult to explain these results, evidence from registry analysis suggests it may be related to attainment of higher dialysis doses. Udayaraj et al. [6] analysed the role of socio-economic status and ethnicity on achievement of dialysis standards in the UK Renal Registry. Examination of 14,117 incident dialysis patients demonstrated South Asians to attain comparable or better standards against whites for most dialysis standards except calcium and phosphate targets. The better dialysis standards could be related to better adherence or smaller body size skewing the urea distribution volume.

However, although studies are suggestive of better survival of South Asians on dialysis, perceived quality of life is inferior amongst South Asians with end-stage kidney disease compared to whites. Bakewell et al. [7] explored the perception of quality of life in 60 South Asians on renal replacement therapy (20 on haemodialysis, 20 on peritoneal dialysis and 20 with a kidney transplant) and compared them with 60 age-matched white Europeans. Quality of life was assessed using Kidney Disease and Quality of Life questionnaire (KDOQI-SF) which explores four aspects of quality of life: physical health, mental health, kidney disease targeted issues and patient satisfaction. Confounders such as social deprivation (assessed using the Townsend score) and renal replacement therapy adequacy were also adjusted for. Quality of life was significantly poorer amongst South Asians for physical health, mental health and kidney disease targeted issues. Quality of life was inversely associated with morbidity. From their analysis, the authors concluded that South Asians considered kidney disease a social burden, even if they get transplanted and raises important issues regarding the socio-cultural aspects of kidney disease and treatment amongst this ethnic group.

Kidney Transplantation Allocation

Due to the poor ratio of South Asian donors on the waiting list (only 2% are registered donors according to NHS Blood and Transplant data [www.organdonation.nhs.uk]), South Asian recipients are disadvantaged when it comes to receiving a kidney due to compatibility issues and this contributes to longer waiting times and less well matched kidneys being offered. Jain et al. [5] performed a prospective, observational study of a multi-ethnic population group in four regional hospitals serving a population of four million UK residents. Within this cohort they observed South Asians were less likely to receive a kidney compared to whites (RR 0.64, 95% CI [0.42-0.97], $p = 0.037$), although the situation was worse for blacks (RR 0.10, 95% CI [0.02-0.34], $p < 0.001$). Data from Rudge et al. [8] examining UK national transplant registry data, demonstrated the median waiting time until kidney transplantation for white patients was 719 days (95% CI 680-758 days) compared with 1368 (95% CI 1131-1605) days for South Asian patients and 1419 (95% CI 1165-1673) days for black patients. Ramanan et al. (9) performed a longitudinal cohort study and, in their logistic regression model, non-white ethnicity was independently associated with less than 50% probability of receiving a deceased-donor kidney (after brain death) within two years of registration to the waiting list (OR 0.47 [95% CI 0.37-0.59], $p < 0.001$). Similar results are evident if deceased-donor kidney after brain death is substituted for deceased-donor kidney after cardiac death or living donor kidney (OR 0.57 [95% CI 0.46-0.71], $p < 0.001$). Not only

are non-whites disadvantaged from kidney allocation once active on the waiting list but they also appear to have difficulties with access to the waiting list in the first instance. Ravanan and colleagues also demonstrated non-whites have a 15% reduced probability for activation on the national waiting list within two years of commencing renal replacement therapy (OR 0.85 [95% CI 0.74-0.97], $p=0.02$). The explanation for such disparity could be centre-specific, as significant variations were seen amongst the 65 renal centres submitting data to the UK Renal Registry which could not be explained by differences in case mix alone.

Although the lack of South Asian donors introduces compatibility issues for organ allocation on the waiting list, there is data from the black transplant population that graft outcomes are worse for black recipients if the donor kidney is from a black rather than white donor. Brown et al. [10] compared short-term outcomes in black patients who received a kidney from either a black ($n = 35$) or white donor ($n = 150$). There was no difference in patient survival, new-onset diabetes after transplantation or polyoma virus occurrence but there was significantly more graft failure (significantly more likely to be due to recurrence or new development of focal segmental glomerulosclerosis), cytomegalovirus and episodes of acute rejection if black recipients received kidneys from black donors. Whether this association is observed in the context of South Asians would be interesting to ascertain. However the lack of South Asian donors is likely to leave such a study under-powered for an outcome such as graft survival.

Barriers to Transplantation

In a structured survey of 100 South Asians on a British street (50 male, 50 female), Ahmed et al. [11] explored South Asian attitudes to organ donation. 90% of respondents were aware of organ transplantation and 69% were aware of the existence of organ donor cards. However, only 16% were registered organ donors. Reasons given for not registering included having ‘not heard of it’ (33%), religious obstacles (7%), personal feelings (26%) and other reasons (33%).

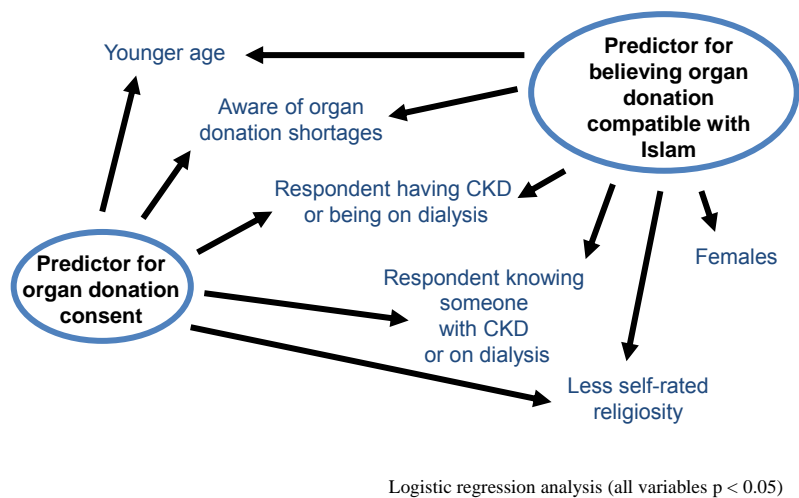


Figure 1. Positive predictors for Muslims who agree with organ donation.

The influence of religion on attitudes to organ donation amongst the South Asian population predominantly focuses on Muslims (whom constitute the majority of British South Asians). Whilst there is clear support for organ donation amongst Hindu and Sikh groups (the other two major South Asian faiths), Muslims have been divided on the legality of organ donation in the context of religious teachings and Holy Scriptures. A qualitative study of 141 British-based Muslim South Asians [12] highlighted the dichotomous views expressed by Muslims, which could explain the poor organ donor rates amongst this religious group. Another important observation in this study was the ‘fatalist’ attitude adopted by some Muslims that the occurrence of any end-stage organ disease was due to an ‘act of God’ and therefore was beyond their control or interference. This behaviour has implications for South Asian Muslims with chronic kidney disease who may not feel the need or desire to engage with healthcare services or treatments to attenuate their medical problems.

Exploring the topic of Islam and organ donation in a quantitative study, an international poll of Muslim attitudes to organ donation [13] collected data on 891 Muslim individuals in an anonymous survey. As survey participation was predominantly internet-based, the population sample was skewed towards the views of a majority ‘Western’ Muslim group (based in Europe, North America or Oceania). Regardless of this participation bias, the results still highlighted an ambivalent view towards organ donation amongst adherents of the Islamic faith. Whilst 67.1% of Muslims agreed with the concept of organ donation, only 36.8% believed it was compatible with their faith. This discrepancy could explain the low figure of 10.5% registered donors amongst this group. Based upon logistic regression analysis many independent variables predictive for Muslims who agree with organ donation, found it compatible with Islam and/or who were registered organ donors were ascertained and included younger age, less degree of religiosity, higher education, awareness of organ shortages and awareness of someone on dialysis or with kidney disease (see Figure 2). The data generated should facilitate specific and targeted campaigning of these important demographics to increase organ donor rates amongst this population.

<u>Whites</u>	<u>Non-whites</u>
<ul style="list-style-type: none"> • Higher median incident age when starting RRT • Less diabetes/hypertension • Less aggressive disease progression • More late presentation for starting RRT (likely due to age and diabetes differences) • Worse survival on dialysis • Shorter wait for kidney allocation on waiting list • Better deceased-donation rates • Better living-donation rates • Better outcomes post-transplantation 	<ul style="list-style-type: none"> • Lower median incident age when starting RRT • More diabetes/hypertension • More aggressive disease progression • Less late presentation for starting RRT (likely due to age and diabetes differences) • Better survival on dialysis • Longer wait for kidney allocation on waiting list • Worse deceased-donation rates • Worse living-donation rates • Worse outcomes post-transplantation

Figure 2. Differences between non-Whites and Whites regarding need for renal replacement therapy (RRT).

It should be appreciated that the Muslim population is diverse and heterogeneous and that the South Asian Muslim community may require tailored strategies. This is highlighted by evidence that South Asian scholars and religious leaders have a more ambivalent or negative view of the sanctioning of organ donation, living or deceased, compared to other ethnic groups such as Arab Muslims [14]. There is likely to be complex interplay of religious, cultural, language and socio-political factors involved in the decision making process for South Asians on the topic of organ donation and transplantation. This myriad of influences will require further investigation to identify targeted strategies to raise awareness and influence attitudes.

Beyond religion, it is clear there are many barriers to transplantation and organ donation amongst the South Asian community such as language, cultural differences and family influences. It is likely the South Asian social network is an obstacle to awareness of organ donation and transplantation. This concept of social networks affecting transplantation embraces not just the lack of social support and ineffective diffusion of information but also the social network itself being involved in the spread of illness or behaviour. Ladin et al. [15] provide an interesting and thought-provoking discussion on the weakness of ethnic minority social networks (specific focus on the black population) as being partly responsible for lack of access for both living donors or deceased-donor allocation from national organ pools. The authors argue deeper understanding of ethnic minority social networks will help mitigate ethnic disparities with regards to access to transplantation. This may involve better education, home visits, efforts to strengthen social support and connectedness of social networks. From a South Asian perspective, Randhawa [16] has reported on South Asian social networks and the implementation of pilot studies where organ donor issues are promoted via informal community-based networks rather than through official Department of Health frameworks. Such practice is likely to be the way forward for promotion of organ donation awareness in such communities and adequate resources will be required to effectively perform this task.

Transplant Tourism

Illegal commercialization of organs for transplantation favours the interests of wealthy recipients who can afford the market rates for organs, especially in the context of transplant tourism. This phenomenon is defined as the trafficking of organs with a commercial component existing outside of legal and professional frameworks. The problems cited with transplant tourism are extensive and include the undermining of transplantation needs of the tourist country, sub-optimal care of the potential recipient and exploitation of the vulnerable donor [17]. With regard to the latter concern the lack of long-term care provided for the donor is contrary to guidelines emanating from the Amsterdam Forum focusing on the standard of care for organ donors [18].

Transplant commercialism is an ugly but inevitable consequence of the chronic organ supply problem. Although criticism of such practice is understandable and justified, it is unlikely to challenge the determination of desperate recipients to overcome the system. Due to the prolonged waiting times South Asian recipients face with regards to receiving an organ, it is inevitable they are more prone to become transplant tourists due to prolonged waiting times. However there are other factors other than prolonged waiting times that encourage

transplant tourism. Krishnan et al. [19] identified 40 patients with advanced chronic kidney disease in the West Midlands region of the UK who were categorised as transplant tourists over a ten-year period from 1996-2006. From these 40, 38 were of South Asian ethnicity (with most travelling to South Asia for transplantation) but only 20% of these South Asian transplant tourists had been on the waiting list for more than 2 years. Interestingly the authors identified 56% of these patients were not on the UK waiting list due to medical reasons, suggesting such patients were becoming tourists not in desperation at prolonged waiting times but to bypass shortfalls in their medical/surgical work up for fitness to transplant. The South Asians who travelled abroad for transplantation in this study not only had inferior survival to South Asian organ recipients in the UK but also to South Asians on dialysis in the UK. Therefore, South Asians contemplating travelling abroad for organs need to be counselled appropriately regarding the risks involved with such practice.

Outcomes for South Asians Post Kidney Transplantation

Emerging data suggests South Asians have worse outcomes post-transplantation compared to other ethnicities. Prasad et al. [20] compared white renal transplant recipients ($n = 550$) with South Asian ($n = 139$), black ($n = 65$) and East Asian renal transplant recipients ($n = 110$) in a retrospective Canadian analysis. Despite there being no significant difference in baseline cardiovascular risk factors, including pre-existing cardiovascular disease, South Asians had a significantly higher risk (4.4/100 patient years) for developing major cardiac events (composite of nonfatal myocardial infarct, coronary intervention and cardiac death) compared to all other ethnic groups ($p < 0.0001$ in comparison to each ethnic group). South Asian ethnicity was the only ethnic group to be independently associated with developing a major cardiac event and was also more likely to experience a major cardiac event within three months post transplantation. Despite the increased cardiovascular burden, patient and graft survival was equivalent amongst the ethnic groups.

In the UK, Dooldeniya et al. [21] combined three databases (Hammersmith Hospital, Long-term Efficacy and Safety Surveillance [LOTESS] and UK Transplant) and compared outcomes between recipients of South Asian ethnicity ($n = 759$) and whites ($n = 9183$). Apart from more diabetes amongst South Asians, the two ethnic groups were otherwise identical. They found patient and graft survival rates were equivalent between the two groups. From a cardio-metabolic viewpoint, although there was no difference between the two groups in incidence of hypertension or hyperlipidaemia, the South Asian group had between a two to three-fold increased incidence of new onset diabetes post transplantation compared to the white group. In two of the databases where multivariate analysis was performed, South Asian ethnicity was an independent risk factor for the development of new onset diabetes after transplantation (Hammersmith Hospital database: OR 3.32, 95% CI [1.09 – 10.10] and LOTESS database: OR 6.37, 95% CI [3.23 – 12.66]). Not only was there a higher incidence of diabetes post transplantation but it also occurred much earlier post-transplantation compared to the white group (5.5 months versus 10.9 months respectively, $p < 0.001$).

There is a lack of clear evidence as to whether South Asian ethnicity, as compared to black ethnicity, is a risk factor for faster graft attrition rates compared to whites. There is

considerable evidence to suggest blacks have accelerated attrition rates compared to whites from examination of the United States Renal Data Services (USRDS) registry data [22]. This is in line with UK registry data from Rudge et al. [8] which suggested inferior 3 year graft survival for black kidney recipients compared to either white or South Asian recipients (76 % versus 82% versus 82% respectively, $p = 0.03$). Possible explanations cited for this persistent effect are differences in either medical pathology (higher incidence of diabetes and hypertension) or socio-environmental factors (time on dialysis, access to transplantation etc.).

Finally, whilst the primary focus of these paragraphs has been on the recipient the possible adverse effects of transplantation on South Asian living donors post-nephrectomy should not be overlooked. There is no evidence specifically on the South Asian community, however Lentine et al. [23] have performed a retrospective analysis of 4650 living donors that included almost a thousand black or Hispanic donors. In a relatively short mean follow up period of 7.7 years, although development of cardiovascular disease, end-stage kidney disease and death was rare, black and Hispanic donors were more prone to hypertension, diabetes and chronic kidney disease post nephrectomy. Interestingly, comparison with general population data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) demonstrated the frequency of these adverse outcomes as essentially equivalent. This would suggest the selection process for black and Hispanic living donors did not abrogate the population-based risk of diabetes, hypertension and chronic kidney disease. It would seem logical to suggest South Asian living donors would have a similar finding to the other ethnic minority groups examined by Lentine et al. as they share the same population-based risks but this has not been confirmed.

Strategies to Increase Organ Transplantation Rates amongst South Asians

In the survey of South Asians on a British high street [11], strategies suggested to increase organ donation awareness included publicity in the Asian media (32%), publicity in Asian languages (26%), religious approval (13%), encouragement from community leaders (3%) and other methods such as informative leaflets at community or religious centres (26%). Community based projects are likely to be fundamental in the drive to increase awareness of organ donation and transplantation. For example, Callender and Miles [24] reported on their initial investigation in the United States to explore reasons for lack of black organ donors and found five major factors: lack of transplantation awareness; religious beliefs and misperceptions; distrust of the medical community; fear of premature declaration of death after signing a donor card; and fear of racism (black donor preference for assurance of black receivership). Based upon these initial findings back in 1978, they were able to invest a cumulative \$10 million in primarily community-based schemes to raise awareness of the lack of minority donors – this was conceptualised through the creation of the National Minority Organ Tissue Transplant Education Program (NMOTTEP) which facilitated many interventions. Their efforts involved increasing media attention, information dissemination and collaboration between multiple influential organisations. However, central to their strategy were community-based projects involving face-to-face discussions with established community speakers who led discussions within their community. A similar local

community-based strategy will be essential for the South Asian community to raise awareness of organ donor issues. It is clear that South Asians are more likely to absorb such information through unofficial sources rather than official Department of Health portals. Khan and Randhawa [25] highlighted the ineffectiveness of ‘ethnically-directed mass media’ and that the majority of detailed information on transplantation is learnt through informal channels such as organ recipients within the community rather than through resources provided by official agencies or departments. Support for such community-based strategies are evident and are currently in process, albeit in fledgling campaigns.

Better education, with cultural and linguistic sensitivity, will also likely be effective in addressing transplant-related issues with the South Asian community. For example, in a national survey of transplant centres in the United States [26], the large Hispanic population is specifically targeted by provision of Spanish education materials (by 86% of centres) or Spanish interpreters (by 82% of centres) to ensure appropriate education is delivered effectively. Such practice may be necessary in facilitating information uptake by the South Asian population in community-based projects.

Conclusion

In an established transplantation programme such as the UK, South Asians constitute a unique ethnic group with regards to their needs for transplantation. Due to their constellation of medical co-morbidities, they are oversubscribed on organ waiting lists but as a group are undersubscribed as organ donors. This results in South Asians having to wait longer for transplantation within national organ allocation frameworks and increasing the risk of morbidity or mortality related to advanced chronic kidney disease or dialysis. In addition, poor access to transplantation encourages the flirtation with transplant tourism which brings its own risks and problems. Those South Asians fortunate to benefit from organ transplantation may still have inferior patient and allograft outcomes compared to their white counterparts as we await definitive long-term data (summarized in Figure 2).

Table 1. Areas of future research to study organ donation issues amongst South Asians

1.	Understanding the socio-economic reasons for poor access for kidney transplantation for South Asians despite earlier referral and younger incident age for commencing renal replacement therapy
2.	Exploring the lack of enthusiasm amongst South Asians regarding organ donation and distinguishing the different components of this
3.	Understanding the impact of religious belief on organ donation consent
4.	Exploring if different South Asians groups have differences amongst themselves regarding incident rates of renal replacement therapy, access for transplantation, donations rates etc..
5.	Strategies to understand how best to engage with South Asian communities and how to facilitate end-stage disease prevention programs
6.	Studying the reasons for different outcomes amongst South Asians compared to other ethnicities in the context of dialysis and post-transplantation

Encouraging organ donation awareness amongst South Asians will require a culturally sensitive approach which overcomes obstacles such as language, apathy, distrust, religious concerns and other socio-political-economic factors. Overcoming the lack of general engagement between the South Asian community and healthcare frameworks requires a new approach with community-based projects the likely interface. Future research projects should endeavor to explore the dichotomous issues outlined in this article (Table 1). Making South Asians aware of their heightened risk of advanced chronic kidney disease and increased need for organs, contrasted with the decreased organ donor rates amongst South Asians, should illustrate the disparity of access to organs and lead to targeted steps to reverse this paradoxical situation.

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Chapter V

Progress in Home Dialysis

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Abstract

Improvements in patient outcomes on dialysis require a fundamental shift in its practice, current technology and service provision. Dialysis at home, can lead to significant patient benefit, but is limited by a range of implementation barriers. This article describes the evolution and progress of home dialysis, from its inception to current practice, with a review of scientific evidence, and discussing a range of initiatives at national and international levels, aiming to provide greater patient choice and autonomy, to enable greater uptake of this modality.

1. Introduction

1.1. Historical Perspective

Thomas Graham, a chemist by profession, in 1861 was the first to offer meaning to the word ‘Dialysis’ which he described as ‘a method of separation of substances, by diffusion through a septum of gelatinous matter’, [38]. It was half a century later, in the August, 1913 issue of *The Times* of London, where John Abel and Leonard Rowntree described the application of this principle in a ‘vividiffusion apparatus’ and coined the term ‘artificial kidney’, for haemodialysis [1]. This ingenious discovery remained largely experimental in its use for at least three decades, until the availability of purified heparin and cellophane. About

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then, the pioneering works of Willem Kolff and Nils Alwall came to light, in the 1940s, with its clinical application in the mid-1950s. Kolff constructed the first haemodialysis machine, a rotating drum kidney, in Kampen (Netherlands) in 1943 [46]. Nils Alwall is credited with the modification of the original dialyzer, in 1946, to incorporate ultrafiltration. Soon after the war was over in 1945, Kolff offered ‘the kidney’ for patients with ‘crush syndrome’ [12], and described its use in 12 patients, published in 1948 [13].

Kolff and Alwall established the treatment of chronic renal failure outside of the UK with varying success. Dr. Frank Parsons was instrumental in the development of the first unit in the UK to use the Kolff-Brigham ‘artificial dialyzer’ at the Leeds Renal Unit. [80] Thus, haemodialysis for chronic renal failure was born in the UK, in 1956. By 1958, three units were established across the UK- Leeds, Hammersmith in London and Royal Air Force unit, Halton [21]. Over the next few years, several teaching hospitals opened their own units.

It was, however, the design of the first usable Teflon arteriovenous shunt, published in a legendary paper titled ‘Chronic haemodialysis using venipuncture and a surgically created arteriovenous fistula’ by Brescia, Cimino, Appell and Hurwich that provided the next major breakthrough [9]. Long-term dialysis for patients with regular access to the blood stream became a real possibility [7]. By 1966, regular haemodialysis was the universally accepted treatment of choice for end stage kidney disease.

2. Treatment Options

2.1. Origins of Home Haemodialysis

As the demand for dialysis therapy increased, general shortage of funds, trained staff and hospital accommodation was apparent [2]. The development of a proportioning system was crucial to dialyzing all patients in hospital units. Home haemodialysis, perceived as a viable, safe and economical procedure, was therefore advocated as the most feasible means of treatment delivery.

In the UK, Shaldon is credited with long overnight home haemodialysis (nocturnal haemodialysis) three times a week, in 1964. The cumulative experience derived from 9 patient years and 1000 overnight haemodialysis demonstrated substantial reduction in cost and in technical complications compared with hospital haemodialysis [5]. No mortality was reported in the 11 patients on home haemodialysis. Patient satisfaction surveys were conducted and patients expressed preference for home treatment [5].

The epidemic of hepatitis B [32] in hospital dialysis units between 1968 and 1973, attributed to overcrowding, shared dialyzers, dialyzer re-use and blood transfusions, provided a further incentive for patients to consider dialysis at home as the primary treatment option.

The selection of patients who could enter the haemodialysis programme was restricted at the time but somewhat similar for the home and hospital dialysis programme. The usual patient selection criteria for home considered, in addition, five key factors i.e. age, disease states, emotional maturity and psychology, space at home and presence of a partner [5].

By 1971, 5 yr. dialysis survival rates of 60-90% were being achieved and home therapy with 30hrs of dialysis a week, was heralded as a big success. For the first time, in 1972, the success of home haemodialysis was measured in terms of patient’s quality of life perception.

There had been some notable discrepancies between the hospital's concept of home haemodialysis and the patient's experience of it. These included the burden of concealed financial costs to the patients, loss of family income, insomnia and fatigue. Importantly, the traditional view of medical decision making without highlighting the social and economic consequences was exposed and had to be fundamentally uprooted [35]. Shaldon pointed to the benefits of home haemodialysis and mentioned of increased self-esteem and sense of control acquired by these patients. [90]

2.2. Technological Advances

The 1980s witnessed new technical advances in haemodialysis. For the first time, the word 'bioincompatibility' was used in 1980 [92] and its significance became apparent in 1984 [48]. Since then, the aim has been to create membranes with high permeability and improved biocompatibility. Long term access technology, saw the introduction of PTFE as a material for implantable subcutaneous grafts [96]. Double lumen vascular access catheters made of soft silicone rubber were introduced in 1988 [99]. The choice of dialysate buffer shifted from acetate to bicarbonate as standard in the 80s [37]. Improvement in membranes, machines, access and safety monitoring equipment meant safer dialysis for a wider group of patients in hospital based units, otherwise not suitable for self care at home.

The publication in 1985, by John Sargent and Frank Gotch, promoted the adoption of a urea-based marker for measuring dialysis efficiency, referred to as the KT/V for measuring urea clearance on dialysis [36]. URR (Urea Reduction Ratio) was a similar concept that gained ground, based on a pre-post reduction in urea concentration across dialysis [58]. The NCDS study (NCDS, 1983) indicated that $URR < 65\%$ may be linked to higher mortality. This linkage of urea solute removal to mortality provided, for the first time, a measure of dialysis adequacy and a quality assurance index, especially for in-centre dialysis where there were constraints of time and limited flexibility of dialysis schedule. Enhanced diffusive dialysis treatment combined with reduction in dialysis hours, widened access to hospital hemodialysis and provided a fundamental shift from long schedules at home to shorter in-centre dialysis.

2.3. Origins of Peritoneal Dialysis

Peritoneal dialysis (PD) offered an alternative home based dialysis therapy. The first PD on a human was performed in 1923 by Georg Ganter at the University of Wurzburg [94]. Between 1924 and 1938, several medical teams attempted peritoneal dialysis for acute renal failure [94] but PD for management of chronic renal impairment was not popular, because of the risk of malnutrition, peritonitis and use of cumbersome glass bottles [50].

In 1965, a seminal paper by Lee Henderson was set to change the understanding and use of peritoneal dialysis [41]. He suggested that ultrafiltration performed using dialysis with hypertonic glucose, resulted in larger urea transfer. In 1976, Popovich, Moncrief and colleagues submitted an abstract "The definition of a novel portable/wearable equilibrium peritoneal dialysis technique". This was rejected by the ASAIO that year [84]. The authors continued to use their technique and renamed the procedure- 'Continuous Ambulatory Peritoneal Dialysis'. The results were subsequently published in the *Annals of Internal*

medicine in 1978 [84] (Popovich RP, Moncrief JW, 1978). In the same year, when Oreopoulos and colleagues described a simplified technique for CAPD using plastic bags, the Toronto Western Hospital Technique for CAPD, Peritoneal dialysis became established as a viable home-based renal replacement therapy [78].

This technique was adopted in the UK in 1978 as an alternative treatment option for end stage renal disease [31]. Gokal and colleagues reported that CAPD offered an exciting future prospect, with huge cost savings, compared to home haemodialysis, but the most significant drawback was the high incidence of peritonitis at, one in twenty patient-weeks [31]. A number of initiatives were adopted world-wide, to deal with such early challenges of CAPD. A significant technological advance in peritoneal dialysis was the advent of the disconnect system. A titanium connector at the end of the catheter (Nolph in 1979) [75] and a twin-bag system employing the 'flush before fill' technique in 1981 by Buoncristiani's group in Italy [11], were some other significant milestones in the development of this form of home dialysis. The International Society for Peritoneal Dialysis (ISPD) was established in 1984, with a view to promoting uniformly good PD practice worldwide through guidelines and recommendations.

The first description of adequate PD was made by Teehan and colleagues [93] and methods for estimating peritoneal clearance were defined [99]. Another important observation was that of persistence of residual renal function with PD compared to HD [88]. Solute clearance would decline with the loss of residual function. So, the permeability of the peritoneum had to be measured and Twardowski's work from 1987 [98], gave us the Peritoneal Equilibration Test that is valid even today. New osmotic agents such as Icodextrin (glucose polymers) described in 1987 provided a strategy to improve ultrafiltration on PD [67].

3. Dialysis Provision and Service Configuration

Intermittent haemodialysis programme in 1980s was expanding rapidly, and there was an urgent need to plan for the increasing demand for dialysis at a time when the therapy was still in its infancy. A paper from the 60s on 'Planning for the future in the UK', presented at the EDTA, 1966 [45], referred to the location of haemodialysis satellite units to meet dialysis demand and reduce travel distance.

A significant change in practice in the 1980s was the acceptance of reduction in the duration of dialysis, to 4 hours of dialysis 3 times a week as the standard, supported by the NCDS study. This became the norm for hospital dialysis patients, treatment adequacy made feasible by highly permeable dialysers and superior and safer machines with highly controlled ultrafiltration. Hospital dialysis units expanded across the UK in the 80s and 90s and 'satellite' units emerged, to accommodate the ever increasing numbers of patients needing long term dialysis therapy. The UK intake and prevalence rates increased from 20pmp in 1980 to 67pmp in 1992. This figure was reset at 80pmp/yr as target following the government's review in the 1990s [106].

Before the introduction of 'satellite' dialysis units in the 1990s, doubling of dialysis population in the 80s was largely from the increasing CAPD cohort [14]. The pre-negotiated, annual budgets of the kidney units in the UK meant that significant expansion of the cheapest

modality was inevitable. This period was also associated with a rise in ESRD due to systemic morbidities such as diabetes. This increased the burden of dialysis and the poor outcome in these patients prompted the allocation of CAPD as the modality of choice to these groups. So, in the 80s and 90s, the elderly and diabetics were more likely to receive CAPD or hospital dialysis as their mode of renal replacement with a steady decline in home hemodialysis.

At about the same time, transplantation with the UK brain death guidelines facilitating retrieval from heart-beating cadaveric donors and the availability of Ciclosporin (since 1983), created a more definitive treatment option in end stage kidney failure.

A review by Nolph et al. in 1988 stated ‘neither peritoneal dialysis nor haemodialysis is the superior long-term dialysis therapy for all patients; the choice depends on numerous medical, social, geographic, and life-style considerations’ [76]. The treatment of dialysis was by now either hospital based haemodialysis or home based peritoneal dialysis until transplantation.

However, over the past two decades, an increasingly aging population with higher burden of comorbidities combined with liberal dialysis selection criteria has led to an continued growth in thrice weekly hospital based haemodialysis. In the 1990s, both forms of home based dialysis (PD and Home HD) started to decline in uptake and prevalence.

4. Registries, Trials and Outcomes

4.1. International Registries

Despite its widespread uptake, advances in dialysis treatment have been limited due to lack of robust trials or collective data to inform best practice. This improved with the setup of national and international collaborative registries (USRDS, UKRR, EDTA, ANZ, DOPPS, IQDR etc.). These began to produce valuable reports on practice and clinical outcomes. An in-depth insight into the natural history of end stage renal disease (ESRD) patients treated by renal replacement therapy demonstrated an alarmingly high annual mortality of 15-20%.

4.2. Clinical Trials and Outcomes

Cardiovascular disease remains the leading cause of death in these patients. [20] Insulin resistance, hypertension, anaemia, dyslipidaemia and hyperphosphataemia are all significant cardiovascular risk factors [109]. In addition, uraemic toxins in ESRD additionally cause endothelial dysfunction [103]. These factors have all been implicated in increasing mortality from cardiovascular disease [43]. It is now evident that many of these factors are poorly controlled by conventional hospital based dialysis regimens.

As early as in 1982, the high death rates associated with shortened thrice weekly dialysis session were presented at the EDTA [49]. The HEMO study [27], two decades later, failed to demonstrate survival benefit of a higher dose of dialysis achieved by enhancing dialyser urea clearances within the thrice weekly in-centre schedule. This has been a turning point in dialysis science, as new approaches to adjusting dialysis time and frequency to improve patient outcomes have become the focus of investigation and trials. (Table 1)

Table 1. Improving outcomes with increased frequency or duration of dialysis sessions

Author	Year	Modality	N	Method	Duration	Location	Significantly Improved Outcomes
Pierratos et al	1998	NHD	12	Prospective Observational CHD patients for Historical Controls	170 Patient- months Over 3 years	Home	kT/V, B2M, BP Nutrition
Woods et al	1999	SDHD	72	Prospective Observational	12 months	In-Centre	BP, Nutrition Haematocrit
Fagugli et al	2001	SDHD	12	Prospective, Randomised Two-period Crossover With CHD	12 months	In-Centre	BP, LVMI
Chan et al	2002	NHD	28	Prospective, Observational Cohort	2 years	Home	BP, LVMI
Ting et al	2003	SDHD	42	Prospective, Observational CHD patients for Historical Controls	793 Patient- Months	In-Centre	QoL, BP, Anaemia Hospitalization rates
Lindsay et al	2004	DHD vs NHD	20	Prospective Observational	3 years	Home	kT/V in both nPNA, Albumin in SDHD Anaemia, BP, Phosphate control, QoL in both Economic Analyses in SDHD
Lockridge et al	2004	NHD	Variable Up-to 25 for 1 yr	Longitudinal, Observational	5.5years	Home	BP, SF-36 Ca x P product Hospital admissions
Ayus et al	2005	SDHD	26	Non-randomised Controlled	12 months	In-Centre	LVMI CRP EPO Resistance Index
Culleton et al	2007	NHD	52	2 group, Parallel Randomised, Controlled trial	6 months	In-Centre	LVMI, SBP Phosphate control

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4.3. Dialysis Time, Frequency and Location– Revisited

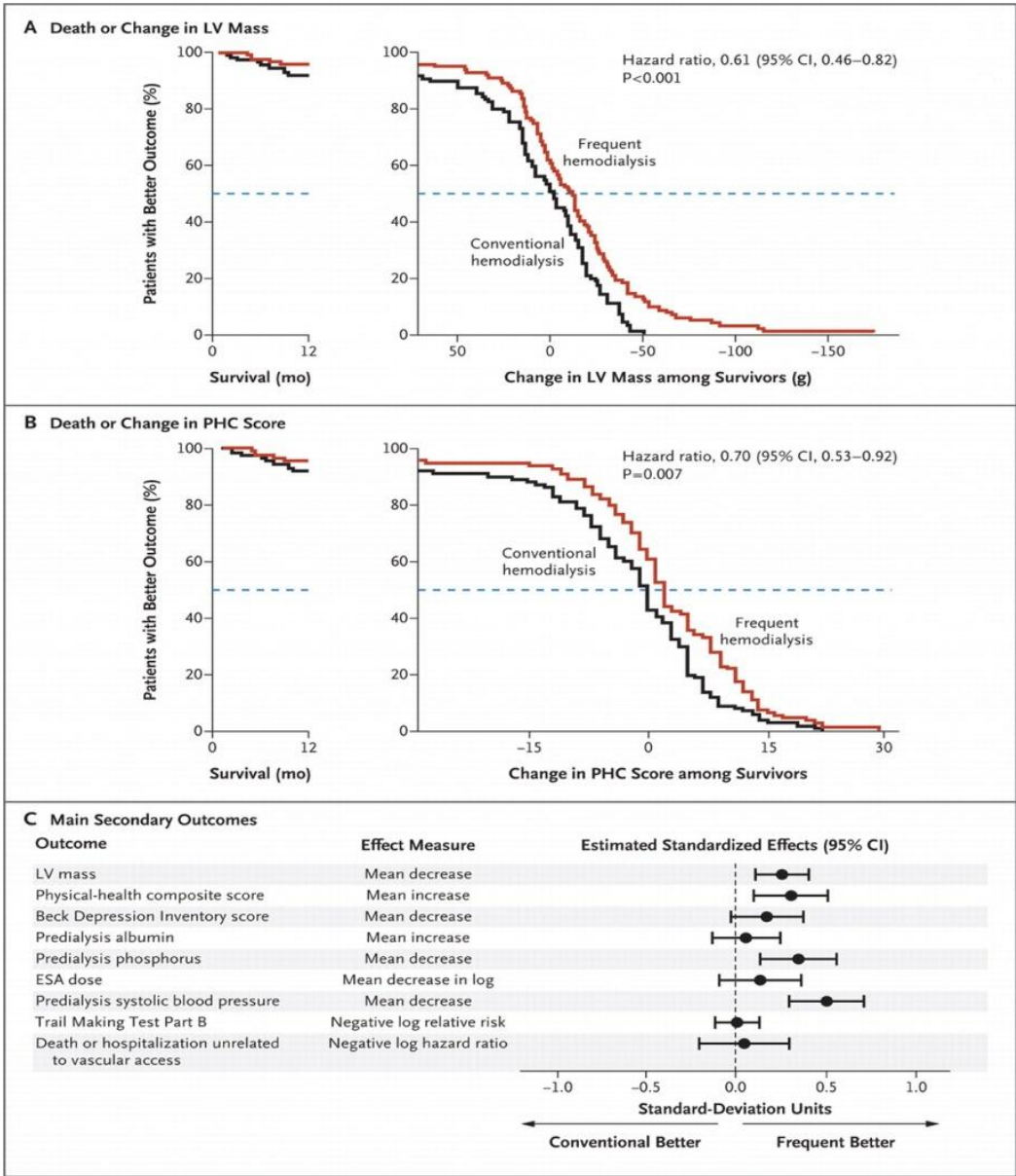
Alternative dialysis schedules such as Short Daily Haemodialysis (SDHD), 2.5-3 hours 6 times per week, and long nocturnal haemodialysis (NHD), 6-8 hours 5-6 times per week, were described in 1968 [23] and 1996 [101] respectively. Preliminary analyses of data suggested 5 year survival exceeding 80% in patients receiving home NHD [73].

SDHD of a minimum of 3 hours is required for adequate phosphate control, but, NHD patients could have their prescriptions for phosphate binders eliminated and even enjoy unrestricted diet [66]. There are case studies related to other cardiovascular improvements with nocturnal haemodialysis including restoration of peripheral vascular flow to lower extremities [17] and resorption of ectopic calcification [47]. Sleep disorders are very common in ESRD patients. Conventional haemodialysis alleviates that to some extent. However home dialysis is more effective in significantly improving complaints and complications associated with untreated sleep disorders in this patient population. There is evidence that sleep apnoea is improved both by nocturnal PD and NHD, however, there has been no systematic evaluation of these modalities of home dialysis on other sleep disorders [40]. The report of a prospective observational study (FREEDOM) demonstrated long-term improvement in the prevalence and severity of Restless Legs Syndrome with SDHD [44]. Both SDHD and NHD reduce blood pressure, in some instances obviating the need for anti-hypertensive drugs and reduce LVMI. Several prospective and retrospective observational studies [107, 28, 55, 3, 16, 105, 57, 97, 82] have demonstrated this, subsequently confirmed in a randomised controlled trial by Culleton et al. [105].

In 2003, the National Institute of Health initiated the FHN (Frequent Haemodialysis Network) study [19] with separate daily and nocturnal trials. The objective was to compare outcomes between patients receiving 'conventional' (3 times weekly) and 'frequent' (6 times weekly) in- centre dialysis treatments. Two co-primary composite outcomes were selected: (1) death or change (from baseline to 12 months) in left ventricular mass (LVM), as assessed by cardiac MRI, and (2) death or change in the physical health composite (PHC) score of the RAND- 36 health survey. The treatment arms had a high compliance rate. Significant LVM (a mortality surrogate) reduction in 245 randomised subjects provided further confirmation of findings of Culleton et al (using MRI) and by Ayus et al. (using echocardiography).

FHN study demonstrated an improvement in most domains with a statistically significant improvement in serum phosphorus levels and systolic blood pressure control in the frequent group. Vascular access interventions occurred significantly more often in the frequent group, but overall failure rates of access were not statistically different. The FHN Nocturnal trial, failed to confirm the benefits observed in the daily trial [86].

Most observational studies have reported either an improvement in quality of life or no difference from baseline, in response to more frequent haemodialysis. In the FHN daily trial the change in PHC score of the RAND-36 survey, demonstrated significant improvement. The PHC score improved from 38.4 ± 11.0 to 41.7 ± 10.7 in subjects in the frequent arm, whereas the PHC score in the conventional arm remained unchanged. In other studies, SF-36 has been employed [97, 57]. Culleton et al used the EuroQol 5-D index. These indices are not directly comparable to each other but the overall impression is one of improvement in parameters of quality of life with increased dialysis frequency. It is worth noting that Culleton et al [105] did not find significant improvement in quality of life indices using the Euro Qol 5- D index, except for the kidney specific aspects.



FHN Daily trial report, (19)Chertow et al. 2010.

Figure 1. Improving clinical outcomes with frequent haemodialysis.

Fewer studies have provided information on hospitalization rates. A study by Mohr et al demonstrated a 43% reduction in unplanned hospital days associated with SDHD or NHD compared with CHD [68]. Another study of 12 home haemodialysis patients in 2007, demonstrated a reduction in hospital days to 0.56 admissions /pt/yr over 234 months [51].

Mark R Marshall et al. 2011, published an observational cohort study that suggests superior outcomes at home compared to hospital HD from the Australia and New Zealand Dialysis and Transplant Registry, using marginal structural modelling to adjust for time-

varying medical co-morbidity, in all patients starting RRT from 1996 and followed up until 2007 (Figure 2).

The majority of comparative studies between PD and HD come from observational registry data that show patient survival on PD to be either similar or even better than on hospital HD, at least for the first few years. The survival results during longer follow-up periods are equivocal; probably because of inevitable differences between the modalities. A review of the quality-of-life literature suggests that patients undergoing PD have an improved quality of life and an enhanced sense of patient satisfaction compared with in-centre HD patients [39].

A holistic view of patient centred care, would lend a place to peritoneal dialysis amongst all other forms of home dialysis modalities, either as an initial modality option or whilst the patient is awaiting live donor transplantation. Indeed PD mortality rates have fallen consistently over the years, even in at-risk patients such as the older, diabetics, heart failure patients, the fast transporters and anurics. Icodextrin, technological advances and cumulative centre experience have shown improved results that might overcome the time associated limitations of PD treatment [87]. APD is gaining a role in the treatment of patients with congestive heart failure [30]. Perhaps, the PD first model practised in Hong Kong that has achieved reasonably good clinical outcome with 2-year patient survival (91%) and technique survival (82%), could be replicated elsewhere [54].

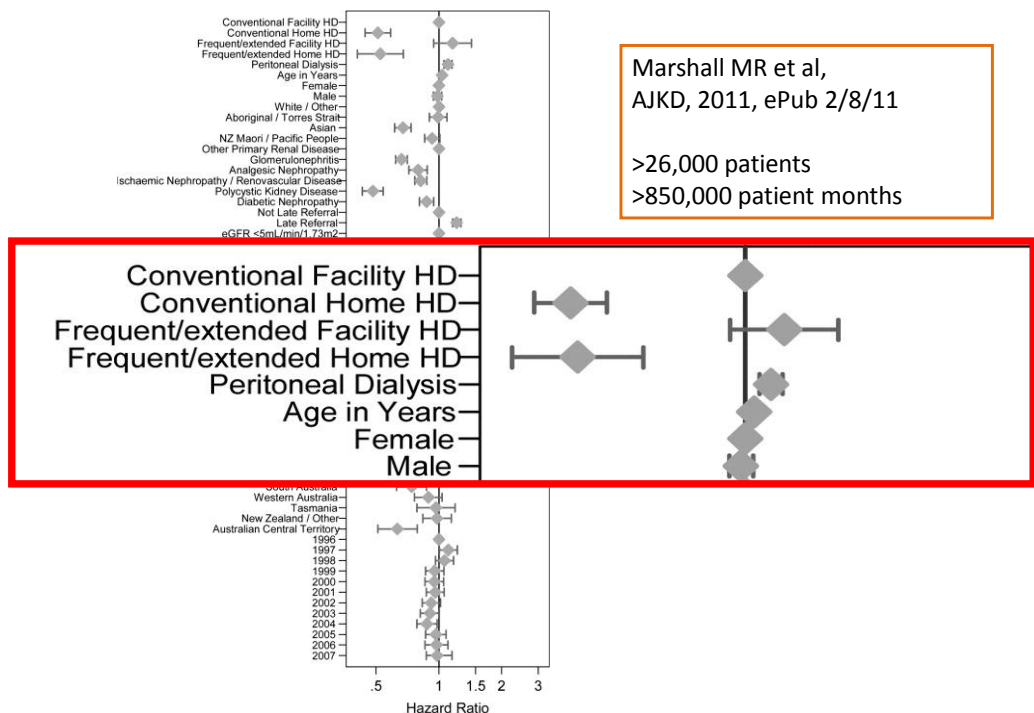


Figure 2. Outcomes with home HD. Dialysis modality was the key determinant of outcome adjusted for confounding variables.

The comparison of PD with HHD tends to suggest superior outcomes in the latter modality. Transplantation is considered the gold standard for management of ESRD. Intensive dialysis options may be a reasonable alternative for individuals unable to undergo transplantation. Literature on their comparison is sparse, but, early observational data suggest that NHD may offer the best outcomes in dialysis long term, comparable with deceased donor transplantation [81]. Comparative analyses of RRT options are difficult due to selection bias, differing methods of clearance and lack of prospective studies of comparative observational cohorts.

Most recently, a paper by Foley et al, provides further evidence of increased mortality after the longer breaks during conventional intermittent hemodialysis [29]. The avalanche of registry information and trials data suggest one unifying message. A loud and clear message: challenging the clinical community to create optimal dialysis care, through solutions that combine effective dialysis clearance with adequate time and frequency to improve outcomes.

5. Adoption Barriers to Intensive Home-based Dialysis

‘There is nothing like staying at home for real comfort’ said Jane Austen (Emma, 1815). Home dialysis therapies offer the flexibility of more frequent and longer dialysis sessions and is conveniently and comfortably done in the patient’s own set schedule, in their own home with their own support [6]. Irrespective of the modality of intervention, the concept of caring for one’s self has the potential to benefit patients.

Home hemodialysis peaked in the mid-1980s and then for several presumed reasons, high rates of attrition were noted in the UK and internationally- with the exception of Australia and New Zealand.

Table 2. Geographical variance in the adoption of home HD within the top 12 UK centres

Renal Unit	% of prevalent dialysis patients on home HD on 31/12/2007	% of prevalent dialysis patients on home HD on 31/12/2008
Manchester	8.6	11.4
Brighton	5.5	5.7
Sheffield	5.2	5.7
Guys	5.1	5.1
Bristol	5.5	5.0
Preston	3.6	4.6
Derby	3.6	3.8
Birmingham Heartlands	3.6	3.2
Oxford	4.1	3.5
Hull	2.8	3.3
Newcastle	2.6	3.1
Liverpool Aintree	1.7	3.1

UK Renal Registry report 2009.

The steep rise in the number of patients with established ESRD [102] an increase in the median age of dialysis population, development of PD (Automated PD, Assisted PD) and success of live donor transplant programmes seem to have been suggested as reasons behind this, although no correlation has been described, between HHD and transplantation or the total RRT programme [60]. There is no evidence that centre use of PD is associated with centre use of HHD ($R^2=0.0004$, $p=0.9$) [102]. Health care systems and reimbursements have been implicated. However there exists wide variation between renal centres in the proportion of patients using a home haemodialysis modality, even within the same health care system (UK Renal Registry from 2008/9, Table 2).

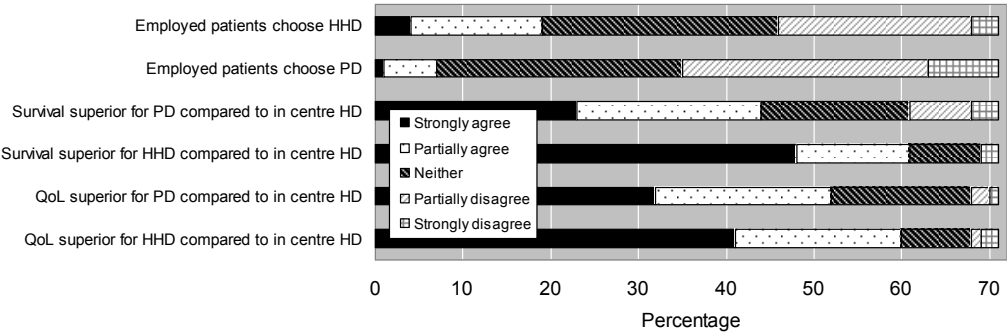
NHS Kidney care workshop [72] conducted at the Symposium on Home Dialysis, Manchester, UK in 2009 collated responses from several multidisciplinary participants outlining the broad categories of barriers as perceived from clinician, patient and resource perspectives, which are outlined in Table 3.

The selection of renal replacement therapy modality lies with the patient and therefore can only be made after they are fully informed of the various choices. Multidisciplinary education and counselling should form a part of the management of all patients approaching ESRD. A USRDS report from 1997, revealed that 84% of PD patients, but only 47% of HD patients believed they had even been involved in choice of modality [103]. A prospective study of patient's choice of dialysis modality revealed that up to half of the patients counselled would accept a home based, in this instance, CAPD therapy [56]. The quality and quantity of pre-dialysis education and the level of support, in the form of a team of specialist nurses, does seem to influence the number of patients choosing a home modality and having a planned start to RRT [34, 61].

Table 3. Perceived barriers to the adoption of home HD

CLINICIANS	PATIENTS	RESOURCES
Lack of knowledge especially amongst junior staff	Lack of genuine choice especially if English not first language	Perceived high capital costs- especially for units with no or limited HHD programme
Inertia, historical practice limits	Lack of knowledge or awareness of benefits/potential	Monitoring and support of home therapy
Difficulties identifying suitable patients	Lack of suitable role models or advocates locally	Availability of new technologies
Preconceptions about ability of patient/carer to cope	Fear of machines and self cannulation	Potential negative impact on new satellite units
Perceived lack of demand	Concerns regarding risks of adverse events at home	Uncertain demand
Physician Bias	No suitable homes or carers	Perceived need for carer at home, lack of support for carers
Lack of clinical champion	In-centre exposure- negative impact	Limited training capacity

Table 4. Perceptions of UK Nephrologists regarding home based therapies



UK Nephrologists survey, UKRR, 2010.

The availability of adequate staff to deliver this information may be variable across different centres. Caskey et al did an association study between social deprivation and survival on RRT in England and Wales between 1997 and 2004 and found inequitable access to RRT of individuals from deprived areas, using the Townsend index [15]. Late referral of patients from these areas was also highlighted. These could potentially have an impact on uptake of home dialysis. Patients who presented within 3 months of requiring dialysis were less likely to receive a home dialysis treatment in a survey by Lamiere et al [52]. An unpublished abstract by [26] Ebah et al (Manchester, 136 patients over 7 years), presented at the EDTA (2010), found that socio demographic deprivation did not impact upon successful completion of training and commencement of self-care haemodialysis, at home.

The UK Renal Registry has also looked at physical limitations that may influence the uptake of home therapies. Twenty-one (33%) of the centres providing home HD responded that space within patients’ homes was almost never a factor preventing home HD whilst only eight centres (12%) responded that space was at least ‘frequently’ a factor preventing home HD. Twenty-five centres (39%) responded that funding restrictions prevented a patient receiving home HD in at least some cases.

Clinician’s bias to one or the other modality seems to play an important role. Poor exposure to PD during training [64, 25, 74, 95] was found to bias clinicians against home dialysis therapies, whereas belief in a superior quality of life associated with home dialysis [65] result in greater advocacy of home therapies. The survey by the Renal Registry (Table 4) demonstrated that a broad range of opinions about dialysis modality related survival and quality of life are held by UK nephrologists, but a majority believe that Home HD provides a superior survival and quality of life than in-centre dialysis.

A systematic study in USA [33] highlighted the current under-usage of home dialysis and identified problem areas including, limited and unmandated home dialysis training of nephrology fellows, lack of synchronised education of ESRD care providers, Medicaid services’ poor reimbursement policies which dis-incentivises home based therapy, business policies and philosophy of dialysis providers, eg. not all PD solutions and HD equipment are available to US patients.

In an Australian survey [59] the most commonly reported impediments to expanding home dialysis services were financial disadvantage for home HD patients, and lack of physical infrastructure for training, support and education. Areas of concern for expanding

home dialysis programmes included psychiatry support, access to respite care and home visits, and lack of support from medical administration and government. The majority of nephrologists would recommend home dialysis to more patients if these impediments could be overcome.

Barriers of physical (decreased strength, manual dexterity, vision) and cognitive nature (language barrier, history of non-compliance, poor memory, psychiatric condition) have been linked to incident PD use, the former being more prevalent [77]. Patients with barriers were generally older and were likely to have a history of vascular disease, cardiac disease and cancer. This prospective observational study demonstrates that, even when home care assistance for PD is available, family support was an important driver of PD eligibility and choice among patients with barriers to self-care PD. Barring medical contraindications to PD, most barriers were considered modifiable and in the generally older population, uptake of PD in incident ESRD population could be encouraged.

The survey looking at reasons why prevalent in-centre haemodialysis patients, did not choose self-care dialysis, revealed human factors were associated with a negative attitude towards self-care dialysis such as, fear of change in general, fear of social isolation, not being prepared to stay awake on dialysis, time constraints preventing self-care, needle phobia and fear of reduced interaction [63].

In one of the largest opinion surveys [53], over 7000 nephrology health-care professionals were given questionnaires at five major international dialysis conferences in 2006. This survey has identified patient motivation as one of the strongest drivers of self-care dialysis at home. The need for dedicated resources for the staff to devote time to developing such motivation is given as one of the major reasons for the slow adoption. Under ideal conditions, it is felt that one-third of all patients starting dialysis can be trained to perform self-care dialysis.

Most published analyses have been limited by examining factors in isolation, or studies based on opinions, questionnaires and surveys which lack consensus. Registry data collection is limited to clinical dataset and do not incorporate delivery aspects, patient reported outcomes and factors that define treatment preference and pathways of this modality. Systematic study of optimal uptake, examining barriers and drivers at various levels has not been undertaken, but necessary to aid development of a model that addresses the complex interplay of adoption barriers and the uptake of home based dialysis therapies.

6. Economic Drivers

The Department of Health in the UK carried out an extensive review of self-care support, encompassing large numbers of systematic reviews, observations and surveys in a wide variety of clinical conditions and found clear evidence of beneficial health outcomes for patients and better use of health and social care resources. In addition to personal benefits to patient's health, the true cost benefits of self-care therapies have been analysed in different health care settings and can be seen to involve therapy related costs and other costs such as those due to infections, hospitalisations due to comorbidities etc. The wider implications on the society through employment or the lack of it and taxation or receipt of benefits ought to be factored in for the true estimation of economic consequences.

In the UK, evidence from NICE suggests that initial set-up costs of home haemodialysis can be high, but these can be recovered over a 14 month period. Treatment thereafter is cheaper at home than in the hospital, largely due to lower staffing costs and transport costs (TA 48, NICE). Baboolal and colleagues [4] did a cost estimate of the different modalities in 2008, in the UK, and demonstrated, cost savings with home haemodialysis technique, which has since been replicated by work from NHS Kidney care. More appropriate economic analysis will require other considerations, such as costs associated with home conversions, travel reduction, return to work and contribution thereby to the economy. Adaptation of existing in-centre dialysis stations to provide for training for home HD could obviate some of the barriers to initial set up costs of a home training program.

A systematic review of 27 studies [69] undertaken between 1978 and 2001, identified 18 studies which considered cost effectiveness. Mowatt et al, concluded, in 2003, that the evidence was very much in favour of low costs for home haemodialysis. This was demonstrated in an Australian study in 2009 and a single centre UK study with significant cost savings predicted in 1 year [42].

The broader societal economic benefits of home dialysis include better full time employment especially in nocturnal dialysis patients [79]. The several million miles on the road also leaves a rather heavy carbon footprint, in the context of current environmental policies.

7. Paradigm Shift in Treatment Delivery

Undoubtedly, dialysis modality selection is complex and consists of a dynamic interplay of (a) physician knowledge and practice, (b) patient autonomy and preference, (c) clinical benefits and limitations, (d) resource allocation and financial incentives, and (e) geographic differences [18].

Evidence is growing on the value of adapting the haemodialysis treatment and technology to provide more frequency and time, where appropriate, with minimal disruption to patient quality of life and lifestyle. The treatment location for delivery of such care needs to be better defined. Home dialysis in the motivated patient encourages responsibility, independence and confidence. Policy in the UK supporting the use of home HD and PD is set by the National Institute for Health and Clinical Excellence (NICE). In 2002, the guidance recommended that at least 10% of all dialysis patients in units could be on home haemodialysis. Most recently, in 2010, the median (IQR) percentage of prevalent dialysis patients using HHD was 2.9% (1.3–3.9) [102]. A recent report from the Royal College of Nursing, UK [10] estimates that there will be a variable decline in nursing workforce in the next decade due to the on-going NHS reforms - therefore a move away from nurse intensive ‘hospital based dialysis’ therapies deserve consideration. This is in line with the NHS agenda of “Care Closer to Home” and there are several UK initiatives in place to promote home based dialysis therapy to all those who might benefit.

Technology remains a limiting factor, and although the present era has seen significant advances, true portability of dialysis systems in the form of a wearable artificial kidney is a concept still in development, three decades since the idea was first conceived [22].

It is evident that a fundamental change in culture and practice, involvement of patient groups, having a 'local champion' for home dialysis and private and public sector initiatives are essential pre-requisites for a more balanced distribution of the modalities. Helping patients develop motivation for self-care is likely, the single most important driver for this change.

Conclusion

Invention of dialysis is one of the most significant discoveries in medical science. Few life-saving medical interventions can rival its global uptake in the past four decades. Growth in demand for dialysis is a testimony of its success. However, there is a growing need to develop methods of improving treatment outcomes and its cost-effectiveness. It is in this context that there is a resurgence of frequent and longer dialysis sessions, treatment most feasibly deployed at home. Benefits of extended dialysis regimen are supported by robust studies, and promise significant advances in patient experience and outcomes. Collaboration and partnerships will be required between physicians, patients, the industry and governments to adopt changes in attitudes and philosophies, with the necessary legislative or regulatory alterations, to implement clinically superior and contemporary dialysis treatment programs suitable for all patients with end stage kidney disease.

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Chapter VI

Planning and Maintaining Functional Vascular Access in a Haemodialysis Population

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Abstract

A reliable form of vascular access is an essential requirement for efficient haemodialysis. The past four decades have seen significant progress in our understanding of the biology of vascular access maturation and failure, and numerous advances in techniques for forming and maintaining vascular access. This period has also witnessed a growing body of evidence demonstrating superior patient outcomes associated with commencing haemodialysis with permanent vascular access, which has in turn strongly influenced dialysis unit policies. Despite this progress, the nephrology community still faces a number of biological, logistic and technical challenges to implementing widespread use of permanent vascular access, and improving early and late patency rates. The persistence of such obstacles has meant that temporary vascular access continues to be widely used. This chapter discusses available forms of permanent and temporary vascular access, the evidence driving policies that promote timely permanent access formation, and the logistic challenges faced in achieving this goal. We discuss our current understanding of the biology of arteriovenous fistula and graft maturation and failure, and critically review the roles of pre-operative imaging, post-operative surveillance, mechanical interventions, and pharmacological agents in improving permanent access

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patency rates. Finally we discuss the complications of temporary haemodialysis vascular access and their management.

Introduction

Arteriovenous Fistulas and Grafts – Placement Sites and Surgical Techniques

A reliable form of vascular access with a blood flow rate of at least 500 ml/min is an essential prerequisite for efficient haemodialysis [1, 2]. In 1966 Brescia, Cimino, Appel and Hurwich published the first detailed description of a surgical technique to create a side to side anastomosis between a native artery and vein, heralding the native arteriovenous (AV) fistula as the mainstay of vascular access in haemodialysis [3]. AV fistulas are preferentially fashioned in the non-dominant upper limb to facilitate patient self-cannulation and minimise interference with dominant limb function. Vessels can be anastomosed using side-to-side, end-to-end, or end-to-side anastomoses with the latter being the most preferred surgical technique [4]. AV fistula placement sites recommended by international societies are, in order of preference, the radial artery anastomosed to the cephalic vein (wrist / forearm fistula) followed by anastomoses between the brachial artery and cephalic vein (upper arm fistula), or the brachial artery and the basilic vein [5, 6]. The rationale behind this ‘distal-first’ recommendation lies in the fact that distal fistulas have a higher primary failure rate than upper arm fistulas, thus an initial attempt at a distal fistula preserves more reliable proximal vascular options should the first fistula fail. Moreover, distal a distal fistula is less likely to cause vascular insufficiency of the limb. Brachiobasilic fistulas often require lateral transposition of the basilic vein and subsequent superficialization of the entire fistula, usually in a two stage procedure [7]. Other options include anastomoses between the ulnar artery and basilic vein, or the brachial artery and the median antecubital vein. If vascular options are exhausted or vessels felt to be unsuitable in the dominant arm then the non-dominant arm may be used. A further option is to transpose a conduit of synthetic (usually PTFE) or biological material in either a straight or looped configuration between a native artery and vein to create an AV graft.

Table 1. Features of haemodialysis vascular access modalities

	Arteriovenous Fistula	Arteriovenous Graft	Central Venous Catheter
Primary Failure Rate ¹	High	Low	Low
Secondary Failure Rate ²	Low	High	High
Re-intervention Rate ³	Low	High	High
Expected Duration of Vascular Access Survival	> 2-years	< 2-years	Months
Achievable Blood Flow Rate & Small Solute Clearance	High	High	Poor
Risk of Infection	Low	High	High

¹Primary failure represents failure of vascular access to ever support haemodialysis adequately and/or reliably. ²Secondary failure refers to late failure of previously functioning vascular access. ³Re-intervention describes the need to apply a mechanical or pharmacological intervention to re-establish adequate blood flow.

These conduits have advantages over native fistulas of lower primary failure rates [8, 9], and ease and immediacy of cannulation, but are associated with a higher risk of subsequent secondary failure due to thrombosis [10, 11] and significant infection [11-13] making them a less desirable option than native AV fistulas [5, 6]. The final option is to form a lower limb native AV fistula or graft. The characteristics of AV fistulas, grafts and central catheters are compared in table 1.

Arteriovenous Access Failure

Primary Failure

Arteriovenous access failure is classified as either primary or secondary depending on the timing of access dysfunction. A consensus definition for primary failure is lacking; being variably defined as either access that has not matured adequately for cannulation and/or failed within 3-months of dialysis commencement [14] or an inability to cannulate AV access within 4-months of formation and/or an inability of the access to deliver a minimum blood flow rate of 300 ml/min for at least 8 dialysis sessions over the next 30 days [15]. In essence, primary failure represents failure of AV access to ever support dialysis adequately and/or reliably. Conversely, secondary failure refers to late failure of previously functioning AV access.

Primary failure rates of native AV fistulas range from 23 – 56% depending on the definition used [11, 16, 17] and placement site, with upper arm fistulas having lower primary failure rates compared to forearm fistulas [18, 19]. Primary failure of AV fistulas is caused by either early thrombosis or “failure to mature”. Compared to native fistulas, AV grafts have a lower primary failure rate of approximately 10% [8, 18], but a significantly higher secondary failure rate (53% vs. 16-35%) (20-23) and are 2.4 – 7.3 times more likely to require re-intervention to maintain patency post-formation [11].

Biology of Arteriovenous Fistula Maturation

Once established, AV fistulas are superior to AV grafts (*see above*). Therefore the goal is to enable all patients to commence haemodialysis with a functioning AV fistula. However, the major obstacle to success with AV fistulas is “failure to mature.” Following the formation of an AV anastomosis, arterial and venous vessel diameters and blood flow rate increase progressively in a process called “maturation”; depending on the rate of maturation, a fistula may be cannulated for dialysis after period of 4-weeks to 4-months [2, 4].

Maturation is accomplished through vasodilatation and arterial wall remodelling. Formation of an AV anastomosis results in an increase in blood flow rate in both vascular limbs of the fistula leading to a rise in vessel wall shear stress which stimulates endothelial cells to secrete the smooth muscle relaxants nitric oxide and prostacyclin resulting in vaso- and veno- dilatation with the result that shear stress is reduced [24, 25]. In addition, the arterial wall undergoes early structural remodelling through the enzymatic digestion of extracellular matrix components by endothelial derived matrix metalloproteinases; reducing

arterial wall cross-sectional area and increasing luminal area [26, 27]. Longer-term changes of the arterial wall are less clear. A longitudinal study of 16 patients undergoing serial ultrasound assessment of the arterial limb wall thickness demonstrated an increase in radial, but not brachial arterial wall thickness at 1-year following AV fistula formation [28]. The observed increase in radial artery wall thickness may represent medial smooth muscle hypertrophy and/or an increase in extracellular matrix in response to increased transmural pressure, but the differential findings between the radial and brachial arteries remain unexplained. In contrast, venous structural remodelling is characterized by an increase in the thickness and cross-sectional area of the venous wall [29]. The exact mechanism of this eccentric hypertrophy is poorly understood but may represent medial hypertrophy in response to the increase in venous transmural pressure [30]. In essence the problem of failure of AV fistulas to mature is the focus of current research. Understanding the mechanisms of failure, effective interventions and the most appropriate time to intervene are the current challenges.

Secondary Failure

The leading cause of secondary failure of both AV fistulas and grafts is a vascular stenosis with/out subsequent thrombosis. The most common site of stenosis is in the venous limb either at the anastomosis with the artery or graft (forearm fistulas and all grafts) or in the proximal vein (upper arm fistulas and grafts) [31-33]. Neointimal hyperplasia, impaired venodilatation or a combination of both processes are thought to be the major mechanisms resulting in venous stenosis. Neointimal hyperplasia results from the migration of myofibroblasts from the media and/or adventitia to the intima where they proliferate to form an eccentric stenosis which encroaches on the venous lumen [34]. This is thought to be a response to foci of low vessel wall shear stress at the juxta-anastomotic venous segment which stimulates hyperplasia and thrombosis [35, 36], and/or an injury response to endothelial damage incurred during surgical handling and manipulation of the vein [37].

In addition, failure of venodilatation due to uraemic related endothelial dysfunction or endothelial denudation during surgery or venipuncture may also be partly or wholly responsible for stenotic segments [37, 38]. Venous run-off into an accessory vein(s) compromising blood flow in the principal venous limb is the a significant cause of failure of maturation; ligation or obliteration of such accessory veins has the potential of salvaging the AV fistula [14].

Predictors of Arteriovenous Fistula Primary Failure

Vessel Size

Cohort studies examining the association between arterial internal diameter and the risk of AV fistula primary failure have yielded conflicting results. Two small cohort studies of 35 and 21 patients respectively undergoing native AV fistula formation reported that an arterial internal diameter ≤ 1.5 mm was associated with a significantly lower blood flow rate at 12-

weeks and increased risk of immediate thrombosis [39, 40]. However, these studies are limited by their small sample size, their use of blood flow rate rather than adequacy for dialysis as the primary outcome, and a lack of control for confounding demographic and co-morbid conditions. A larger cohort study of 102 patients reported that an arterial internal diameter < 1.6 mm was associated with a significantly increased risk of AV fistula failure within 24-hours of construction in a multivariate regression analysis [41]. However, the authors did not report the on the more clinically important outcome of suitability for dialysis. In contrast to these findings, five cohort studies using more robust outcome definitions did not demonstrate an association between arterial internal diameter and risk of primary failure [42-46], although one of these studies only included patients with an arterial internal diameter > 2.0 mm [45]. Similarly, four cohort studies did not demonstrate an association between venous internal diameter and the risk of primary failure [42, 45-47], while one small cohort study of 44 patients reported that a venous internal diameter < 2 mm was associated with a significant increase in the risk of primary failure; however no adjustment was made for age or co-morbidity in the latter study raising the possibility that the observed association may be due to unaccounted confounding variables [48]. At the present time small vessel size should not be considered an absolute contraindication to constructing a native AV fistula, but should prompt an earlier attempt at an anastomosis to allow further attempts to be considered should the first fistula fail.

Vascular Functional Indices

The demonstration that successful fistula maturation requires progressive dilatation of both the arterial and venous limbs led to the hypothesis that primary failure may be predicted preoperatively by manoeuvres that induce arterial dilatation and venous distension.

Under resting conditions large arteries demonstrate a triphasic pattern of blood flow with an initial systolic upstroke followed by reverse flow due to elastic recoil of distal arterial beds and finally forward diastolic flow at a low rate. Fist clenching or upper arm arterial occlusion using an inflated blood pressure cuff for 2 – 3 minutes induces a short period of ischaemia, which when released results in vasodilatation of distal arterial beds, a fall in total peripheral resistance, and consequent hyperaemia. This response alters the flow in the feeding artery from a triphasic to a biphasic pattern characterised by a systolic upstroke followed immediately by forward diastolic flow at a higher rate than that seen during rest [49]. Failure of the arterial flow pattern to change from triphasic to biphasic in response to hyperaemia suggests persistence of high distal arterial resistance due to lack of arterial dilatation. In a cohort study of 116 patients undergoing radiocephalic AV fistula formation, Malovrh and colleagues reported that a high radial artery resistive index following fist clenching assessed preoperatively was an independent predictor of thrombosis within 24 hours of anastomosis [41]. The more important outcome of adequacy for dialysis was not reported. In contrast to these findings, three cohort studies have failed to demonstrate a significant association between the arterial response to ischaemia/hyperaemia and primary failure defined as a fistula unable to support dialysis reliably at 6-months [43, 50, 51]. Thus the role of this manoeuvre remains unclear and cannot be used reliably at the present time to predict access outcome during the access planning process. An increase in vein calibre following external compression by a blood pressure cuff according to a standardised protocol has been proposed

as a surrogate measure of the functional capacity of a vein to dilate; the association between venous distensibility tested in this manner and the risk of AV fistula primary failure has been investigated in 2 cohort studies. A study of 116 participants reported a significantly lower venous distensibility among fistulas that thrombosed within 24-hours of formation in a univariate analysis, however, this association was lost in a multivariate analysis suggesting that it represents confounding [41]. A second cohort study of 17 patients reported significantly greater venous distensibility among fistulas used successfully for dialysis, however given its small sample size, it was unable to report if this association remained significant after adjustment for demographic and co-morbid conditions [46]. As with arterial hyperaemic response, the use of venous distensibility during AV access planning cannot be recommended at the present time and requires further investigation.

Demographic Factors

A number of cohort studies have explored associations between primary failure, and demographic and co-morbid conditions in an attempt to identify high-risk groups who might benefit from an earlier attempt at AV fistula formation. A retrospective single centre cohort study of 422 patients reported that features associated with an increased risk of primary failure were age ≥ 65 -years, peripheral vascular disease, coronary artery disease and black race in a multivariate analysis [52]. The authors subsequently developed a predictive scoring system based on these features to categorise patients into one of four risk categories for failure to mature.

A prospective external validation of this equation showed higher scores were associated with a significant risk of failure to mature (70% of high-risk individuals experienced failure of maturation vs. 25% of low-risk individuals). The effect of this score on vascular access choice and clinical outcomes (catheter avoidance, infection, hospitalisation, and mortality) has not been investigated. These associations were corroborated by a prospective cohort study of 348 patients which demonstrated that increasing age, history of cerebrovascular or cardiovascular disease, and dialysis dependence at the time of AV fistula formation were all significantly associated with an increased risk of failure to mature in a multivariate analysis [53]. The impact of female gender and diabetes mellitus on risk of primary failure is unclear, having been identified as risk factors in some studies [1, 17, 54, 55] but not others [52, 53, 56]. At the present time there is no definitive evidence that either of these characteristics impact on AV fistula primary failure.

Preoperative Imaging

Doppler ultrasound scanning to locate, and assess the structural and/or functional characteristics of vessels is widely employed during preoperative planning of AV fistula formation. This modality has been shown to be accurate in assessing both arterial and venous dimensions with good agreement between preoperative imaging and direct intraoperative measurements [41, 57]. The principal advantage of preoperative vascular imaging lies in its superior ability to locate candidate vessels compared to physical examination alone, thereby

increasing the number of individuals considered to be suitable candidates for AV fistula formation.

This was illustrated in 2 prospective cohort studies examining the influence of preoperative vascular imaging on surgical decision making. Patients underwent physical examination by an experienced surgeon in addition to preoperative vascular ultrasound performed by an independent operator. While blinded to the imaging findings, surgeons recorded their assessment of a patient's candidacy for AV fistula formation and the planned procedure; imaging results were then provided to the surgeon and any change in candidacy / procedure recorded. In the first study 48/62 patients (77%) deemed to have poor/absent veins on physical examination were shown to have suitable candidate veins on ultrasound [41], while in the second study preoperative imaging led to a change in the procedure performed in 31% of patients, and 8/52 patients (15%) initially deemed not be AV fistula candidates subsequently proceeded to successful AV fistula formation [58]. These findings are also supported by observations that the number of AV fistula formations attempted and the proportion of North American haemodialysis patients dialysing through native AV fistulas has increased substantially since the introduction of routine preoperative vascular mapping [45, 56, 57], although some of this improvement may also be attributable to accumulating surgical experience and/or governmental policy directives such as the 'Fistula First Breakthrough Initiative' (www.fistulafirst.org).

Studies investigating the impact of preoperative vascular mapping on primary failure rates have yielded conflicting results. These studies employ a retrospective cohort design whereby rates of primary failure following the introduction of universal preoperative vascular mapping are compared to a matched historical cohort in which no such preoperative imaging was undertaken. One such study reported a significant decrease in primary failure rates from 36% to 8% [57], two reported no significant change in primary failure rates [45, 59], while one reported an increase in primary failure rates [60].

The most significant limitation of these studies is their retrospective cohort design which despite subject matching introduces a significant risk of unaccounted confounding including changing surgical experience, governmental policy directives, and patient co-morbidities which may bias the findings.

Furthermore it is not surprising that primary failure rates may not improve following universal introduction of vascular mapping given that the anatomical and functional vascular determining primary failure remain undefined.

Interventions Prevent Primary AVF and AVG Failure

Pharmacological Interventions to Improve AV Fistula Primacy Patency

Pharmacological interventions have been tried to reduce early thrombosis and/or improve AVfistula maturation. These have primarily involved use of anti-platelet agents. Only one study has been published to date which has had adequate power to address whether these agents are effective. This study [9] demonstrated that clopidogrel reduced the rate of thrombosis rate of AV fistula from 19.5% to 12.2% ($p=0.18$). However, there was no effect

on the more important outcome of fistula suitability failure. There is currently underway an Australasian study assessing the effects of aspirin and fish oil in a factorial design in an adequately powered randomised controlled study examining thrombosis rates and fistula suitability rates [32, 61]. At present however, there is as no definitive benefit has been shown on AV fistula suitability for dialysis, these agents are not routinely recommended.

Mechanical Interventions to Improve AV Fistula Maturation and Improve Useability

Post-operative evaluation to ensure an AV fistula is maturing has been recommended but there is currently no consensus about when this should occur and what can be done. However, there are three remediable problems including a focal stenosis in the draining vein; ligation of accessory veins; and superficialisation of deep fistulas [14, 32, 62-64]. Well conducted randomised studies are needed to establish the role of such interventions. Moreover, studies are needed to address the more difficult problem of failure of adaptive changes to occur in the artery and vein necessary to effect AV fistula maturation.

Pharmacological Interventions to Improve Primary AV Graft Patency

There have been a number of studies exploring pharmacological interventions to improve AV Graft patency although many have been small and inconclusive. However, Dixon et al [8] demonstrated that the combination of aspirin and dipyridamole increased the primary unassisted patency at 1 year from 23% to 28% without adverse bleeding events. However, with such a modest improvement this therapy is unlikely to be adopted as routine care. A randomised placebo controlled study using fish oil is underway [65] following a report of a small study suggesting such therapy might be efficacious. [66]

Timely Access Formation

Commencing Hemodialysis without Permanent Vascular Access

Over the last 10 years there has been increasing recognition of poor outcomes in patients who commence haemodialysis without permanent vascular access. Numerous large registry based observational studies have consistently demonstrated that commencing dialysis with a catheter (either temporary or a cuffed catheter) is associated with an 1.5 to 2 fold increased risk of death compared to commencing with a AV fistula [67-70]. The results have been consistent across studies in different countries and in subgroups such as the elderly. However patients commencing dialysis with a catheter are also less likely to receive pre-dialysis care from a nephrologist and have a greater burden of comorbidities [71]. This therefore makes it difficult to eliminate all such confounding factors in the vascular access mortality relationship. However, aside from the biological plausibility of the relationship - catheters are associated with high risk of bacteremia and reduced dialysis efficiency [72] - subjects who

change from a temporary to permanent vascular access demonstrate reductions in their mortality risk adding weight to an independent effect [73, 74]. Thus it is clear that avoiding both short and long term exposure to catheters is an important treatment goal.

In addition to the mortality benefits with commencing dialysis with an AV fistula, there is evidence for significant costs saving to the health system. The maintenance of vascular access in haemodialysis patients is estimated to account for at least 25% of all dialysis patient hospital admissions in the USA [75, 76], with a total annual global cost of 14 to 17% of all spending on haemodialysis per year at risk (USRDS 1997). Two studies have specifically performed a cost analysis of vascular access [77, 78] both from Canada. The first study considered the costs of maintaining a functioning access in prevalent patients, demonstrating significantly lower access related costs per patient per year for patients who were using an arteriovenous fistula compared to those with an arteriovenous graft and catheter [77]. Total costs including access related interventions and hospital stays were US \$2191 for catheters, US \$3345 for AVG and US \$404 for AV Fistula ($p < 0.001$). The lower total cost of arteriovenous fistula reflected the lower occurrence of complications and the need for interventions to maintain patency. The same group then prospectively studied the costs for the establishment and maintenance of vascular access in an incident cohort of subjects. In that time 18.4% of all hospital admission was vascular access related. Again the mean cost of access care per patient-year at risk was lowest for AV Fistulas compared to catheters and AV Grafts: CAN\$9180 for maintaining a catheter exclusively, CAN\$11685 for attempting an AVG and CAN\$7989 for attempting an AVF ($p = 0.01$) [78]. Finally Markov modelling suggests a modest benefits of using an arteriovenous fistula versus an arteriovenous graft in quality-adjusted survival (average cost of \$446 for each year of perfect health saved) [79].

Current Practice and the Optimal Time to Place an Arteriovenous Fistula

Despite the known limitations of commencing haemodialysis with a catheter the majority of patients in many countries commence dialysis with a catheter. Incident catheter rates however vary considerably across different countries from and while differences in patient comorbidity can explain some of the disparity, specific practice patterns have an important role [80]. Wide variation in catheter, AV graft and AV fistula rates are also seen within countries which cannot be accounted for patients alone [81-83]. While particular patient characteristics are associated with a higher likelihood of commencing without permanent vascular access (eg female gender, age, peripheral vascular disease), these are largely unmodifiable. Clinical practice guidelines vary in the suggestions for timing of AV fistula placement. The KDOQI guidelines suggest the AV fistula should be placed at least 6 months before the anticipated start of dialysis without reference to eGFR thresholds [84] while the Canadian guideline suggest placement at an eGFR of 15 to 20 ml/min in patients with progressive kidney disease [85]. The European Best Practise Guidelines suggest a 2 to 3 months window in which to place the AV fistula [86]. Recent work suggests that referral by the nephrologists for surgical assessment occurs late (mean eGFR 8 ml/min) with AV fistula construction too close to the anticipated time for dialysis commencement [87]. Early patient CKD and dialysis modality education also seems to play an important role. Patients who received formal pre-dialysis education either as group sessions or one on one with an educators are less likely to commence with a catheter [87, 88]. It is clear that timely

placement of permanent vascular access, despite being a seemingly simple concept, has proved difficult in the increasingly older and comorbid dialysis population and requires a co-ordinated team approach to predialysis care [89].

Vascular Access Surveillance

The development of progressive vascular access stenosis with the subsequent failure of the access (thrombosis and/or revision) contributes significant morbidity to patients on haemodialysis. Therefore the ability to identify an AV fistula or AV graft at risk for failure through the detection of a significant stenosis with subsequent elective repair without interruption to the dialysis treatment is clinically attractive. In this section we review state of evidence to support the practice of vascular access surveillance and the evidence that it improves AV fistula and AV graft survival.

Rationale and Definitions

Vascular access monitoring and surveillance are often used interchangeable. However they have quite specific definitions [90]. *Vascular access monitoring* refers to the physical examination (inspection, palpation and auscultation) of the AV fistula or AV graft to detect physical signs of dysfunction whereas *vascular access surveillance* is the periodic evaluation of the vascular access by means of specialised tests that involve special instrumentation [90]. These tests can include measuring access flow, ultrasound assessment and intra-access pressure. It should be noted that both methods are complementary.

The rationale for vascular access screening is that early identification and correction of a vascular access stenosis will prevent access failure and prolong access life. Thus ideally screening will reduce patient co-morbidity by utilising elective repair as opposed to emergency repair reducing the need for temporary catheters and reduce costs associated with maintaining access patency. Therefore success of any surveillance program relies on a number of principles: that the surveillance technique will detect an underlying asymptomatic stenosis; that the stenosis found is clinically ‘significant’; that correction of the stenosis will prevent thrombosis and prolong access patency; and finally that the surveillance technique is cost effective. The success of screening program must therefore be determined from well-designed randomised controlled trials.

Physical Examination of the Vascular Access - Vascular Access Monitoring

Physical examination of the dialysis access is the most important first step in the assessment of the vascular access. It is often underrated and poorly taught. Two recent prospective studies [91, 92] suggest that a well performed, standardised physical examination can detect important venous and/or arterial abnormalities in the AV graft or AV fistula performing just as well as other techniques including venous pressure and blood flow measurements. Physical findings suggestive of a significant access stenosis include oedema of the access extremity (central stenosis), prolonged bleeding post-venipuncture, and changes in

the physical characteristics of the pulse or thrill. The reader is referred to excellent reviews on techniques used in examination of the access [93, 94].

Blood Flow Surveillance

Vascular access blood flow (Qa) can be measured by a number of different techniques but these are broadly categorised into those using indicator dilution techniques (first described and validated by Krivitski [95]) or those directly estimating Qa (largely using doppler ultrasound). Other recent techniques include the variable flow Doppler method [96], the transcutaneous flow monitor [97] and the glucose pump test [98]. The ultrasound dilution velocity method is the most well-validated method for measuring access blood flow [95, 99] and is considered to be the gold standard method [100]. Doppler ultrasound assesses blood flow velocity, and combined with the assessment of cross-sectional area Qa can then be calculated. Unfortunately estimated Qa can be inaccurate due to the operator dependence on determining the blood velocity, and subject error in estimating the cross sectional error and the Doppler angle [101, 102]. For a detailed discussion of the validation and methodology of blood flow measurement in vascular access the reader is referred to recent review on the subject [103].

Prospective studies have established an association between Qa and the risk of thrombosis and/or the presence of a stenosis [104-106]. The risk of thrombosis differs depending on vascular access type, with AV grafts at risk of thrombosis at higher flows (cut offs 500 to 750 mL/min) [106] compared to AV fistula where thresholds are lower (300 to 500 mL/min) [105]. Four randomised controlled trials have examined the effect of Qa surveillance (by ultrasound dilution) and pre-emptive repair (angioplasty in the majority of studies) on AV graft thrombosis rates [107-110]. The two largest and well designed studies both demonstrated a significantly higher detection rate of stenosis on the intervention arms however, despite this, no effect of the subsequent intervention was seen on AV graft thrombosis rate or survival [107, 108]. In contrast the only randomised controlled trial to access AV fistula thrombosis and abandonment suggests a benefit of blood flow screening with the risk of failure in the control group nearly four fold higher [111]. However significant methodological problems including randomisation by coin toss and no blinding of surveillance allocation make confirmation of this result in a larger well designed randomised controlled trial preferable. The same group also reported a further RCT which randomised functioning but stenotic AV Fistulas to angioplasty or no treatment. This study also demonstrated significantly improved AV Fistula survival with the angioplasty procedure [112].

Ultrasound Screening

Ultrasound scanning is a non-invasive procedure that provides anatomic information on the vascular access. As such, it has been advocated as a screening technique to identify vascular access at risk of thrombosis by identifying the anatomical presence of a significant stenosis. The main disadvantage is that it requires specialised equipment, skill, and is expensive. Five randomised controlled trials (=AV graft only) assessed ultrasound screening for access stenosis combined with either angioplasty or surgical repair on thrombosis and survival. Similar to the studies assessing blood flow screening, all but one trial was negative despite increased stenosis detection rates in the intervention arms [113-115].

In the positive study, subjects in the ultrasound screening group had a significantly longer graft patency compared to the usual screening group ($p < 0.001$) with a higher rate of interventions (2.1 versus 1.3 per graft) [113]. However as access blood flow assessments were also performed this study actually tested a combination of stenosis screening and blood flow reductions.

Systematic Review

The effect of vascular access blood flow and/or ultrasound surveillance on AV fistula and AV graft survival has been summarised in a recent systematic review [114]. The review included 11 randomised controlled trials with a total of 1,164 patients. Seven studies assessed AV graft alone, 3 AV fistula alone and one included both with vascular access thrombosis, vascular access loss (defined as vascular access abandonment) and resource use as the analysed outcomes. As vascular access type was significantly associated with the risk of thrombosis associated with surveillance the meta-analysis was performed separately for fistulas and grafts.

For AV grafts screening significantly increased the number of angioplasties (relative rate 1.29, 95% C.I. 1.04 – 1.60, 5 trials) but with no resulting reduction in either the risk of thrombosis (RR 0.94, 95% C.I. 0.77 – 1.16, 6 trials) or graft loss (RR 1.08, 95% C.I. 0.83 – 1.40, 4 trials). In contrast to AV grafts, a significant reduction in AV fistula thrombosis was seen with screening (RR 0.47, 95% C.I. 0.28 – 0.77, 4 trials). In the 2 trials that reported access loss, no effect was seen in screening (RR 0.65, 0.28 – 1.51). One trial reported both a reduction in catheter insertions (relative rate 0.20, 95% C.I. 0.04 – 0.88) and hospitalisations with screening (relative rate 0.37, 95% C.I. 0.16 – 0.87).

Other Surveillance Techniques

Other techniques utilised in screening include the measurement of access recirculation (AR), dynamic venous pressures, static venous pressures, and intra-access pressure. Vascular access recirculation occurs when the dialysed blood returning via the venous needle is taken up again through the arterial needle thus by-passing the systemic circulation. It occurs once flow within the access is less than the dialyser blood flow [115]. With AV grafts the utility of recirculation measurements is limited, as the risk of thrombosis is higher at blood flows greater than typical dialyser blood flows [103]. However in AV fistulae, blood flow can decrease to lower than prescribed dialyser blood flow while still maintaining patency. Therefore assessment of recirculation can be a useful tool to detect AVF stenosis. No randomised controlled trials have assessed the measurement of recirculation on thrombosis or AV fistula survival. However as recirculation reduces dialysis efficiency, its presence should prompt evaluation of the AV fistula and subsequent repair of any stenosis.

Venous pressure is measured either at the venous drip chamber during dialysis (dynamic venous pressure) or with the blood pump stopped (static venous pressure). High dynamic venous pressure in an AV graft suggests a venous stenosis and should prompt evaluation of the AV graft. Whether this prolongs AV graft survival however has not been assessed in a randomised controlled trial. In AV fistulae, the presence of collaterals will prevent the rise in venous pressure despite a reduction on Q_a due to a stenosis thus screening using dynamic venous pressures is not recommended. One randomised controlled trial in AV grafts did not show any benefit of screening with static venous pressures [116].

Summary

In summary, there is a strong rationale behind vascular access monitoring and surveillance but the evidence base to support these practices is limited and inconclusive. Despite this, monitoring and surveillance particularly using vascular access blood flow are commonplace in clinical practice. Further randomised trials are required to determine whether such practices are justified both in terms of patient outcomes and cost utility.

Management of Central Venous Haemodialysis Catheters

Central venous catheters are most commonly utilised in those requiring emergency acute dialysis or in the chronic haemodialysis patient with vascular access difficulties such as access creation not timed appropriately or failure of AV fistula to mature. There are two main types of catheter: non tunnelled non-cuffed catheters and tunnelled cuffed catheters. Tunnelled cuffed central venous catheters possess cuffs made of silicone, silastic or carboethane elastomer. The subcutaneous tunnelled tract that accommodates the catheter serves to stabilise it. The cuff acts as a barrier to the entry of organisms hence reducing the rate of bloodstream infections.

There are a variety of tunnelled catheters available. The first generation catheter was the Permcath™, an oval catheter with two circular canals within. Since then the VacCath™ and Tesio™ (a two catheter system) have been made available. There is currently no evidence favouring one long term catheter over another.

Rates of Dysfunction

A significant drawback of catheters is their relatively high rate of failure. 50% of catheters fail within one year [117]. The mean patency rate is 73-84 days [118, 119].

Definition and Causes of Loss of Patency

A catheter is deemed dysfunctional when it cannot sustain a dialyser blood flow of 300ml/min at a pre-pump pressure of -250mmHg [6]. The most common causes of catheter dysfunction are thrombus, fibrin sheath formation, displacement, and infection.

Catheter failure may be early or late. Early catheter failure is usually due to catheter position. Early catheter failure can be minimised by placing catheters under fluoroscopic guidance. Late catheter failure is usually due to either partial or total thrombosis. Catheter thrombosis accounts for up to 40% of catheter failures [118, 120-123]. In the dialysis population thrombi occlusion affects 3-10% of all haemodialysis sessions.

Fibrin sheath thrombus is the most common form of catheter thrombus. A fibrin sheath was detected in 47-82% of prevalent haemodialysis patients [124, 125] and all 55 deceased haemodialysis patients during an autopsy study [126]. Animal studies have elucidated the

process of fibrin sheath synthesis; thrombus from the point of catheter insertion becomes progressively organised to form a fibroepithelial tissue sleeve, and ongoing fibrin deposition promotes elongation of the sheath structure [127, 128].

Maintaining Patency

Although there are few head-to-head studies, dual catheters with independent lines and side holes at the tip give higher flows than dual lumen catheters. Catheters placed in the right internal jugular vein provide better flow than other sites [129].

Detecting Loss of Patency

Haemodialysis facilities are recommended to adopt a proactive approach to monitoring blood flow in central venous catheters. Estimations of effective blood flow rate, venous and arterial pressure values, recirculation rates and dialysis dose delivery [130] should be recorded in a database.

Primary Prevention

Attempting to prevent clot in the inter-dialytic period is crucial. This is routinely done by instilling an anti-thrombotic lock solution in between dialysis sessions. This solution may be unfractionated heparin, low molecular weight heparin or sodium citrate all of which have been shown to be effective. With any anticoagulant catheter lock solution there is a risk of systemic overspill. In vitro studies have demonstrated early onset leak of anticoagulant into the peripheral circulation just 30 seconds after administration, with a more sustained leak up to 30 minutes later [131].

The utility of systemic anticoagulation has been studied. The use of low dose warfarin has not been found to reduce the incidence of catheter dysfunction [132-135]. Anti-platelet agents have also proved unsuccessful [133].

A recent study [136] however demonstrated in incident central catheters that prophylactic recombinant tissue plasminogen activator (rt-PA) substituted for heparin at the mid-week dialysis session reduced catheter dysfunction and also infectious outcomes without an increase in bleeding risk.

Secondary Prevention

Treatment of Catheter Dysfunction

A catheter that demonstrates complete thrombotic obstruction warrants immediate action. Treatment should be also initiated in any catheter with an extracorporeal blood flow rate of less than 300ml/min.

There is some geographical variation in guidance surrounding treatment of catheter thrombosis. In the United States a malfunctioning catheter is preferentially exchanged over a guidewire as the first choice in treatment, whereas in Europe intradialytic thrombolytic is recommended as first line therapy. A fibrin sheath stripping procedure is sometimes attempted.

Intra-dialytic Thrombolytic Agents

When poor flows are detected, an intra-dialytic thrombolytic agent may be used. Urokinase is a synthetic protease that converts plasminogen to the active serine protease plasmin, hence leading to the proteolytic cascade. In some countries, urokinase has been superseded by the recombinant tissue plasminogen activators (tPA) such as Alteplase™, Reteplase™ and Tenecteplase™. Currently tPA is the sole thrombolytic agent approved by the United States Food and Drug Association as a result of evidence from a single centre open-label study in the paediatric population [137]. tPA may be viewed as having a good short-term effect on catheter patency. A study of alteplase in 570 catheters demonstrated a median survival advantage gained from each repetitive treatment of tPA to be 10-18 days, allowing for a median of only 5-7 additional dialysis sessions before a further intervention was required. tPA has been found to have superior thrombolytic actions over Urokinase [138-142].

Catheter Replacement

Catheter exchange is advantageous as it has a high rate of success, is safe, enables preservation of the exit site and is less costly than fibrin sheath stripping. Some authors have demonstrated a low rate of infection in catheters replaced over a guidewire [143, 144]. Catheter survival following an exchange was evaluated in 3930 patients and decreased with each exchange [145].

Fibrin Sheath Stripping

During the fibrin sheath stripping procedure a 'lasso' snare catheter is introduced through the femoral vein and advanced as far up the shaft of the dialysis catheter as possible such that it surrounds the catheter's external margin. The snare is closed around the catheter and simultaneously pulled down its length to disrupt the fibrin sheath. Multiple such stripping passes are attempted [146]. A number of uncontrolled interventional studies have investigated the efficacy of fibrin sheath stripping for restoring adequate blood flow rates in malfunctioning catheters defined as an inability of a catheter to sustain a blood flow rate of 200 – 250 ml/min during haemodialysis on one or more occasions [147-149]. Technical success was defined as the ability to aspirate and flush the catheter at the time of the procedure and demonstrable patency on venography, while clinical success was defined as restoration of a blood flow rate ≥ 300 ml/min and/or restoration of the previous baseline blood flow. The procedure was reported to achieve technical success in 89-100% of cases, however clinical success was often short lived with a median duration of primary patency ranging from 2-weeks to 3-months [147-149]. Furthermore two randomized controlled trials comparing fibrin sheath stripping to catheter exchange over a guide wire [150] or transcatheter lytic enzyme infusion [151] reported that guide wire exchange was significantly

superior producing higher rates of primary patency for a longer duration, while lytic enzyme infusion was at least as effective as fibrin sheath stripping.

Heparin-coated Catheters

Historic studies have looked at the anti-thrombogenic properties of heparin-coated catheters. More recent studies did not demonstrate a significant effect on the use of anti-thrombolytic agents, rates of catheter malfunction or cumulative catheter patency of heparin-coated versus non-coated catheters [152].

Prevention of Central Venous Catheter Infection

The most important strategy for preventing central venous catheter infection is to minimise the duration of catheter use and adhere to robust aseptic technique when accessing catheters. Formation of biofilms by gram-positive and negative bacteria is thought to play a key role in subsequent bacteraemia risk. There is growing interest in strategies to reduce risk of infection such as using antimicrobial locks including gentamicin [153], minocycline [154], taurolidine [155] and citrate [156], clearing biofilms using rt-PA [136], and using catheters coated with bacteriocidal agents such as Bismuth. This latter strategy was investigated in a randomised controlled trial of 103 patients randomised to receive either a non-tunnelled bismuth coated catheter or a standard non-tunnelled catheter [157]. The study reported no difference in catheter survival between the two groups, but a significantly lower catheter bacterial colonization rate in the bismuth group. This study was limited by its high drop out rate, small sample sizes, lack of reporting of infectious complications, and short duration of follow-up. Other strategies to reduce risk of infection include application of topical antimicrobial agents at the exit site: polysporin ointment [158, 159] and Medihoney have been studied [160].

Management Central Venous Catheter Related Infection

Bacteraemia is a frequent event in catheter-dependent haemodialysis patients with a reported incidence of 2 – 4.6 episodes per 1000 catheter days [161, 162]. The diagnosis is usually made on the basis of bacteraemia in a patient with a central catheter, with(out) clinical signs of systemic infection and in the absence of other infectious aetiologies [161]. Gram positive bacteria, especially *S. aureus* and Coagulase negative staphylococci, are the most common pathogens isolated (62 – 81%) followed by gram negative rods (20 – 30%) and Enterococci (5 – 20%) [162-164]. Treatment for catheter related bacteraemia should be initiated as soon as the diagnosis is suspected and once blood cultures have been drawn from both the central catheter and peripheral veins. Initial empiric antibiotic therapy should combine adequate staphylococcal and gram negative cover. The choice of anti-staphylococcal agent depends on local bacterial resistance patterns. If the patient is known to be colonised with methicillin resistant *S. aureus* (MRSA) and/or local rates of MRSA are known to be high then Vancomycin should be used, alternatively if no such pre-conditions exist then cefazolin or flucloxacillin may be used as the first line anti-staphylococcal agent. Gentamicin is the antibiotic of choice for gram negative coverage. Antibiotic therapy should be altered once the causative organism is isolated and antibiotic sensitivities established [84, 100, 165, 166]. Opinion is divided as to whether antibiotic therapy should be accompanied by leaving the infected catheter in-situ, changing it over a guide wire or replacing it with a new catheter.

This decision should be guided by the patient's clinical state, response to antibiotic therapy, and availability of alternate dialysis access [165].

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Chapter VII

Cardiac Swinging Calcified Amorphous Tumors (SCAT) and Stroke in End-Stage Renal Failure

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Abstract

Cardiac calcified amorphous tumors (cardiac CATs) are unusual non-neoplastic cardiac masses that were originally described in 1997 by Reynolds et al. We recently encountered two patients with a left ventricular cardiac CAT who were successfully treated surgically. Both patients were on hemodialysis for end-stage renal failure and had mitral annular calcification (MAC). In one patient there was massive cardiac calcification. These tumors were fragile, and easily detached from the endocardium. The histological findings were thrombus with angiogenesis and fibrin and calcium deposition. These tumors might be included a special entity of cardiac CATs and may account for some of the strokes or sudden deaths that occur in end-stage renal failure patients who are on hemodialysis. Through the case presentation and literature review, the characteristics and the etiology of the tumor are discussed. The descriptive term of cardiac *swinging calcified amorphous tumor* (cardiac SCAT) is proposed to describe this special risky subgroup of cardiac CATs.

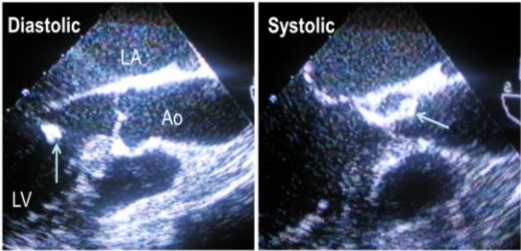
In the Framingham study, mitral annular calcification (MAC) is predictive of a doubling in the risk of stroke after adjustment for multiple risk factors. However, it is still unknown whether the MAC itself is a factor that directly causes stroke or only a marker of increased risk in association with some other unknown factor.

In this chapter, through two clinical cases and literature review, the essence of the cardiac SCAT is discussed.

Cases

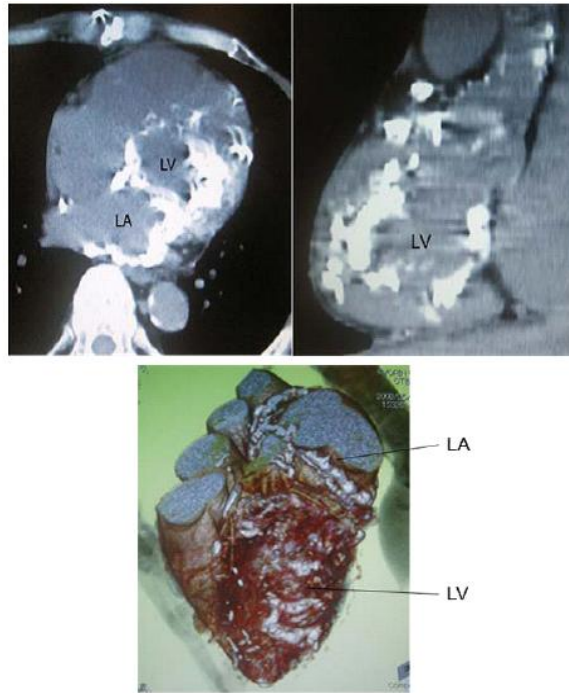
Case 1. A 64 y.o. female was referred to our hospital with a diagnosis of pneumonia. She had been on hemodialysis for five years because of diabetic nephropathy. A chest X-ray showed diffuse consolidation in both lung fields. Computed tomography revealed heavily calcified mitral annulus. The leukocyte count was 12,400/ml, and C-reactive protein was 6.4 mg/ml. A blood culture was negative. An echocardiogram showed moderate aortic and mitral regurgitation, and a pedunculated, crotchet shaped mobile tumor that originated from the annulus of the anterior comissure of the mitral valve. The tumor was visualized as a hyper- and homogeneous echo measuring 3 mm x 27 mm (Figure 1). In the systolic phase, it swung widely and its head plunged through the aortic valve into the ascending aorta. A small low-echoic lesion was seen at the center of the tumor head. Routine echocardiography two months before did not show any evidence of a tumor in the heart. The preoperative diagnosis was infectious endocarditis and pneumonia, and at that time, the tumor was thought to be a vegetation. Because the tumor grew fast, to prevent stroke or systemic embolism, emergency aortic and mitral valve replacement with mechanical valves and tumor resection was performed. Although both valves showed degenerative change, there was no evidence of infectious endocarditis. A soft, fragile, club-shaped tumor that arose from the anterior mitral comissure was easily removed from its origin with forceps without exerting force. There were no other tumors. The postoperative course was uneventful. The patient recovered from pneumonia. She is alive and well with no evidence of recurrence of the tumor as of three years of follow up.

Case 2. A 44 y. o. male who had been on hemodialysis for nine years because of lupus nephritis consulted a cardiologist because routine echocardiography had revealed a mobile tumor in the left ventricle. Computed tomography showed a densely calcified left ventricle, mitral annulus, and left atrial wall (Figure 2). Laboratory data showed no evidence of an inflammatory reaction. The tumor was hyperechoic, measured 5 mm x 18 mm, and originated from the base of the anterior papillary muscle (Figure 3). A small low-echoic lesion was seen at the center of the tumor head. Because follow-up echocardiography 6 weeks later showed that the tumor had grown to 5 mm x 28 mm, elective surgical treatment was performed. The inside of the left ventricle was visualized with the cardioscope inserted through the orifice of the mitral valve.



The head of the tumor was detected in the left ventricle in the diastolic phase (arrow). The tumor plunged through the aortic valve into the ascending aorta in the systolic phase (arrow).

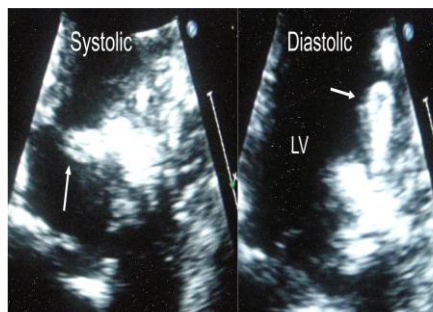
Figure 1. Transesophageal echocardiography.



A computed tomographic scan showed a densely calcified left ventricle, mitral annulus, and left atrial wall. There was no coronary artery stenosis.

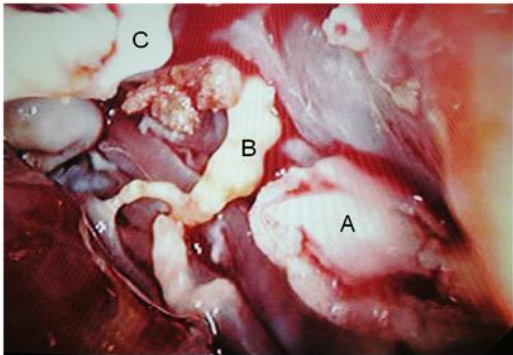
Figure 2. Computed tomography and 3-D computed tomography.

Three tumors were detected inside the left ventricle (Figure 4). One was a mobile tumor that had been detected preoperatively (A), and the other two were immobile and firmly attached to the left ventricle (B and C). All tumors were resected from their origin. The mobile tumor was fragile and removed from the left ventricular wall without force, whereas the other two tumors were firmly anchored to the tuberculum of the left ventricle, and were resected with scissors. The postoperative course was uneventful. Aortic and mitral valve replacement using mechanical valves was performed because of both stenosis and regurgitation one year after tumor resection. The patient is alive and well with no evidence of the tumor three years after the initial operation.



Echocardiography revealed a mobile swinging pedunculated tumor (arrows) originating from the left ventricle. A small, low echoic area at the center of the tumor head could be detected.

Figure 3. Base of the anterior papillary muscle.

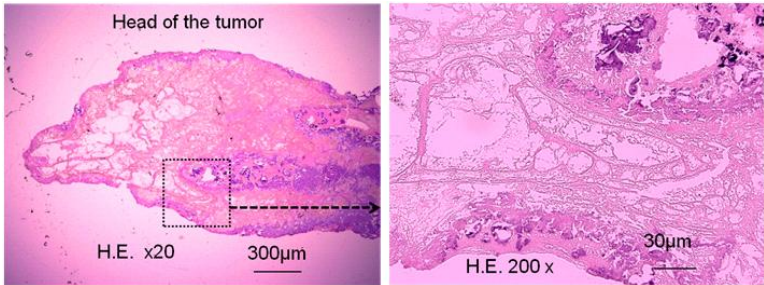


Tumor “A” was a mobile tumor; only the head portion is shown. Tumor “B” and “C” were immobile and firmly attached to the myocardium.

Figure 4. Thoracoscopic view of the left ventricle.

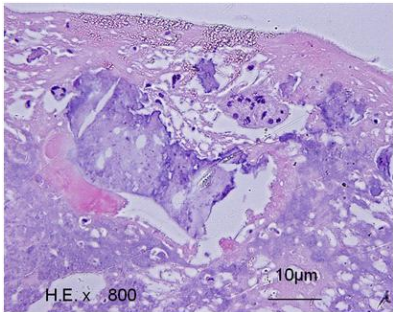
In case 1, pathological examination revealed that the tumor consisted of fibrin. Calcium deposits were detected around the fibrin, but there was no thrombus or capillary angiogenesis (Figure 5). At the proximal part of the stalk, beside the calcified portion, foreign body giant cells were identified (Figure 6).

In case 2, there was red thrombus and capillary angiogenesis in the center of the head of the mobile tumor, which was compatible with the low-echoic lesion. The red thrombus was covered by fibrin and calcium deposition (Figure 7).



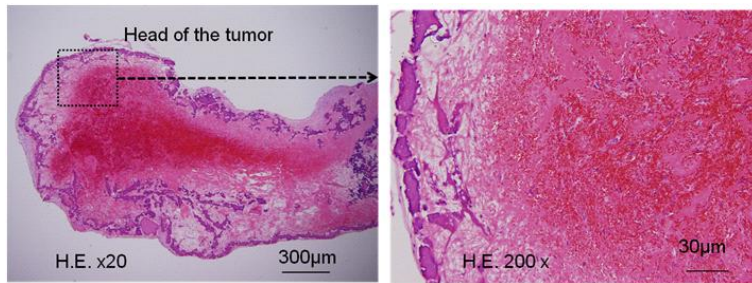
Calcium deposits around the fibrin are seen.

Figure 5. Microscopic appearance of the mobile tumor head in patient 1.



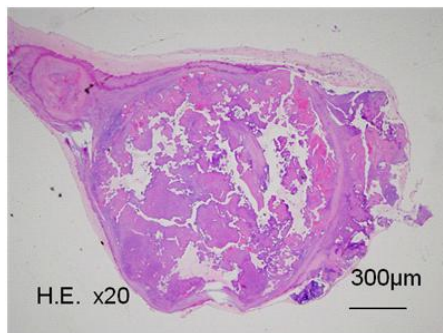
At the proximal part of the stalk, beside the calcified portion, foreign body giant cells were identified.

Figure 6. Microscopic appearance of the mobile tumor stalk in patient 1.



Fibroblasts and capillary angiogenesis are seen in the red thrombus. Fibrin and calcium deposits are seen covering the thrombus.

Figure 7. Microscopic appearance of the mobile tumor head in patient 2.



No thrombus or fibrin was seen. It was characterized by monotonous calcification (= ossification).

Figure 8. Microscopic appearance of the immobile tumor in patient 2.

The two immobile tumors were characterized by monotonous calcification (=ossification) and no any structure, e. g. no thrombus or fibrin (Figure 8).

Review

The cardiac calcified amorphous tumor (cardiac CAT) originally described in 1997 by Reynolds et al. is very rare non-neoplastic cardiac mass, and their etiology, clinical manifestations, and treatment are still unclear [1]. We encountered two cases of cardiac mobile CAT described above. Both two cases were in end-stage renal failure, and required hemodialysis. They also showed severe mitral annular calcification [2]. In the Framingham study, mitral annular calcification (MAC) is predictive of a doubling in the risk of stroke after adjustment for multiple risk factors [3]. However, it is still unknown whether the MAC itself is a factor that directly causes stroke or only a marker of increased risk in association with some other unknown factor. Since the report of a stroke in a patient with MAC by Rytand and Lipstich in 1946 [4], the association between MAC and stroke has been studied by numerous investigators [5-7]. In the Boston Area Anticoagulation Trial for Atrial Fibrillation, MAC was associated with an increased risk of stroke [8]. Postmortem studies have long suggested that MAC may directly cause cerebrovascular accident (CVA) by serving as a source of calcific or thrombotic emboli [9, 10]. Some neuroimaging studies have documented calcific deposits in

the cerebral arteries of patients with MAC and CVA [11-13]. In an elderly, longitudinally followed cohort of the Framingham study, Benjamin and coworkers examined the relation between mitral annular calcification and the incidence of stroke in a population-based study [3]. The incidence of stroke during eight years of follow-up was analyzed with a proportional-hazards model adjusting for the mitral annular calcification, age, sex, systolic blood pressure, diabetes mellitus, cigarette smoking, atrial fibrillation, and coronary heart disease or congestive heart failure. As a result, among 1159 subjects whose echocardiograms could be assessed for mitral annular calcification and who had no history or current evidence of stroke at the index examination (51% of all subjects), the prevalence of MAC was 10.3% in the men and 15.8% in the women. Multivariate analysis demonstrated that the presence of MAC was associated with a relative risk of stroke of 2.10 (95% confidence interval, 1.24 to 3.57; $p=0.006$). There was a continuous relation between the incidence of stroke and the severity of MAC; each millimeter of thickening as shown on the echocardiogram represented a relative risk of stroke of 1.24 (95% confidence interval, 1.12 to 1.37; $P<0.001$). Furthermore, even when subjects with coronary heart disease or congestive heart failure were excluded from the analysis, subjects with MAC still had twice the risk of stroke. With these results, they concluded that in an elderly, longitudinally followed population-based cohort, MAC was associated with a doubled risk of stroke, independently of traditional risk factors for stroke. De Bono reported echocardiographic features of extensive MAC in 8 of 151 consecutive patients (5%) with cerebral or retinal ischemic episodes but in none of 188 control patients [14]. Nair et al. followed a cohort of 107 patients with MAC and 107 age- and sex-matched control subjects without MAC were studied and followed for a mean of 4.4 \pm 2.4 years. Patients with MAC had higher incidence of cerebrovascular events, occurred in 10% of them as opposed to in 2% in matched control patients [15]. However, it is still unknown whether such calcification contributes direct causally to the risk of stroke or is merely a marker of increased risk because of its association with other precursors of stroke remains unknown.

Reynolds et al. originally reported 11 cases of cardiac CAT in 1997 [1]. Surgical excision was the treatment of choice in 10 patients. The lesions were firm, yellow-white, and partially calcified, and arose in any of the four chambers. Microscopically, all lesions were similar and composed of nodular deposits or flecks of calcium within a background of eosinophilic, amorphous, sometimes fibrillary material. They hypothesized that it was possible that these masses had been ordinary thrombi that had undergone mummification and calcification rather than organization, at the same time, they posed questions for this hypothesis because none of the tumors showed the characteristic laminations observed in typical organizing thrombi and only three patients had hemosiderin deposition. In this patients series, there was only one patient who had end-stage renal failure as an underlying disease. Although there are no description about tumor mobility or growth speed, only one tumor showed club-shaped (0.3x0.3x1.5 cm) in contrast to the others showed ball shaped. It is noteworthy that this club-shaped tumor was found in a patient who had end-stage renal disease with tumoral calcified left ventricle (the site was undescribed). Pathologically, giant cell was detected only in this patient.

Tsuchihashi et al. reported four cases of rapidly growing mobile cardiac calcinosis accompanied by MAC [16]. One of the patients had right hemiplegia, and another died suddenly after four months of follow up. One patient died of acute myocardial infarction secondary to multivessel disease, and surgical resection was performed in the fourth patient.

A few older postmortem case reports and studies suggested a pathophysiologic link between MAC and stroke. Ulceration of the mitral annulus and extrusion of calcium through the overlapping cusp was observed by Pomerance in 5% of 258 autopsy cases [9], and calcific emboli to the brain and other organs from ulcerated MAC were then reported by Ridolfi and Hutchins [17].

In 1995, Stein and Soble described two patients with cerebral embolism who had mitral valve calcification and a soft mobile mass that appeared to be thrombus on the calcified portion of the mitral apparatus [18], and they confirmed resolution of the masses in both patients after antiplatelet and anticoagulation therapy using Aspirin and Warfarin. They concluded that these cases supported the hypothesis that thrombus formation is a pathophysiological link between ischemic cerebral events and MAC in some patients. They mentioned that whether antiplatelet or anticoagulant therapy might prevent cerebral embolism in patients with MAC is unknown and is worthy for further study.

Willens et al. treated rapidly progressing mobile components associated with MAC in patients with chronic renal failure with the phosphorus lowering agent sevelamer HCL and aspirin and obtained resolution. Eicher et al. focused on the echocardiographic findings and the association between MAC and risk of thromboembolism [19]. Among 182 patients who underwent both transthoracic (TTE) and transesophageal echocardiography (TEE) after an arterial thromboembolic event, they identified 10 patients (5.5%) who had MAC and no any other potential embolic substrate. In 3 of them (1.64%), TEE disclosed a long, pedunculated, vegetation-like mass attached to the posterior part of a heavily calcified fibrotic mitral annulus. All 3 patients were treated by anticoagulation with aspirin or dipyridamole concomitant with fluindione. Since regression and complete resolution were achieved, they proposed that when a mitral annular thrombus is diagnosed, anticoagulation therapy and antithrombotic agents should be given for a synergistic effect. They also suggested pedunculated thrombi of the mitral annulus are a possible “missing link” between MAC and stroke.

Although some reports try to distinguish thrombi from CATs, the pathological findings in our two cases and the courses of the reported clinical cases described above suggest that, cardiac CAT may be the late phase of chronological changes of thrombus in the early phase. The reason why cardiac CATs originate mainly from MAC is unclear. Considering that MAC occurs in >40% of the patients with end-stage renal disease, as our second case shows, they not only originates from MAC but from everywhere the calcified part of the heart and MAC is only the most popular portion to be calcified [20]. It is not clearly understood why the cardiac base is vulnerable to calcium deposits. In extraskeletal calcinosis, Ca-P deposits on the multifollicular fibrous wall are also seen frequently in the hyperkinetic joint capsule. The similarity of the histological and pathophysiological background of the target tissue may explain the deposit of fibrous tissue in cardiac base. But the clinical significance of cardiac calcinosis is very different from joint calcinosis. Injury and erosion of the endocardium or myocardium caused by calcium deposition and inflammation may be related to the initial development of the CAT. Continuously, with the expose to the bloodstream, thrombi with capillary angiogenesis grow with the fibrin exudation and calcium deposition. Secondary hyperparathyroidism may also plays a key role in the cause of cardiac calcification, where the $\text{Ca} \times \text{P}$ product is <50 [21]. Serum magnesium, vitamin D, and serum aluminum are all influential factors. A further symptom of rapid cardiac calcinosis is hypoparathyroidism. Patients on hemodialysis with hyper parathyroidism had a higher incidence of metastatic

calcification, which resulted from the decreased reservoir function of bone for absorbed calcium and phosphate from the intestine [22]. Moreover, generally administered calcium and active vitamin D₃ could exacerbate hypercalcemia, and might increase the risk of tumoral calcinosis in the cardiovascular system of patients with end stage renal disease and hypoparathyroidism. As the calcium deposition progresses over time, the capillary vessels, fibrin, and thrombus may disappear. Abnormal calcium and phosphate metabolism due to chronic renal dysfunction and the inflammatory state associated with hemodialysis may contribute to the endothelial erosion postulated to underline these rapid growth and rapid pathological change [23]. The appearance of the foreign body giant cells may represent the relationship with the immunological and inflammatory reaction. However, we cannot find any reason to explain why there are two types of calcified tumor in even though the same patient as case 2: immobile firmly attached one to the heart or mobile, clubbed shaped, rapid growing and fragile tumor.

The definition of cardiac CAT is still in vague. In the literature, cardiac CATs are described as consisting of a wide spectrum of tumor morphologies and pathological characteristics. A case report described a case of diffuse calcific infiltration of the left ventricular myocardium without mobile component as a cardiac CAT [24]. Other authors reported a right ventricular nonmobile calcified 1.5-cm mass involving the annulus of the tricuspid valve as a cardiac CAT [25]. Massive cardiac calcification, cardiac calcified mass or porcelain heart may be suitable expression to describe such tumorous calcification [26]. Based on the intraoperative findings in our two cases and literature review, mobile CATs that exhibited a swinging motion clearly indicate an impending risk of stroke, myocardial infarction, or other systemic embolism. They may occupy some part of the possible “missing link” between MAC and stroke in hemodialyzed end-stage renal disease patients. Thus, mobile, swinging cardiac CATs should be regarded as distinct from the porcelain heart or immobile cardiac CAT. We propose the descriptive term of *swinging calcified amorphous tumor* (SCAT) to describe this high risk subgroup of cardiac CAT. SCATs are soft, fragile tumor that easily detach from the endocardium, whereas immobile CATs are firmly anchored to the myocardium. They are usually found in patients who require hemodialysis, and originate from any calcified part of the heart. MAC is known as the main site, however, MAC is not the specific site as their origin. As differential diagnosis, other cardiac masses e.g. myxoma, fibroelastoma, vegetation due to infectious endocarditis, malignant cardiac tumors etc. are listed. Especially, calcified tumors e.g. calcified myocardial tuberculomas, tophaceous pseudogout, and osteosarcoma should be carefully differentiated [27].

The incidence of this special category of intracardiac tumor is unclear. However, in view of fact that two cases were treated in same year at a single institution, awareness of this tumor and routine echocardiographic evaluation of patients with MAC or cardiac calcification who are on hemodialysis may lead to the discovery of more cases. Further serological and pathological investigation will reveal the mechanism of the development, growth, and chronological changes in SCATs. Anticoagulation therapy and antithrombotic agents may affect not only on the outside of the tumor but from inside via capillary vessels. As cases accumulate, proper protocol of treatment will be established.

Conclusion

In conclusion, routine follow-up echocardiography is recommended for the patients with MAC or cardiac calcification who are on hemodialysis. Although the efficacy of a preventive anticoagulant is a matter of controversy, immediate anticoagulation, anti-inflammation and thrombolytic therapy should be started whenever a mobile hyperechoic tumor originating from a calcified site, especially in the left-side of the heart is detected. The indications for emergency surgery are also a matter of controversy, when a tumor exhibits rapid growth despite appropriate medical therapy, complete surgical resection should be considered to prevent strokes or sudden death in patients with end-stage renal failure.

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Chapter VIII

Assessment of Monoclonal Proteins in Patients with Renal Diseases: New Methods and Their Clinical Utility

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Abstract

Renal impairment is a common feature of monoclonal gammopathies affecting nearly 50% of patients at presentation of multiple myeloma. When reversible causes have been excluded the renal injury predominately relates to the circulating monoclonal immunoglobulin free light chains (FLC). In the setting of acute kidney injury the tubulointerstitial lesion cast nephropathy (myeloma kidney) predominates. In contrast, AL amyloidosis and light chain deposition disease more frequently present with proteinuria and a progressive renal failure. Historically, the presence and quantity of monoclonal FLCs have been measured with urine protein electrophoresis (UPE). Clinically, however there are several barriers to the usefulness of this technique: 1) as a result of the re-absorption of FLCs in the proximal tubules urine FLC concentrations are not a direct reflection of their serum levels; 2) up to 50% of patients with a monoclonal gammopathy never have a urine sample assessed by the laboratory; 3) laboratory issues can result in false positive cases. Recently the introduction of immunoassays for FLC measurement in the serum has enabled a more sensitive and direct quantification of the nephrotoxic FLC burden and is significantly advancing the management of the patients with renal failure and multiple myeloma. In this chapter, we will summarise recent studies examining the role of the monoclonal FLC assays in the diagnosis and management of patients with monoclonal gammopathies and renal impairment, and identify key areas that would benefit from further clinical studies.

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Introduction

Free light chains (FLC) are a bi-product of intact immunoglobulin synthesis [1]. Always produced in a slight excess to heavy chains, by the plasma cells, these 'spare' light chains are released into the circulation at low levels in health as polyclonal FLCs. Historically these polyclonal FLCs have been difficult to quantify as their serum levels are typically low due their rapid removal from the circulation by the kidneys. The FLCs are then predominately re-absorbed in the proximal tubules and as a result the urinary concentration of polyclonal FLCs, in health, are typically only 5-10mg/L, well below the detection limit of historic assays.

In contrast, in the setting of a plasma cell dyscrasia where there is a monoclonal proliferation of one line of plasma cells, very high rates of FLC production can occur. These monoclonal FLCs can occur in isolation or in association with an intact immunoglobulin. As the serum levels of FLCs rise, the ability of the proximal tubules to re-absorb the proteins become overwhelmed and the monoclonal FLCs can be readily identified in the urine.

Renal injury is a frequent consequence of a monoclonal FLC; it can be the first presentation of the underlying plasma cell dyscrasia and is one of the original criteria for the initiation of disease specific treatment in multiple myeloma [2]. During the last decade sensitive immunoassays for measurement of FLCs in the serum have become commercially available and adopted into clinical practice. The purpose of this chapter is to review the role of these new assays in the clinical management of patients with renal injury and multiple myeloma.

Laboratory Methods for the Assessment of Monoclonal Free Light Chains

Urinary Analysis

Serum protein electrophoresis (SPE) is routinely used for the detection of monoclonal proteins. Due to their identical size and charge, monoclonal proteins (M-proteins) migrate as discrete bands on an electrophoretic gel. This appears as a peak on a densitometric trace (M-spike), the size of which can provide a semi-quantitative value for the amount of M-protein. Serum immunofixation electrophoresis (IFE) is then required for confirmation of clonality and subsequent typing. The major technical limitation of serum electrophoresis techniques is their limited ability to detect low level monoclonal proteins, particularly FLCs. The analytical sensitivity of SPE is between 500-2000mg/L, depending upon whether the monoclonal protein co-migrates with other serum proteins on the electrophoretic gel [3]. Serum IFE is approximately 10-fold more sensitive and may pick up additional monoclonal proteins that are undetected by SPE [3]. However, patients with oligosecretory diseases, such as light chain multiple myeloma (LCMM), AL-amyloidosis and light chain deposition disease (LCDD) often do not produce monoclonal FLCs at a level sufficient to be detected by either SPE or serum IFE [4-6].

For over 150 years, monoclonal FLCs in the urine, known as Bence-Jones protein (BJP), have been an important diagnostic marker for multiple myeloma and current protocols for the

detection of monoclonal FLCs still commonly incorporate the testing of a urine sample. Renal manifestations associated with monoclonal FLC production are often accompanied by light chain proteinuria, which occurs as a result of overproduction of the FLCs or their decreased re-absorption in the proximal tubules. Patients with high-level FLC excretion in the urine (>10g/day) are at a significantly greater risk of developing an acute kidney injury (AKI) compared with patients with low level urinary FLCs [7]. Urine protein electrophoresis (UPE) and urine IFE are the current gold standard for detecting monoclonal FLCs and are more sensitive than serum electrophoresis techniques. FLCs can be detected in the urine at <20mg/L, although most laboratories claim a FLC detection limit of 40-50mg/L.

Despite the additional sensitivity offered by UPE and urine IFE, these techniques are not without their technical and practical limitations. First, FLC levels in the serum must increase significantly before the proximal tubular re-absorptive mechanisms are overwhelmed and the FLCs appear in the urine. Nowrousian et al. [8] reported that the median levels of monoclonal κ and λ FLC required in the serum before Bence Jones proteinuria occurred were 113mg/L and 278mg/L, respectively. Therefore urine BJP tests are not a direct reflection of the underlying monoclonal FLC production rate and low level monoclonal FLCs in the serum will not be detected in the urine. The second important consideration for routine clinical practice is the delay associated with obtaining a urine BJP result. Early detection of monoclonal FLC facilitates rapid treatment initiation which may preserve renal function [9]. Delays can occur due to poor urine compliance, the requirement for 24-hr urine collection, batch testing of urine samples by the laboratory and the need to re-test samples due to non-reportable results. A recent study assessing the diagnostic pathways of multiple myeloma found that only 30% of the requested urine samples were supplied to the laboratories within 7 days of the serum sample being received, and only 57% had been received within 3 months [10]. Previous studies have reported compliance values of between 5% and 59% [11-14]. Using a screening algorithm which relies on urine tests for the detection of monoclonal FLC may lead to delayed diagnosis in the common event that a urine sample is not sent in a timely fashion or not supplied at all.

The third potential limitation of urine based algorithms for the identification of monoclonal FLCs is that the interpretation of electrophoresis results is somewhat subjective. The detection of low level monoclonal FLCs is particularly problematic and the appearance of false positive bands on UPE gels is not infrequent. These false bands can be caused by the clearance of some drugs, antibiotics, radiographic dyes amongst other reagents, highlighting the importance of confirmation of the UPE result by urine IFE [15]. IFE, however, is not quantitative and the majority of staining is due to background polyclonal antibody so the monoclonal contribution is difficult to determine. False positive bands may also appear on urine IFE gels due to precipitating antibodies against the FLC that are not completely specific and may cross-react with other urine proteins. 'Ladder banding' in concentrated urine samples may also give the false impression of monoclonality, and heavy proteinuria containing polyclonal FLCs may give high background staining hindering accurate interpretation.

Due to the highlighted limitations of urinalysis, attention is now focussed on using an assay to measure FLC in the serum rather than the urine.

Serum Free Light Chain Assays

In 2001, the availability of automated serum FLC immunoassays (Freelite, Binding Site, UK) enabled the routine and sensitive laboratory quantification of this important tumour marker. The FLC assays allow the serum measurement of the two FLC isotypes, κ and λ , independent of those light chains which are incorporated in the intact immunoglobulins. The calculation of a ratio of the κ to λ FLCs provides a sensitive numerical indicator of clonality. In patients with plasma cell dyscrasias, the excess clonal production of only one FLC type, frequently with bone marrow suppression of the alternate FLC, leads to often highly abnormal κ/λ ratios. The assays can measure FLC concentrations as low as 1.5mg/L and 3mg/L for κ and λ FLCs, respectively. These levels are well below normal serum concentrations [16] and therefore allow the measurement of κ/λ ratios with considerable sensitivity. This increased sensitivity has proved particularly important in patients with presumed non-secretory multiple myeloma where use of these assays actually identifies a monoclonal FLC in 70% of patients [4].

The diagnostic utility of these assays has been widely assessed and reported. In an assessment of 1,877 patients with plasma cell dyscrasias, Katzmann *et al.* found that SPE and a quantitative serum FLC assay identified 100% of patients with multiple myeloma and Waldenströms macroglobulinemia, 99.5% of patients with smoldering multiple myeloma, 96.5% of patients with AL amyloidosis and 78% of patients with LCDD [2, 17]. International guidelines recommend that screening of serum alone (with SPE and a quantitative serum FLC assay) for plasma cell dyscrasias is a viable alternative to urinary assessment [18, 19].

Use of Free Light Chain Assays in Renal Impairment

Serum FLC levels are dependent upon the balance between production and clearance. In health, the production rate of κ FLCs is approximately twice that of λ FLCs. However this is not represented in their serum ratio as the smaller κ FLC monomers are filtered more freely by the kidneys than the λ FLC dimers, hence the serum half life of κ is shorter than λ . Thus, the published reference range for the serum κ/λ ratio is 0.26-1.65 with a median value of 0.6 in a healthy individual [16].

Renal impairment however promotes a change in the FLC ratio range as the dynamics of FLC clearance alters. As the rate of glomerular filtration reduces, the clearance of FLCs becomes more dependent upon the reticulo-endothelial system which shows no size preference and clears both κ and λ FLCs at the same rate. Therefore, as renal impairment becomes significant, the serum half-life of κ FLCs approaches that of λ FLCs as their serum levels become more influenced by their underlying production rates. The κ/λ ratio can therefore be expected to increase above the published reference range in patients with renal impairment, without a monoclonal protein. Indeed, the serum FLC ratio increased progressively with increasing CKD stage in a cohort of 688 patients with pre-dialysis CKD and no evidence of monoclonal gammopathy [20]. In this patient cohort, the median κ/λ ratio was raised from 0.6 to 1.1, with a 100% range of 0.37-3.17. To ensure good specificity for the detection of a monoclonal FLC, a κ/λ reference interval of 0.37-3.17 has been proposed for patients with renal impairment [13]. By utilising the renal reference range the specificity of

these assays for detecting a monoclonal protein was increased from 93% to 99% in a study of 142 patients with dialysis-dependent AKI, with no loss of assay sensitivity [13].

Commercially Available Free Light Chain Assays

The original immunoassays for the measurement of FLCs in the serum were developed using polyclonal antibodies, raised in sheep. All work to date assessing the clinical utility of FLC measurements were undertaken using these assays. In late 2011 new immunoassays for the measurement of FLCs became available based on monoclonal antibodies raised against the FLCs opposed to the original polyclonal antibodies.

Clinical studies are now underway to evaluate how these new assays compare with the established FLC assays. For safe clinical practice it is important that the two types of assays perform in a highly comparable manner both at diagnosis and during the monitoring of plasma cell dyscrasias. An initial comparison has been undertaken at the Department of Nephrology, University Hospital Birmingham, Birmingham (U.K.). This group compared the two assays in patients with AKI secondary to multiple myeloma. Two concerns were raised from this work: firstly some patients with λ FLCs were not identified at all by the new assays, and secondly the correlation between the reported levels of the monoclonal FLCs was poor.

These preliminary results indicate that these two assays cannot be used interchangeably in clinical practice without further work demonstrating the utility of the new monoclonal assay.

Diagnostic Assessment of Renal Disease in Plasma Cell Dyscrasias

Renal failure is a significant cause of the morbidity and mortality associated with monoclonal gammopathies. Indeed, up to 50% of patients with the plasma cell dyscrasia multiple myeloma will have renal insufficiency at presentation of their disease, with 12-20% developing AKI and 10% becoming dialysis dependent [21-24]. However, when there is an early improvement in the renal function of these patients, their survival also improves [21, 23, 25]. The likelihood of achieving a renal recovery in this setting is dependent on both the severity of the renal injury at presentation and the speed of response to treatment [21, 26]. Enabling an early diagnosis and timely therapeutic intervention is therefore critical to improve patient outcome.

The clonal production of nephrotoxic FLCs is the predominant cause of the renal injury associated with multiple myeloma and related monoclonal gammopathies. Although non-FLC induced renal injury from mechanisms such as contrast, drugs or hypercalcaemia are also common, these processes are typically reversible with correction of the causative factor. Monoclonal FLCs can induce a number of different pathologies within the kidney, which in turn can each result in different clinical presentations. Of these, the most common presentation of FLC induced renal injury is AKI secondary to the tubulointerstitial pathology cast nephropathy. In contrast, the glomerular injuries AL-amyloidosis and LCDD more frequently present with proteinuria and a progressive renal impairment. The type, site and

severity of the renal injury associated with a given monoclonal FLC appear to be predominately influenced by the inherent properties of the individual FLC and its interactions with different proteins [27, 28].

Found in approximately 90% of dialysis-dependent multiple myeloma patients [13], cast nephropathy is the most common cause of renal impairment in multiple myeloma. In myeloma cast nephropathy, also known as myeloma kidney, the FLCs have two principal sites of injury, initially as the high levels of FLCs pass through the proximal tubules the megalin and cubulin multi-ligand receptors become overwhelmed and a tubular injury results as excessive FLC endocytosis can induce a spectrum of inflammatory effects that include activation of redox pathways and expression of nuclear factor kappa B (NF κ B) and mitogen activated protein kinases, leading to transcription of inflammatory and profibrotic cytokines, such as interleukin 6 (IL-6), monocyte chemoattractant protein (MCP)-1, interleukin 8 (IL-8) and transforming growth factor (TGF) β 1 [9, 11, 29-33]. Excessive FLC endocytosis can also trigger apoptotic pathways and alter the phenotype of proximal tubule cells (PTCs) into fibroblasts through epithelial-mesenchymal transition *in vitro* [29, 33, 34] and *in vivo* [35]. The second site of injury in myeloma kidney is in the distal tubules where precipitation of FLCs in the lumen of the distal nephron leads to interstitial inflammation and fibrosis (Figure).

Both κ and λ FLCs bind to a common 9 amino-acid binding domain on Tamm Horsfall protein (THP) [36]. Different nephrotoxic light chains bind to THP with varying affinities; the affinity of a particular FLC clone for THP determines the tendency for cast formation [37, 38]. Co-factors such as hypercalcaemia and dehydration that enhance the aggregation of FLC with THP [38] are commonly encountered in patients with multiple myeloma, and therefore rapid initiation of supportive rehydration therapy and hypercalcaemia treatments are vital to minimise cast development.

Screening algorithms designed to enable the rapid diagnosis of myeloma kidney as the cause of AKI have been recently proposed [39]. In essence, these algorithms propose that the first priority in assessing a patient with unexplained AKI is to determine if there is a FLC clone present or not. To enable this, either serum immunoassays or urine IFE can be utilised, but given the limitations of urine analyses described above many centres now use serum analysis first line. However, when serum FLC analysis is not available locally and must be performed at a referral laboratory, there is the potential for significant delays. Therefore, a close collaboration with the local laboratory to enable a rapid urinary assessment is essential to avoid diagnostic delays. When a FLC clone is present, the absolute level of the serum concentration of the clone can provide significant guidance as to the likelihood of myeloma kidney as the renal pathology. Typically myeloma kidney is associated with high monoclonal FLC levels (Table 1) and a cut-off of 500mg/L is commonly used as the level above which cast nephropathy is the likely pathology. A small number of patients with a high concentration of monoclonal FLCs may have an alternative diagnosis to cast nephropathy [34] and so a renal biopsy can be undertaken for confirmation. The principal concern relating to undertaking a renal biopsy in this setting is the possible increased risk of a haemorrhagic complication, but a recent study from the United Kingdom demonstrated that in a large population of patients with AKI and myeloma the risk was not increased in comparison to the control population [35].

Table 1. Baseline monoclonal serum FLC concentrations in patients with biopsy-proven cast nephropathy

Publication	No. of patients	Baseline serum FLC range (mg/L)
Hutchison CA (26)	39	103-6960
Hasegawa M (74)	2	4140-27,100
Shum HP (75)	1	10,500
Basanyake K (76)	4	1990-9918
Chenine-Khoualef L (77)	1	78,000
Hutchison CA (13)	25	1,030 – 69,430
Leung N (58)	14	1570 – 69,600
Bachmann U (78)	3	3100 – 10,700
Basnayake K (79)	1	15,700
Pillon L (80)	1	11,800
Hutchison CA (31)	13	1100 – 42,000

AL-amyloidosis is another cause of renal injury associated with monoclonal FLCs and is found in up to 30% of patients with multiple myeloma [33]. Unlike cast nephropathy, AL-amyloidosis is not commonly associated with an AKI, rather it more frequently presents with a progressive renal impairment in the setting of proteinuria, frequently nephritic range. In around 10% of patients however, amyloid deposition is predominately in the vasculature or tubulointerstitium resulting in renal failure without proteinuria [40]. AL-amyloidosis is more frequently associated with λ FLCs than κ . It is a protein misfolding disorder characterised by the accumulation of amyloidogenic FLCs or their fragments as insoluble amyloid fibrils which disrupt tissue architecture and function. Structural characteristics of FLCs differentiate amyloidogenic from non-amyloidogenic FLCs. Amino acid substitutions in the variable (VL) region of the light chains influences the propensity of FLC to self-aggregate and precipitate as amyloid fibrils through thermodynamic instability [30]. The amyloid deposits commonly affect the heart and kidney, but the skin, peripheral nerves and other organs may be involved. Renal involvement is found in at least 60% of patients [32, 41], where all compartments of the kidney may be affected but glomerular deposits seem to predominate. The amyloid deposits exhibit apple-green birefringence under polarised light when stained with Congo red dye, and can be detected by histological examination of a tissue biopsy. An additional diagnostic feature and common finding is the presence of a monoclonal protein in the serum and urine of patients with AL-amyloidosis.

In contrast to myeloma kidney, in patients with AL-amyloidosis the underlying plasma cell dyscrasia is often subtle, with low level monoclonal FLC secretion [32]. A paraprotein is detected in the serum or urine in only around 50% of cases by routine electrophoresis, and IFE increases the detection rate to only 80% [42]. An abnormal serum FLC ratio is not found in all cases [6, 43-45] probably because the low level monoclonal FLCs are masked by the polyclonal non-tumour FLC levels. The 100% diagnostic sensitivity of a serum only screening algorithm for patients with multiple myeloma is therefore not achieved for patients with AL-amyloidosis [17], and the IMWG recommend the inclusion of urine IFE alongside serum FLC, SPE and serum IFE in a screening algorithm for these patients [18]. A definitive

diagnosis of AL-amyloidosis with renal involvement is determined by performing renal biopsy for histological evaluation [46].

Also characterised by precipitating monoclonal FLCs, LCDD shares a number of similarities with AL-amyloidosis. Almost all patients with LCDD have renal insufficiency at presentation and 65% have underlying multiple myeloma [47]. The disease can also cause failure of a number of other organs, with extra-renal complications involving the heart and the liver in 30% of cases [47]. In contrast to AL-amyloidosis, the precipitating FLCs are more commonly κ than λ . Renal LCDD deposits accumulate on the basement membranes of renal tubules, glomeruli and blood vessels and renal function is more severely and rapidly compromised in LCDD than in amyloidosis. Whilst a definitive diagnosis is achieved by histological examination of a renal biopsy, the vast majority of LCDD patients will have monoclonal FLCs that can be detected in the serum and/or the urine [47]. Eighty-four percent of patients have proteinuria of $>1\text{g/day}$ [47]. Renal recovery is rare in patients with LCDD, and the disease has a poor prognosis. Median survival time is 4.1 years, and both multiple myeloma and a λ FLC are independent risk factors associated with reduced survival [47].

Monitoring of Plasma Cell Dyscrasias with Free Light Chain Assays

The predictive value of baseline serum FLCs for prognosis extends to most monoclonal gammopathies, including AL-amyloidosis [48-51]. However, the serial measurement of serum FLCs is potentially of additional value for monitoring patients with multiple myeloma as a method for preventing AKI. Historically, monoclonal protein levels have been monitored using serum and urine electrophoretic techniques. Due to their short half-life, the measurement of serum FLCs in multiple myeloma provides a more rapid indication of disease progression and response to treatment [52, 53]. FLC assessment is particularly beneficial for the early detection of light chain escape (LCE) in patients diagnosed with intact immunoglobulin multiple myeloma [54]. This phenomenon, defined as a relapse of multiple myeloma with the production of monoclonal FLC alone, occurs in 5% and 15% of patients with IgA and IgG multiple myeloma, respectively [55]. A relapse of this type can cause a significant nephrotoxic burden on the kidneys; approximately 50% of patients with LCE have renal impairment [54]. In this setting, serial monitoring of intact immunoglobulins would not identify patients with LCE who are at risk of renal impairment; this scenario could be avoided by regular FLC monitoring in addition to the regular SPE/IFE monitoring [54, 56].

Myeloma Kidney: Targeting Free Light Response

Multiple myeloma combined with renal failure is associated with a poor survival for those affected [21, 57]. However an early reduction in serum FLCs is associated with an increased chance of renal recovery and improved survival [26]. The importance of achieving this significant early reduction in FLCs for renal recovery has been emphasised in studies which have demonstrated that the relationship between renal recovery and FLC reduction is

linear and a target of achieving at least a 50% reduction in serum FLCs has been proposed [26, 58]. The key question therefore becomes how this early reduction in circulating FLC concentrations is achieved. Beyond any doubt the most important factor is to initiate effective chemotherapy to suppress the clonal production of FLCs as rapidly as possible. In addition, there may be a role for the direct removal of FLCs by extracorporeal therapies in specific situations.

Historical chemotherapy regimes, including VAD (vincristine, doxorubicin and dexamethasone), high dose dexamethasone, and melphalan and prednisolone, are often being replaced by, or combined with, novel multiple myeloma therapies with improved efficacy, such as bortezomib, thalidomide or lenalidomide. The introduction of these novel chemotherapies has significantly increased the survival time of patients diagnosed with multiple myeloma [59-61]. Bortezomib, in particular, has proven efficacy in both newly diagnosed and relapsed/refractory multiple myeloma and is safe and efficacious in patients with renal impairment [62-64]; it can be administered at full dose in patients with renal impairment since its pharmacokinetics are not influenced by kidney function [65]. In a consensus statement published on behalf of the IMWG, a treatment regime combining bortezomib with dexamethasone is recommended for patients with multiple myeloma and renal impairment of any grade [66].

Although reducing the production of the FLC clone can be achieved by effective chemotherapy regimens, the individual patients' tumour response cannot be predicted and may be delayed. Moreover, the effect of chemotherapy alone on the serum FLC levels may be limited by the prolonged serum-half live of FLCs in patients with renal failure [20]. The direct removal of FLCs from the serum by extracorporeal therapies could be a useful complementary therapy to chemotherapy in patients with severe renal impairment. Approaches currently being considered for physical FLC removal are plasma exchange (PE) and high cut-off haemodialysis (HCO-HD). The effectiveness of PE at directly removing FLC is questionable. Data from two small studies were conflicting [67, 68], and a subsequent larger randomised controlled trial failed to demonstrate any benefit of PE in multiple myeloma patients with AKI in terms of renal recovery or patient survival [69]. The apparent lack of efficacy of PE could be explained simply by a dose effect. Free light chains are small molecules and therefore distribute in the extravascular as well as intravascular compartments. Whilst PE will clear the intravascular compartment very effectively, the short duration of the treatment means that the extravascular compartment cannot be cleared. A kinetic mathematical model has suggested that only around 25% of total body FLCs may be removed by PE over a three-week period [31].

The same mathematical modelling indicates that an extended duration therapy such as haemodialysis (HD) using a protein permeable dialyser, so called high cut-off (HCO), is a more effective methodology for achieving a sustained removal of serum FLCs. Prolonged HCO-HD could reduce FLC concentrations by as much as 93% over 3 weeks.

The ability of HCO-HD to reduce serum levels of FLCs (in combination with chemotherapy) was evaluated in a single centre prospective pilot study [34]. The inclusion criteria were a diagnosis of multiple myeloma and dialysis-dependent renal failure, with biopsy proven cast nephropathy. Of the 19 patients that met the study criteria, 13 had sustained early reductions in serum FLCs and became dialysis-independent after HCO-HD. Each of these patients had uninterrupted chemotherapy over a 6 week period. In contrast, all of the 6 patients that did not become dialysis independent after HCO-HD had early

chemotherapy interruptions, mainly due to infective complications, and did not achieve sustained early FLC reductions. This data highlights the importance of effective chemotherapy in addition to HCO-HD to facilitate renal recovery. The pilot data is promising; however the absence of a control group prevents definitive conclusions to be made regarding clinical benefit. Subsequently, two randomised controlled trials evaluating the clinical utility of HCO-HD for recovery of renal function in patients with multiple myeloma have been initiated, EuLITE [70] and MYER [71].

The EuLITE study is a prospective, randomised, multicentre open label trial which commenced in May 2008, with the intent to recruit 90 patients with dialysis-dependent renal failure and myeloma cast nephropathy. The rationale for only recruiting patients with severe renal impairment is that those patients with mild or moderate renal impairment are more likely to have enough FLC clearance for an effective chemotherapy regime to be sufficient alone. The trial chemotherapy consists of bortezomib, doxorubicin and dexamethasone, a regime with proven efficacy for patients with multiple myeloma [72;73] and renal impairment. The haemodialysis protocol involves two Gambro HCO 1100 dialysers in series, and extended haemodialysis sessions of up to 8 hours/day. A detailed trial protocol has been previously published and at the time of writing, two thirds of the population have been recruited and it is anticipated recruitment will close by early 2013 [70].

Conclusion

Monoclonal FLCs are integrally involved in the pathogenesis of AKI in patients with multiple myeloma. Recent work has demonstrated that when treatment achieves an early reduction in the serum concentrations of these nephrotoxic proteins renal recovery can occur in the majority of patients. Immunoassays which utilise polyclonal antibodies against FLCs provide a highly sensitive tool for the diagnosis and monitoring of patients with AKI secondary to multiple myeloma and their use in clinical practice should lead to improved patient outcomes.

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Chapter IX

Prevention of Acute Kidney Injury in Critically Ill Patients

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Abstract

Acute kidney injury is associated with significant short and long-term complications and increased mortality. The key elements of primary and secondary prevention are prompt recognition of the patients at risk, timely goal directed resuscitation of the circulation with fluids and vasoactive drugs, and avoidance of additional renal damage. A mean arterial pressure ≥ 65 mmHg should be aimed for but higher targets may be necessary in patients with severe sepsis / septic shock and/or pre-existing chronic hypertension. There is no role for diuretics, thyroxine, statins, erythropoietin, natriuretic peptide, aprotinine, activated protein C, tight glucose control, steroids or calcium channel blockers to prevent AKI in critically ill patients. If possible, nephrotoxic drugs should be discontinued. Strategies for prevention of AKI across a range of different groups are discussed, including patients with cardiac disease, liver cirrhosis, tumour lysis syndrome, rhabdomyolysis and intra-abdominal hypertension.

Introduction

Acute kidney injury (AKI) is a significant problem that frequently complicates the course of critical illness. The major causes are sepsis / systemic inflammatory response syndrome, renal hypoperfusion, volume depletion and nephrotoxicity, but in most cases the aetiology is multifactorial. Several types of surgical procedures are associated with an increased risk of AKI, in particular coronary artery bypass graft (CABG) surgery, cardiac valve replacement,

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biliary surgery and vascular procedures. Multiple pathomechanisms have been suggested to explain the high incidence of AKI after surgery, including hypotension, hypoxia, generation of reactive oxygen species, endothelial activation, release of inflammatory mediators and atheroembolization. Patients with pre-existing comorbidities including diabetes, cirrhosis/hepatic failure, congestive heart failure, pre-existing chronic kidney disease (CKD), peripheral vascular disease and advanced age are at particular risk of AKI during surgery and/or critical illness [1-3]. There is increasing recognition that AKI is independently associated with a longer stay in hospital, a higher risk of complications, significant health care costs and higher mortality [4-9]. Survivors of AKI incur an increased risk of CKD and end-stage renal failure compared to those without AKI [10, 11].

Table 1. Scoring systems to predict risk of AKI post cardiac surgery

Variable	SRI Score (83)		Mehta Score (84)		Cleveland Score (85)	
	Descriptor	Points	Descriptor	Points	Descriptor	Points
Age	-		varies	varies	-	-
Gender	-		-		female	1
Race	-		non-white	2	-	-
Pre-existing renal function	GFR* 31-60ml/min	1	serum creatinine	variable	serum creatinine 1.2 - 2.1 mg/dL	2
	≤30 ml/min	2			>2.1 mg/dL	5
CCF	-		-	-	Yes	1
NYHA Class	-		Class IV	3	-	-
LVEF	≤40%		-	-	<35%	1
Cardiogenic shock	-		Yes	7	-	-
Recent MI (<22d)	-		Yes	3	-	-
COPD	-		Yes	3	Yes	1
Diabetes mellitus	requiring Rx	1	on oral Rx	2	requiring insulin	1
			Insulin requiring	5		
Type of surgery	other than CABG or ASD only	1	CABG	0	CABG only	0
			Aortic valve only	2	Valve only	1
			Aortic valve + CABG	5	CABG + valve	2
			Mitral valve only	4	Other	2
			Mitral valve + CABG	7		
Urgency of surgery	non-elective surgery	1	-	-	emergency surgery	2
Previous surgery	Yes	1	Yes	3	Yes	1
Pre-op IABP	Yes	1	-	-	Yes	2
Total points		0 – 8		0 - 83		0 – 17

Abbreviations: SRI = Simplified Renal Index; ASD = atrial septal defect; CABG = coronary artery bypass grafting; CCF = congestive cardiac failure; MI = myocardial infarction; d = days; NYHA = New York Heart Association; COPD = chronic obstructive pulmonary disease; Rx = treatment; GFR = glomerular filtration rate; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; preop = preoperative.

* According to Cockcroft-Gault equation.

They also report significantly worse quality of life even when renal function has recovered [12].

There is no specific therapy for AKI other than supportive care. Given the impact of AKI on morbidity and mortality, it is important to prevent even the mildest form of AKI, especially in high risk patients and the elderly. Preventive strategies include means to preserve renal function in patients undergoing high risk procedures (primary prevention) as well as measures to prevent progression of AKI after an initial renal insult (secondary prevention). Although primary prevention of AKI is relevant to patients in most acute settings from the emergency department to acute medical and surgical wards, most data stem from studies in patients undergoing high risk surgery or patients exposed to contrast media.

Efforts to reduce the incidence of AKI after surgery rely on careful characterisation of risk factors, identification of high risk patients, and appropriate adjustment of clinical management. Several prediction models are available to assess the risk of AKI after cardiac as well as general surgery [1, 13-17]. (Table 1) Data of >75,000 patients who underwent general surgery in 121 centres in the US showed that 1% of patients developed AKI (as defined by a rise in serum creatinine >196 $\mu\text{mol/L}$) during the 30 day period postoperatively [13]. 30-day mortality in this group was 42.0% compared to 8.6% in patients without AKI. Independent risk factors for AKI were age ≥ 56 years, male gender, emergency surgery, intraperitoneal surgery, diabetes mellitus, congestive heart failure, ascites, hypertension and pre-existing CKD. The presence of 6 or more factors was associated with a 9% risk of developing AKI post-surgery. Although these risk factors are predominantly non-modifiable, the use of prediction models serves to counsel patients pre-operatively and may also guide management intra-operatively.

Preventive Strategies

Fluid Therapy

Adequate and timely fluid resuscitation is essential to avert or limit AKI in patients with fluid depletion and/or low cardiac output. Prophylactic fluid therapy is indicated for primary prevention of nephrotoxicity in patients receiving amphotericin B, contrast media, foscarnet, and drugs causing crystal nephropathy [18-26].

The most commonly used fluids are crystalloids and colloids, including gelatins, human albumin and hydroxyl-ethyl starches (HES) with varying effects on volume expansion. Among crystalloids, balanced solutions are generally recommended. 0.9% saline has been associated with a risk of hyperchloraemic metabolic acidosis and worsening acid-base balance. Data on the safety of different colloids are conflicting [27]. High molecular weight HES have been associated with an increased risk of AKI, greater need for renal replacement therapy (RRT) and higher mortality, and should therefore be avoided [28-30]. Human albumin has been judged to be safe [28, 29, 31]. In the perioperative setting, different types of fluids have been compared with no convincing evidence that one type of fluid is superior to others [32, 33].

Although timely fluid resuscitation is important to prevent AKI in conditions associated with volume depletion, there is increasing evidence that excessive fluid administration

beyond correction of deficits can be harmful. Several studies in critically ill patients and patients undergoing elective surgery have confirmed an association between fluid overload, organ dysfunction and adverse outcomes [34-38]. The risk of complications or death is significantly higher in patients with AKI who are fluid overloaded compared to AKI patients without fluid overload.

To avoid both hypo- and hypervolaemia, fluid prescriptions need to be individualised and tailored to the cardiovascular status of the patient. Frequent evaluation of the patient is essential. Haemodynamic monitoring may be necessary to distinguish fluid responsive patients from those who are hypotensive due to vasodilation. In such situations, the use of vasopressor therapy will help to restore blood pressure, and consequently renal perfusion without causing fluid overload.

Vasoactive Drugs

In health, renal blood flow is stable within a wide range of mean arterial pressure (MAP) due to renal autoregulation. However, in critically ill patients, in particular in patients with septic shock, derangements in microcirculation and vasoreactivity alter the MAP threshold that guarantees autoregulation. Data on the optimal MAP to prevent the development and/or progression of AKI are conflicting. Current recommendations for the prevention of AKI in the ICU propose a target MAP ≥ 65 mmHg but indicate that haemodynamic goals need to be individualized, especially in patients with pre-existing chronic hypertension [29]. Two interventional prospective studies of limited size showed that increasing MAP from 65 to 75 or 85 mmHg in patients with septic shock did not increase urine output or improve serum creatinine [39, 40]. In contrast, a subsequent study in 12 post-cardiac surgery patients with Noradrenaline-dependent vasodilatory shock and AKI concluded that restoration of MAP from 60 to 75 mmHg improved renal oxygen delivery, glomerular filtration rate and the renal oxygen supply/demand relationship [41]. A retrospective cohort study suggested that a MAP > 75 mmHg may be necessary to insure renal protection during sepsis and septic shock [42]. Finally, a prospective observational study in 217 patients with sustained shock concluded that a MAP of 72-82 mmHg may be necessary to avoid progressive AKI in patients with septic shock and initial renal impairment [43]. This link between MAP and progressive AKI was less obvious in patients with shock of other origins. Despite some inconsistent results, these studies suggest that higher blood pressure targets may be necessary in patients with sepsis / septic shock who are at risk of AKI or have already developed early AKI.

Historically, vasopressor use was limited by concerns over renal vasoconstriction and consequent ischemia. However, the available evidence suggests that the use of vasopressors in vasodilatory shock is in fact associated with increased renal blood flow, restoration of urine output and improved creatinine clearance [44-49]. In contrast, there is no role for “renal-dose” dopamine in either preventing or ameliorating AKI in critically ill patients [50-52].

Fenoldopam, a selective dopamine A-1 receptor agonist, has been shown to reduce the need for RRT and improve survival in patients after cardiovascular surgery [53,54]. However, in patients exposed to contrast media, fenoldopam failed to prevent contrast-induced nephropathy (CIN) [55]. The role of fenoldopam in other groups of critically ill patients is still being investigated in clinical trials.

Table 2. Different means of “haemodynamic optimization” and targets to protect renal function in surgical patients

Mode of optimization	Goals
Fluids, blood, dopamine	<ul style="list-style-type: none"> • $CI \geq 2.8$, PAOP 8 - 15
Fluids, blood, dobutamine	<ul style="list-style-type: none"> • $CI \geq 4.5$ and $DO_2 \geq 670$
Fluids, blood, dohexamine	<ul style="list-style-type: none"> • $CI > 3.0$ and $DO_2 > 600$
Fluids, blood, any inotrope	<ul style="list-style-type: none"> • $DO_2 > 600$ or • $SVV < 10\%$, $CI > 2.5$, $DO_2 > 450$, $ScvO_2 > 70\%$ or • $ScvO_2 > 70\%$ and lactate ≤ 2.0 or • $CI > 3.5$, DO_2 550-600, $MAP > 70$ and PAOP 18

The data were extracted from the paper by Brienza et al. [58].

Abbreviations: CI = cardiac index; PAOP = pulmonary artery occlusion pressure; DO_2 = oxygen delivery; SVV = stroke volume variation; $ScvO_2$ = central venous oxygen saturation; MAP = mean arterial pressure.

Goal-directed Haemodynamic Optimisation

Research in surgical patients has provided clear evidence that pre-emptive strategies of haemodynamic monitoring and optimisation can reduce postoperative mortality and morbidity, including the incidence of AKI [56-58]. A significantly reduced risk of AKI and death was observed in patients who received both fluids and inotropes either pre-, intra- or postoperatively according to a goal directed protocol [58]. However, there was wide variation in the optimisation protocols and actual haemodynamic targets between individual studies. (Table 2)

To date, it remains unclear whether similar means of haemodynamic optimisation can also prevent progression of AKI and/or death in critically ill ICU patients with early AKI.

Diuretics

There is no role for diuretics in preventing or treating established AKI. Three meta-analyses confirmed that the use of diuretics in established AKI did not improve renal function or change mortality but carried a significant risk of side-effects, including electrolyte derangement, ototoxicity and vestibular dysfunction [59-61]. There is also no role for diuretics in speeding up recovery of renal function after RRT [62]. However, in patients with progressive fluid accumulation, diuretics can minimize fluid overload and may make patient management easier, especially if RRT is not immediately available [63].

Tight Glucose Control

In single centre studies, tight glycaemic control with intensive insulin therapy was associated with a reduced incidence of severe AKI requiring RRT [64]. Other studies failed to demonstrate a beneficial effect. A meta-analysis including twenty-nine randomized controlled trials (RCTs) totalling 8432 patients concluded that there was no evidence of a renoprotective effect with intensive insulin therapy [65]. A subsequent large international RCT in 6104 critically ill patients comparing intensive glucose control aiming for glucose levels between 81 to 108 mg/dl (4.5 to 6.0 mmol/L) with glucose targets of 180 mg/dl or less (≤ 10 mmol/L) found no difference in the proportion of patients who developed AKI or needed RRT [66]. Mortality was significantly higher in patients in the intensive glucose control arm. Therefore, there is no role for tight glucose in the prevention of AKI.

Other Pharmacological Therapies

Numerous drugs have been investigated for prevention of AKI in different clinical settings with little success. Studies exploring the role of N-Acetylcysteine (NAC) for prevention of CIN or AKI post surgery have had conflicting results. Most meta-analyses have reported a reduced risk of CIN but were limited by study heterogeneity [67-71]. High risk patients undergoing cardiac surgery, NAC was not found to be beneficial [72-75].

Statins have theoretical benefits for patients at risk of AKI and have been investigated in clinical studies [76, 77]. However, a large meta-analysis including data of >30,000 patients confirmed that preoperative statin therapy exerted substantial clinical benefit on early postoperative adverse outcomes in cardiac surgery patients but did not reduce the risk of AKI [77].

There is no consistent evidence for routine use of natriuretic peptide, aprotinin, activated protein C, steroids or calcium channel blockers to prevent AKI in critically ill patients [29, 78, 79]. Additional “cytoprotective” interventions for prevention of AKI have also been explored, such as remote ischaemic preconditioning, hypothermia, thyroxine, erythropoietin and insulin-like growth factors. Although theoretically beneficial, they have not been shown to have consistent benefit in randomized trials [80].

Discontinuation of Nephrotoxic Drugs

Nephrotoxic drugs should be discontinued / limited where possible. Appropriate dose adjustment according to renal function is essential for all drugs, even if they are not directly nephrotoxic [81].

The preoperative management of patients on regular angiotensin-converting enzyme (ACE) inhibitors is uncertain. In general, ACE inhibitors and angiotensin receptor blockers (ARBs) confer renal protection, especially for patients with diabetes and/or impaired left ventricular function. Benedetto et al analysed data of 536 patients undergoing CABG surgery of whom 281 received ACE inhibitors preoperatively [82]. The incidence of postoperative AKI was 6.4% in patients who had received ACE inhibitors preoperatively and 12.2% in

patients who had not ($p = 0.02$). In contrast, a study in 504 patients undergoing gastric bypass surgery showed that body mass index, hyperlipidemia and preoperative use of ACE inhibitors or ARBs were independent risk factors for AKI [83]. Length of stay in hospital was greater in patients with AKI versus no AKI (4.0 versus 2.7 days; $p = 0.0003$).

A prospective, single centre study evaluated the frequency of CIN in 412 patients of whom 269 patients were taking an ACE inhibitor or ARB [84]. Multivariate regression analysis showed that even after adjustment for confounding comorbidities, treatment with an ACE inhibitor or ARB was an independent risk predictor for CIN.

Results of further studies investigating the impact of preoperative use of ACE inhibitors or ARBs on AKI are awaited. Until then it is acceptable to continue ACE inhibitors / ARBs during the perioperative period but to remain vigilant and to discontinue treatment if AKI occurs.

Prevention of Acute Kidney Injury in High Risk Groups

Cardiac Disease

The incidence of AKI in acute decompensated heart failure and acute coronary syndrome is estimated to be 24-45% and 9-19% respectively [80]. Impaired baseline renal function in acute heart failure and/or early deterioration in renal function is associated with increased morbidity and mortality. In principle, any treatment for acute heart failure aimed at increasing cardiac output and renal blood flow has a beneficial effect on renal function [85]. Therapeutic options include fluids, inotropic support and if necessary, cautious introduction of norepinephrine. Occasionally more invasive treatments including intra-aortic balloon pump or left ventricular assist device may be necessary.

Rhabdomyolysis

Rhabdomyolysis is characterized by the release of myoglobin and other muscle components into the extracellular fluid and circulation. Estimates from small studies suggest that 20-50% of patients with rhabdomyolysis develop AKI as a result of intravascular fluid depletion, fluid sequestration in injured muscle, renal hypoperfusion, intratubular heme pigment cast formation and tubular obstruction. There may be additional secondary renal injury due to free radical production and myoglobin induced nitric oxide scavenging [86]. The cornerstone for prevention of myoglobinuric AKI consists of aggressive volume resuscitation. Initially, this is achieved primarily with isotonic crystalloid solutions at 10-15ml/kg/hr aiming for a target urine output of >200ml/hr [87]. Isotonic bicarbonate at 50-100mmol/L can be added aiming for a urine pH >6.5 to increase the solubility and renal excretion of tubular myoglobin. Although there are theoretical benefits for adding mannitol (ie. inhibition of intratubular myoglobin deposition and cast formation, osmotic diuresis, radical scavenging), these benefits are not supported by evidence from randomized controlled trials [88]. Complementary measures have been tried, including haemofiltration to remove myoglobin,

allopurinol to reduce uric acid production, pentoxifylline to improve microcirculatory blood flow, deferoxamine to chelate circulating free iron and dantrolene to reduce intracellular calcium, but all of these strategies lack robust data [89].

Liver Disease

Patients with liver cirrhosis have abnormal hemodynamics including splanchnic vasodilation with decreased effective arterial circulating volume, increased sympathetic nervous system activity and increased renin/angiotensin levels, all of which can result in renal arterial vasoconstriction. AKI in patients with cirrhosis is associated with poor acute and long-term prognosis. Preventive measures include timely correction of intravascular hypovolaemia, discontinuation of diuretics and consideration of large volume paracentesis with plasma expansion using albumin. Pharmacologic therapies that have been reported to be effective with varying degrees of supporting evidence include α agonists, norepinephrine, vasopressin analogs, midodrine and octreotide [90].

Tumour Lysis Syndrome

Tumour lysis syndrome describes the metabolic derangements that result from rapid destruction of malignant cells and the release of intracellular ions, nucleic acid and metabolites into the extracellular space. Hyperuricaemia, hyperkalaemia, metabolic acidosis and hyperphosphataemia can occur and may lead to deposition of uric acid and calcium phosphate crystals in the renal tubules and AKI. Preventive measures consist of aggressive fluid loading and allopurinol administration at least 2 days before chemotherapy or radiotherapy in patients at risk [91]. Prophylaxis with Rasburicase, which catalyzes the oxidation of uric acid to the more water soluble allantoin, appears to be more effective than allopurinol in reducing the incidence of uric acid nephropathy [92]. Although urine alkalinization with sodium bicarbonate may reduce uric acid precipitation in renal tubules, it also promotes calcium phosphate deposition in tissues and is therefore not recommended [90].

Intra-abdominal Hypertension

Intra-abdominal hypertension can lead to AKI, in particular if intra-abdominal pressure is consistently >20mm Hg. However, the critical intra-abdominal pressure that causes AKI varies from patient to patient due to differences in physiology and pre-existing comorbidities. Recommendations by an international consensus group of multidisciplinary critical care specialists for the management of patients with sustained intra-abdominal hypertension include the use of sedation and analgesia to increase abdominal wall compliance, evacuation of intraluminal contents, evacuation of abdominal fluid collections, and correction of positive fluid balance [93]. In patients who fail to respond to these medical interventions, surgical

abdominal decompression may be necessary to prevent progressive organ dysfunction, including AKI.

Future Strategies

Anti-inflammatory strategies: There is increasing evidence that AKI is an inflammatory process, characterised by neutrophil activation, increased adhesion molecule expression, cytokine production within the kidney and activation of several inflammatory cells [94]. New treatments aimed at these inflammatory processes are being explored. However, the strategy of limiting the inflammatory cascade of severe sepsis by early application of continuous veno-venous haemofiltration failed to limit or improve organ failure [95]. In fact, early haemofiltration resulted in worse outcomes, more organ dysfunction including AKI and prolongation of organ support. Other anti-inflammatory treatments, including immunosuppressants are being investigated.

Stem cell therapy: The potential role of mesenchymal stem cells in endogenous repair of AKI is under intensive investigation [96]. Preclinical studies indicated that their administration both ameliorates renal injury and accelerates repair. In addition, infusion of stem cells has also been shown to be effective in preventing CKD post AKI.

Conclusion

The key elements of primary and secondary prevention of AKI are prompt recognition of the patients at risk, goal-directed resuscitation of the circulation with fluids and vasoactive drugs, and avoidance of further renal insults. To mitigate the development of fluid overload, a strategy of careful early guided fluid resuscitation, followed by frequent reassessment and timely initiation of vasopressor / inotropic support should be followed. A MAP ≥ 65 mmHg should be aimed for but higher targets may be necessary in patients with sepsis / septic shock and/or pre-existing chronic hypertension. Review of all medication and dose adjustment is mandatory. If possible, nephrotoxic drugs should be discontinued. There is no single drug which can prevent or treat established AKI but results of future developments are awaited.

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Chapter X

Renal Failure: Causes

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Abstract

Normal kidney function is crucial in the maintenance of volume, electrolyte and acid-base homeostasis. The structural and functional integrity of the renal parenchyma results from a complex interaction between the glomerular and tubular functions. Based on pathophysiology, the causes of acute renal failure are traditionally divided into three categories: 1. Pre-renal, secondary to prolonged hypoperfusion as a consequence of clinical conditions associated with, either hypovolemia or reduced circulating effective blood volume. Specific clinical syndromes such as cardiorenal, hepatorenal or sepsis are often associated with this type of renal failure. 2. Intrinsic, when the renal tissue is directly affected. Any segment of the nephron may be involved (i.e. glomerulus, tubule, interstitium or small vessels), but the most common cause is acute tubular necrosis (ATN). This clinical condition may result either from prolonged ischemia or a direct toxic effect on the tubular epithelial cell. A large number of exogenous administered or endogenously generated substances may provoke acute renal failure. 3. Post-renal, secondary to an obstruction of the urinary tract (renal pelvis, ureters, urinary bladder or urethra) impedes normal urinary flow and, potentially leads to permanent damage if left untreated. Given the multitude of the potential causes of acute renal failure, understanding of the underlying pathophysiologic mechanisms is essential for the clinician to choose the appropriate preventive and therapeutic measures.

1. Introduction Definitions

Acute Renal failure (ARF) is an abrupt and sustained reduction in Glomerular Filtration Rate resulting in decreased ability of the kidney to balance the electrolyte, acid base and fluid status of the body [1]. Acute kidney injury (AKI) is the recently preferred terminology. ARF

and AKI are used interchangeably in this chapter. In most studies a quantitative definition of ARF is used and creatinine, as well as creatinine clearance is both implemented. A group of intensive care specialists and nephrologists created the Acute Dialysis Quality Initiative (ADQI). The purpose of this initiative was to develop a widely accepted definition of ARF. By consensus the so-called RIFLE criteria were adopted. RIFLE are the initials of three categories of injury (Risk, Injury and Failure), followed by two outcomes (Loss and End Stage Renal Disease) [2,3]. According to RIFLE:

- A 1.5-fold increase of serum creatinine or 25% decrease of GFR or urine output <0.5 ml/kg/hour for 6 hours is defined as Risk
- A 2-fold increase of serum creatinine or 50% decrease of GFR or urine output <0.5 ml/kg/hour for 12 hours is categorized as Injury
- A 3-fold increase in serum creatinine or 75% decrease of GFR or urine output <0.3 ml/kg/hour for 24 hours is considered as failure

All the above can lead to, either a need of renal replacement therapy for more than four weeks (Loss) or a complete loss of kidney function requiring renal replacement therapy for more than 3 months which is the worst outcome termed End Stage Renal Disease (ESRD).

Although RIFLE criteria provided a more uniform definition of ARF, practice has shown that there are limitations. First the criteria of each category are unequal and their use is supported by inadequate evidence. Secondly, creatinine and creatinine clearance depict statically and not dynamically a rapidly deteriorating renal function. Oftentimes, previous creatinine values are not available in a given patient. Thus, the quantitative criteria can not be solely used.

Taking into account all the above limitations, the Acute Kidney Injury Network (AKIN) formulated the revised RIFLE criteria [4-6]. The term Acute Kidney Injury (AKI) supplanted the older term Acute Renal Failure (ARF). According to AKIN there are three stages of AKI based on clinical evidence:

- Stage 1: increased of serum creatinine ≥ 0.3 mg/dL (≥ 26.4 $\mu\text{mol/L}$) or 1.5-2-fold from baseline or urine output <0.5 ml/kg/hour for at least 6 hours.
- Stage 2: two-three-fold increase in serum creatinine from baseline or oliguria <0.5 ml/kg for more than 12 hours.
- Stage 3: More than a three-fold increase in serum creatinine from baseline or acute increase in serum creatinine ≥ 0.5 mg/dl (44 $\mu\text{mol/L}$) when the baseline is >4.0 mg/dL (354 $\mu\text{mol/L}$). Otherwise, urine output <0.3 ml/kg/hour for 24 hours or anuria for 12 hours characterizes stage 3 AKI [4].

The cutoff point of 0.3 mg/dl absolute increase is not arbitrarily chosen. It is based on clinical evidence of increased mortality even with small increases of serum creatinine of 0.3-0.5 mg/dl [7].

The AKIN criteria take effect only when obstruction of the urinary tract is excluded and volume status is corrected.

AKIN and RIFLE criteria serve as an alert for the clinician to identify and manage the consequences of AKI in order to decrease the incidence of ESRD and mortality. Biomarkers

like the troponin in acute coronary syndrome would be more practicable. Although, as discussed in the prevention section, several biomarkers are promising, at the moment a similar marker for AKI is not widely available. For this reason, serum creatinine as well as creatinine clearance is used for this purpose.

In the following we will describe the causes of acute renal failure focusing on pathophysiology. This description will facilitate the understanding of the prevention and treatment of renal failure depending on the etiology.

The causes of renal failure are divided into pre-renal, when prolonged hypoperfusion leads to a reduced GFR; intrinsic, when the renal parenchyma is affected (glomerulus, tubule, or interstitium); post-renal, when there is an obstruction of urine flow in the urinary tract (renal pelvis, ureters, urinary bladder or urethra). We will analyze next the causes of AKI (ARF) separately.

2. Causes of AKI

2.1. Pre-Renal

2.1.1. Pathophysiology

Kidney is a highly perfused organ that accepts approximately 25% of the cardiac output. (Renal Blood Flow, RBF=250 ml/min). That fact makes the kidney very vulnerable to hypoperfusion and to the effect of exogenous toxins.

Hypovolemia and reduced cardiac output decrease renal perfusion and mean arterial pressure (MAP). This change of the arterial pressure is detected by the baroreceptors of the carotid bodies and the aortic arch resulting in activation of the compensatory mechanisms (sympathetic nervous system, renin-angiotensin-aldosterone system and non-osmotic ADH secretion by the posterior lobe of hypophysis) [8]. The effects of this activation is splachnic and cutaneous vasoconstriction, positive inotropic and chronotropic effect, brain vasodilatation and stimulation of thirst in order to maintain adequate perfusion of the brain and heart.

Renal hypoperfusion decreases ultrafiltration pressure and glomerular filtration rate (GFR). Consequently, renal autoregulation is activated leading to dilatation of the afferent arteriole by means of [9,10]:

- stimulation of sensory receptors and smooth muscle relaxation (local myogenic reflex)
- production of prostaglandins (PGE_2 , PGF_2 , NO)
- activation of the tubulo-glomerular feedback mechanism (decreased release of NaCl in the macula densa results in adenosine A1 receptor activation and dilatation of the afferent arteriole [11]).
- Angiotensin II by its turn causes constriction of the efferent arteriole.

All the previously described mechanisms preserve the ultrafiltration pressure and GFR when systolic arterial pressure (SAP) is at least 80 mmHg. If SAP is further reduced the counter-regulatory mechanisms are not adequate anymore. The afferent arteriole is

constricted more intense than the efferent resulting in pre-renal ARF. The presence of clinical conditions associated with vascular dysfunction such as diabetes mellitus, hypertension or atherosclerosis evokes pre-renal failure at higher SAP values.

There are many causes of renal hypoperfusion that lead to pre-renal azotemia (Table 1). Decreased fluid intake or increased losses from the kidneys (diuretic overuse, osmotic diuresis, post-obstructive ARF, diabetes insipidus), gastrointestinal tract (vomiting, diarrhea, fluid drains, bleeding), and skin (sweating, extensive burns). Moreover, post-operative or trauma-associated bleeding and fluid loss in the third space (pancreatitis, peritonitis, crush syndrome) may cause hypovolemia.

Table 1. Causes of pre-renal azotemia

I.	Hypovolemia
1.	Dehydration
–	Decreased fluid intake (infants, elderly)
–	Increased fluid losses: renal (diuretics, osmotic diuresis, postobstructive polyuria, central or nephrogenic diabetes insipidus), gastrointestinal (vomiting, gastric lavage, diarreal syndromes, bleeding) or cutaneous (sweating, burning)
2.	Fluid losses in the third space (pancreatitis, peritonitis, compartment syndrome)
3.	Decreased effective extracellular volume (heart failure-cardiorenal syndrome, cirrhosis-hepatorenal syndrome, nephrotic syndrome)
II.	Decreased cardiac output
–	cardiac disease (myocarditis, cardiomyopathy, pericarditis, endocarditis, arrhythmias)
–	pulmonary hypertension
–	obstructive shock (massive pulmonary embolism, tension pneumothorax, constrictive pericarditis)
III.	Peripheral vasodilation
–	sepsis
–	anaphylaxis
–	drugs (antihypertensives, anesthetics)
IV.	Alteration of intrinsic renal hemodynamics
–	NSAIDs, selective COX-2 inhibitors, ACE inhibitors, ARBs, calcineurin inhibitors, epinephrine, norepinephrine

Abbreviations: NSAIDs, non steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; ACE, angiotensin converting enzyme; ARBs, angiotensin’ receptor blockers.

Heart failure, liver cirrhosis and nephrotic syndrome constitute clinical conditions characterized by fluid retention and reduced effective circulating blood volume.

Furthermore, other cardiac disorders such as myocarditis, cardiomyopathies, pericarditis, endocarditis, arrhythmias, pulmonary hypertension and shock (massive pulmonary embolism, tension pneumothorax, constrictive pericarditis) may lead to pre-renal AKI.

Finally, conditions that produce generalized peripheral vasodilatation such as sepsis, anaphylactic shock, antihypertensive drugs, and anesthesia or vigorous intrarenal vasoconstriction (calcineurin inhibitors, epinephrine, and norepinephrine) may result in pre-renal azotemia.

2.1.2. Specific Syndromes and Situations Associated with Pre-Renal AKI

a) Cardiorenal Syndrome

Cardiorenal syndrome (CRS) is the combination of cardiac and renal failure wherein acute or chronic dysfunction of one organ leads to dysfunction of the other [12]. It is divided into five subtypes. The development of ARF secondary to acutely decompensated heart failure is called Type 1 or acute cardiorenal syndrome. (Table 2) The pathophysiologic mechanisms that contribute to the CRS are complex and interrelated [13]:

1. Activation of the renin-angiotensin-aldosterone system (RAAS).
2. Imbalance between NO, oxidative stress and increased synthesis of reactive oxygen species (ROS).
3. Prolonged stimulation of the sympathetic nervous system and secretion of neuropeptide Y.
4. Inflammation.

Table 2. Classification of cardiorenal syndrome

Type 1 (acute cardiorenal):	Acute cardiac dysfunction leading to acute kidney injury
Type 2 (chronic cardiorenal):	Chronic heart failure leading to renal dysfunction
Type 3 (acute renocardiac):	Acute kidney injury leading to acute cardiac dysfunction
Type 4 (chronic renocardiac):	Chronic renal failure leading to cardiac dysfunction
Type 5 (secondary):	Systemic condition causing cardiac and renal dysfunction

b) Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a functional disorder of the kidneys, manifested in patients with liver cirrhosis and portal hypertension. It is estimated that 10% of patients with liver cirrhosis and ascites will develop HRS, while at 5 years the likelihood is 39% [14].

It is caused from the progressive renal hypoperfusion due to intense intrarenal vasoconstriction that runs in parallel with the deterioration of renal function [15].

Portal hypertension increases production of vasodilatory substances (NO, glucagon, VIP, PGI₂). These substances decrease the effective circulating blood volume (ECBV) causing the activation of vasoconstricting mechanisms (sympathetic nervous system, RAAS, ADH). In compensated cirrhosis the above described mechanisms maintain the mean arterial pressure in normal levels mainly through vasoconstriction of the intrarenal vessels. In decompensated cirrhosis splanchnic vasodilation leads to an increase in lymph production, continuous accumulation of ascitic fluid and eventually further reduction of the ECBV. Concurrently, activation of hepatorenal neural reflex and endotoxemia due to portosystemic anastomoses lead to domination of vasoconstrictive mechanisms (TXA₂, endothelin) resulting in vigorous efferent arteriolar constriction and reduction of the GFR [16].

There are two types of HRS with different prognosis and outcome [17]:

Type 1 (acute HRS) is characterized by rapid deterioration of renal function defined as the doubling of serum creatinine to values >2.5 mg/dL or a 50% decrease in creatinine clearance to a level below 20 ml/min at an interval of less than 2 weeks. Oftentimes a precipitating factor precedes the development of HRS (gastrointestinal bleeding, infection or

dehydration). This type is associated with a high mortality rate and a mean survival time 2 weeks from the onset of renal dysfunction.

Type 2 (chronic HRS) is characterized by slower progression of renal dysfunction and an increase of serum creatinine to a value >1.5 mg/dL within months. Clinically the patients present ascites refractory to treatment with diuretics. It is associated with high mortality within 6 months if remains untreated.

Diagnosis of HRS requires exclusion of other pre-renal, renal or post-renal causes of renal dysfunction. Criteria for the diagnosis of HRS defined by the International Ascites Club are listed in Table 3 [18].

Table 3.Diagnostic criteria for hepatorenal syndrome

Major Criteria	
1.	Chronic or acute liver disease with advanced hepatic failure and portal hypertension
2.	Low glomerular filtration rate (serum creatinine > 1,5mg/dl (133μmol/l) or 24-hr creatinine clearance <40ml/min)
3.	Absence of shock, bacterial infection and current or recent treatment with nephrotoxic drugs
4.	Absence of gastrointestinal fluid losses
5.	Absence of renal fluid losses in response to diuretic therapy (weight loss>500 g/day for several days in patients without peripheral edema or 1000g/day in patients with peripheral edema)
6.	No improvement in renal function after diuretic withdrawal and administration of 1,5 liters of isotonic saline
7.	Proteinuria<500 mg/day and normal renal ultrasonography
Additional criteria	
1.	Urine volume<500 ml/day
2.	Urine Na ⁺ <10 mmol/l
3.	Urine osmolarity >plasma osmolarity
4.	Urine blood cells<50 per hpf
5.	Serum Na ⁺ <130mmol/l

c. AKI and Sepsis

In the ICU setting, sepsis is the cause of AKI in 30-50% of cases. In the context of multiple organ dysfunction syndrome AKI is associated with 70% mortality rate [19].

Although sepsis is characterized by generalized arteriolar vasodilation and resistance to the effect of vasoconstrictive substances, inside the kidney vasoconstriction takes place [20]. Endotoxemia triggers secretion of pro-inflammatory cytokines (TNFα), which in turn stimulate iNOs and increases production of NO [21]. Reduction of mean arterial pressure is sensed by baroreceptors and vasopressor systems are stimulated (SNS, RAA, ADH). In renal tubules the initial vasodilating action of iNOs subsides and the effect of endothelin and other vasopressors increase (TXA₂, leukotrienes, PAF). Endotoxemia induces inflammatory changes, increased production of reactive oxygen species (ROS) and complement' proteins, coagulation and activation of the fibrinolytic system. The end result is endothelial dysfunction with microthromboses [22]. The previously described pathophysiologic mechanisms contribute to the development and evolution of renal injury.

d. Drugs and Pre-Renal AKI

Drugs which act by altering intrarenal hemodynamics such as NSAIDs, ACE-i, ARBs and calcineurin inhibitors can cause pre-renal ARF.

More specifically, the non-selective cyclo-oxygenase inhibitors, COX-1 and COX-2 also inhibit the synthesis of vasodilating prostaglandins. Although they do not reduce GFR in healthy subjects, they can cause pre-renal ARF under certain conditions such as hypovolemia, dehydration, or pre-existing CKD [23]. Selective COX-2 inhibitors have a similar mode of action [24].

The ACE-i and the ARBs both inhibit angiotensin II effect on the efferent arteriole. They can induce reversible functional ARF in hypovolemic conditions, and also in the presence of renovascular disease on both kidneys or on a single kidney [25]. An increase of serum creatinine levels $\leq 30\%$ from the baseline value is acceptable after initiation of an ACE-I or an ARB.

The calcineurin inhibitors cyclosporine and tacrolimus, apart from a chronic, irreversible renal damage due to interstitial fibrosis, acutely induce constriction of the afferent arteriole through increased endothelin and TXA₂ synthesis resulting in reduction of GFR. This effect is considered dose-dependent and is reversible after drug discontinuation [26].

2.2. Intrinsic

2.2.1. Acute Tubular Necrosis Secondary to Ischemia or Drugs/Toxins

The commonest cause of intrinsic ARF is acute tubular necrosis (ATN) [27] (Table 4). It may be caused by ischemia or a direct toxic effect on the epithelial cell during reperfusion (ischemia reperfusion injury). Furthermore, ATN may complicate post-operative patients or can be secondary to drugs or toxins.

Table 4. Commonly causes of toxic acute tubular necrosis

1. Therapeutic agents
– Antimicrobial (aminoglycosides, amphotericin B, polymyxins, adefovir, cidofovir, tenofovir)
– Chemotherapy (cisplatin, ifosfamide)
– Biphosphonates (zoledronate, pamidronate)
– Hyperosmotic (mannitol, hydroxyethyl starch, sucrose, low molecular weight dextrans)
2. Iodized radiocontrast agents
3. Heme pigments (Hb, myoglobin)
4. Heavy metals (cadmium, mercury, lead, chromium, arsenic, bismouth, lithium)
5. Organic solvents (CCl ₄ , C ₂ Cl ₄)
6. Other toxins (paraquat, amanita phalloides)

The most vulnerable to ischemia parts of the tubules are the straight segment of the proximal tubule (S3) and the thick ascending segment of the loop of Henle which are located in the outer zone of the medulla.

Normally 90% of the RBF is distributed in the cortex serving the glomerular filtration and blood enters in the medulla with $pO_2 = 100$ mmHg. While flowing into the vasa recta pO_2

decreases progressively due to the increased metabolic demands of the epithelial cells. Consequently, the final segment of the outer zone of the medulla is relatively hypoxic ($pO_2=10-20$ mmHg).

The straight segment of the proximal tubule (S3) and the thick segment of the ascending loop of Henle are structures with high metabolic activity and energy requirements due to the function of basolateral Na/K ATP-ase pump.

Hemodynamic factors participate in the development of ischemic AKI, which in combination with endothelial dysfunction and inflammation result in epithelial damage [28, 29].

In ischemic ATN the following hemodynamic changes occur:

1. Altered renal autoregulation. Normally, when SBP ranges between 80-180 mmHg, adaptation of the intrarenal vessels is mediated by dilation of the afferent arteriole and constriction of the efferent arteriole (blood pressure effect) in order to maintain GFR. In ischemic ATN the above mechanism is destabilized probably due to the increased intracellular concentration of calcium in the proximal convoluted tubule [30].
2. Intrarenal vasoconstriction. In ATN the increased effect of vasoconstrictive substances such as angiotensin II, endothelin-1, PGH_2 , TXA_2 , adenosine, LTC_4 , and LTD_4 result in decreased RBF by 30-50% [31].
3. Endothelial and smooth muscle cell dysfunction with reduced production of vasodilatory amines (NO, PGE_2) and vascular tone derangement due to increased responsiveness to vasoconstrictors, decreased responsiveness to vasodilating agents and potent vasoconstrictive response to hypotension [31].
4. Inflammation. Ischemic ATN is characterized by increased synthesis of pro-inflammatory cytokines, chemokines and reactive oxygen species [32]. In the phase of ischemia-reperfusion there is increased endothelial expression of adhesive molecules VCAM and ICAM-1 which limits blood flow and activates polymorphonuclear cells, lymphocytes and endothelial cells. The net result is potent vasoconstriction [33].

The above hemodynamic changes lead to exhaustion of energy of the epithelial cell, increased intracellular Ca^{2+} , activation of phospholipases and proteases by the fibrated epithelium and intracellular acidosis. The final outcome is epithelial cell injury [34].

The following lesions of the epithelial tubular cell structure are observed:

- a. Degradation of actin cytoskeleton [35]. Transport of Na/K ATP-ase (36) and integrins α_3 and β_1 [37] to the luminal surface resulting in polarity loss and cell's detachment of the matrix.
- b. Epithelial cell apoptosis and necrosis [38]

These structural lesions lead IN epithelial cell detachment from the glomerular basement membrane, intratubular obstruction by epithelial cells that bind Tamm-Horsfall protein [39], and back leaking of infiltrate through epithelial cell clefts.

The epithelial cells participate in the inflammation via production of pro-inflammatory cytokines (TNF α , IL-1, IL-6), chemotactic factors (MCP-1, IL-8, RANTES, ENA-78), and TGF β [40].

The recovery phase of the epithelium is characterized by immigration of viable epithelial cells. These cells may either be dedifferentiated epithelial cells or a subpopulation of the progenitor cells derived from the renal tissue itself and not from the bone marrow. The reintroduction of growth factors like IGF-1 and HGF in the epithelium poses an important role in this process [41]. Bone marrow cells secrete factors which moderate inflammation and contribute to recovery [42].

Postoperative AKI

AKI frequently complicates major operations and its etiology may variate. Risk factors include the following:

- General health status and co-morbidities such as pre-existent CKD, diabetes mellitus, peripheral vascular disease, congestive heart failure or COPD.
- Type and duration of surgery. Most commonly AKI complicates cardiac, vascular or hepatobiliary surgery.
- Hypotensive effect of anesthesia, duration of cardio-pulmonary bypass, fluid and blood losses.
- Fluid imbalance, sepsis and administration of nephrotoxic drugs during the post-operative period.

The incidence of AKI after cardiac surgery, defined as the >50% reduction of eGFR from baseline, reaches 10%, while AKI requiring renal replacement therapy decreases in less than 5% of the cases [43, 44]. An increase in serum creatinine >0.3 mg/dl constitutes an independent risk factor of morbidity and mortality [45]. The incidence of AKI after heart transplantation is lower (6%) probably due to the use of immunosuppression regimen [46].

Toxic Acute Tubular Necrosis

The kidney is the site in which drugs, substances used for diagnostic and therapeutic purposes, as well as environmental factors are metabolized and excreted. Many of these substances exert a toxic effect. The most common nephrotoxins are summarized in Table 4.

There is a wide variability in the presentation and severity of toxic ATN. This is due to the complexity of predisposing factors that can be classified into three categories [47]:

1. Patient-specific: age>65 years, female sex, dehydration, pre-existent chronic kidney or liver disease, electrolyte disorders (e.g. hyperkalemia or hypomagnesemia) or abnormal urine pH, liver or kidney enzymatic system or transporter mutations.
2. Kidney-specific: increased blood flow, increased sensitivity of the tubular segments of the outer medulla (S3 of the proximal convoluted tubule, thick ascending limb of the loop of Henle) with high energy rhythm that functions under conditions of marginal hypoxia, increased drug intake by the proximal convoluted tubule through endocytosis or membrane anionic and cationic transporting systems.

3. Drug-specific: direct nephrotoxic effect, prolonged administration at high doses, concomitant use of nephrotoxins, competition between endogenous and exogenous toxic substances for the transport systems.

A. Antimicrobial Agents

1. Aminoglycosides

The nephrotoxicity of the aminoglycosides is due to their cationic load (number of NH_4^+). After intravenous administration they are not metabolized but excreted through glomerular filtration. In the proximal convoluted tubule aminoglycosides bind with the anionic membrane phospholipids and enter the cell via endocytosis mediated by the megalin protein receptor. In the lysosomes they inhibit the action of phospholipases resulting in accumulation of phospholipids and formation of myeloid bodies. These are filamentous structures consisting of membrane segments and destroyed organelles. Hereupon follows the rupture of lysosomal membranes, accumulation of aminoglycosides and myeloid bodies in the cytoplasm and epithelial cell death [48].

The clinical picture of aminoglycoside-associated AKI is characterized by polyuria and proximal tubular dysfunction with glycosuria and loss of electrolyte (potassium, phosphate, magnesium), as well as Type 2 renal tubular acidosis. Reduction of GFR occurs after 5-7 days. Aminoglycoside-associated AKI has generally favorable prognosis and renal function normalizes in 4-6 weeks. Risk factors for the development of aminoglycoside-associated nephrotoxicity are advanced age, dehydration, pre-existent CKD, diabetes mellitus, liver disease, sepsis, metabolic acidosis, hypokalemia, hypomagnesemia, and concurrent administration of other nephrotoxic agents [49].

2. Amphotericin B

Amphotericin B acts through binding of cell membrane's sterols of the fungal wall resulting in pore formation. The binding of cell membrane cholesterol in the tubular epithelial cells, as well as the formation of pores increases ion permeability resulting in cell swelling, exhaustion of energy and, finally, cell lysis. Deoxycholate contributes to the pathogenesis of kidney damage. It is the solvent of the standard formulation of amphotericin B that exerts direct nephrotoxic effect [50].

Amphotericin B nephrotoxicity is dose-dependent. It is low at daily doses less than 0.5 mg/kg of body weight or a total dose less than 600 mg and increases at total doses above 2-3g.

Kidney damage from amphotericin B is located in the distal convoluted tubule. Epithelial injury is manifested with loss of urine concentration and polyuria, waste of potassium and magnesium and, finally, distal renal tubular acidosis. Renal function recovers after several months.

3. Polymyxin

Colistin is an antibacterial agent, effective against gram negative, multiresistant organisms. It causes dose-dependent renal damage in up to 20% of cases. D-amino acid and fatty acid component increases permeability of the epithelial cell membrane resulting in cation and water insertion and cell lysis [51].

4. Antiretrovirals

Adefovir, a nucleoside HIV-reverse transcriptase analogue enters the proximal convoluted tubule through the organic anion transporter-1 (OAT-1), inhibits DNA γ -polymerase in the mitochondria causing cell damage. Tenofovir causes similar mitochondrial damage, while cidofovir after entering the proximal convoluted tubule through the OAT-1 forms a complex with phosphocholine which influences the synthesis of membrane phospholipids [52]. Within the kidney these antivirals cause tubular dysfunction manifested with Fanconi syndrome, nephrogenic diabetes insipidus or ATN that may lead to AKI. On biopsy severe mitochondrial damage and ATN with intact glomeruli are found. However, renal replacement therapy is rarely needed.

B. Chemotherapeutic Agents

Cisplatin is an alkylating agent used in the treatment of solid tumors. It exerts dose-dependent nephrotoxicity in up to 20% of patients receiving high doses [53]. Cisplatin enters the cell through the organic cation transporter-2 and reaches the highest concentrations in the S3 segment of the proximal convoluted tubule [54]. Inside the cell it is metabolized to toxic thioles whereas in conditions low in intracellular chloride it forms monohydrate complexes which are toxic as well [55, 56]. Cisplatin alters the expression of many genes which regulate cellular structure and function, induces oxidative stress through the increased production of ROS and RNS (reactive nitrogen species) as well as apoptosis via direct stimulation of caspase-3. Stimulation of the transcription factor NF-Kb increases synthesis of cytokines (TNF α), chemokines (MCP-1), adhesive molecules and TGF β resulting in inflammation and fibrosis (53).

Renal dysfunction appears 48-72 hours after the administration of the drug and is manifested with polyuria and loss of electrolyte (Na⁺, K⁺, Mg²⁺, and Ca²⁺). Permanent kidney damage occurs after prolonged administration of high doses.

C. Bisphosphonates

Bisphosphonates exert anti-osteoclastic action and are indicated for the treatment of osteoporosis (post-menopausal, corticosteroid-induced), hypercalcemia of malignancy, osteolytic metastases and Paget's disease. They chelate calcium and stabilize hydroxyapatite crystals in the bone matrix. Their anti-resorptive action is accomplished through the inhibition of the mevalonate metabolic pathway resulting in derangement of many intracellular functions and degradation of cell cytoskeleton [57]. Nitrogen-containing zoledronate is not metabolized and is excreted unchanged in the urine. Its intrarenal half-life is long [58]. In the tubular epithelial cell causes ATN [59]. Kidney damage is usually reversible when zoledronate is early discontinued. However, prolonged administration may lead to permanent damage.

Pamidronate is toxic to the podocyte and induces collapsing FSGS. However, cases of ATN have been described as well [60].

Osmotic nephrosis occurs after the administration of hyperosmolar agents (mannitol, hydroxyethyl starch, sucrose, low molecular weight dextrans, first or second generation iodine contrast agents). Histologically it is characterized by focal and less frequently diffuse isometric vacuolization and edema of the proximal convoluted tubule with preservation of the brush border. The vacuoles contain the osmolar agent along with lysosomal enzymes [61].

The functional AKI that develops usually subsides after withdrawal of the offending agent. However, in up to 40% of cases temporary renal replacement therapy may be needed [62].

D. Radiocontrast Nephropathy (Contrast-Induced Acute Kidney Injury)

The incidence of radiocontrast nephropathy (contrast-induced acute kidney injury, CI-AKI) has risen due to the extensive use of contrast agents for diagnostic and therapeutic purposes (CT scan, intravenous pyelography, angiography, coronary artery angiography etc.). It is defined as an increase of serum creatinine of at least 0.5 mg/dl and/or 25% reduction of GFR from baseline within 48 hours after exposure to the IV contrast. It is the third most common cause of nosocomial AKI, with an incidence as high as 11% [63]. The presence of risk factors such as CKD [64], diabetes mellitus [65], use of ionic high-osmolar contrast agents, dehydration, concurrent use of nephrotoxic agents (NSAIDs, ACE-I, cyclosporine) [66] increase the likelihood of CI-AKI. Although nephropathy is usually non-pliguric, 7% of the patients will need dialysis or will develop ESRD [67].

The pathogenesis of CI-AKI is not yet fully clarified. The contrast agent causes a biphasic alteration in renal microcirculation. Initially, temporary vasodilation, lasting only a few seconds, is observed followed by intense vasoconstriction mainly mediated by adenosine [68], endothelin, and increased intracellular calcium concentration. This vasoconstrictive response seems to be the result of the activation of the tubuloglomerular feedback mechanism in macula densa by the hyperosmotic fluid. The iodine contrast agents inhibit synthesis of vasodilatory NO and prostaglandins, while induce direct tubular injury to the epithelial cell through increased production of reactive oxygen species (ROS).

E. Heme Pigments

Hemoglobin and myoglobin can exert direct toxic effect to the tubular epithelial cell.

1. Hemoglobinuria. Conditions in which intravascular hemolysis occurs such as transfusion of incompatible blood, hematological disorders (autoimmune hemolytic anemia, G6PD deficiency, paroxysmal nocturnal hemoglobinuria [69]), infections (malaria), drugs (dapsone), and prosthetic valves or valvular heart disease [70] can cause hemoglobinuria.

The presence of heme proteins inside the tubular epithelial cell can cause injury through three main mechanisms [71]:

- Direct cytotoxic effect. The heme molecule exerts pro-inflammatory, oxidative and apoptotic effects. Mitochondria are particularly vulnerable [72], their function is deranged and accumulate into autophagic vacuoles.
- Induction of renal vasoconstriction
- Interaction with Tamm-Horsfall protein and formation of cylinders.

2. Rhabdomyolysis. Rhabdomyolysis is a syndrome characterized by skeletal muscle damage and release of organic and inorganic intracellular components into the circulation. It is a life-threatening condition caused by crush injuries, drugs, toxins or infections [73] (Table 5).

Independently of the etiology the depletion of energy in the muscle cell which in turn causes dysfunction of the sarcolemma transporters (Na^+/K^+ ATPase, Ca^{2+} ATPase) consists

the main pathophysiologic mechanism. The influx of Na^+ and H_2O causes osmotic lysis, while the accumulation of Ca^{2+} stimulates proteases. Cell death results in release of enzymes (CK, LDH, AST, aldolase), electrolytes (potassium, phosphate), heme pigments (myoglobin), uric acid and lactate [74].

Development of acute renal failure in rhabdomyolysis is based on three main factors:

- Myoglobin's nephrotoxic effect. Myoglobin is a small molecule with a molecular weight of 17 kD. It undergoes glomerular filtration and is reabsorbed in the apical convoluted tubule. Inside the lysosomes myoglobin is degraded into ferriheme and globin with subsequent deposition of Fe^{2+} into ferritin. In the case of rhabdomyolysis, increased intracellular concentration of myoglobin causes liberation of Fe^{3+} and formation of OH^- (Fenton reaction) [75].
- Hypovolemia and dehydration cause renal vasoconstriction which in turn exacerbates the toxic effect of myoglobin [76].
- Intratubular formation of cylinders. Apoptosis of the renal epithelium and hyperuricemia contributes to the tubular obstruction.

Table 5. Causes of rhabdomyolysis

I. Traumatic or physical factors-related

1. Trauma (crush syndrome)
2. Excessive muscular activity (strenuous exercise, status epilepticus, status asthmaticus, severe dystonia)
3. Prolonged immobilisation (anaesthesia, coma)
4. High voltage electric injury (lightning strikes, electrocution by high-voltage power supplies)
5. Temperature extremes (heat stroke, neuroleptic malignant syndrome, malignant hyperthermia syndrome)

II. Non traumatic

1. Drugs and toxins
 - statins, fibrates,
 - antipsychotics (phenothiazines, haloperidole, phenylpropanolamine)
 - antidepressants and sedatives (SSRIs, barbiturates, benzodiazepines)
 - anaesthetics and paralytics (halothane, propofol, succinylcholine)
 - other drugs (corticosteroids, daptomycin, salicylates, quinine, theophylline, ϵ -aminocaproic acid)
 - alcohol, methanol, ethylene glycol, toluene, heroin, methadone, cocaine, caffeine, ecstasy
 - venoms (snakes, spiders, bees)
 2. Infections
 - viral (influenza, EBV, CMV, HIV, herpes simplex, varicella, ECHO virus, Coxsackie, West Nile virus)
 - bacterial (Legionella, Salmonella, Streptococcus, Staphylococcus aureus, Leptospira, E. Coli)
 - -ther (Mycoplasma, fungi, malaria falciparum)
 3. Electrolyte disorders (hypokalemia, hyponatremia, hypernatremia,)
 4. Endocrine disorders (hypothyroidism, hyperthyroidism)
 5. Genetic disorders (deficiencies of glycogenolytic enzymes, Duchene's muscular dystrophy, Becker's muscular dystrophy)
 6. Connective tissue disorders (polymyositis, dermatomyositis)
 7. Unknown
-

Abbreviations: EBV, Epstein- Barr virus; CMV, cytomegalovirus; HIV, human immunodeficiency virus; ECHO, enteric cytopathic enteric orphan.

a. Crush syndrome

Rhabdomyolysis may occur after extensive trauma and crush injury during natural disasters (earthquakes, bombing) [77]. During muscle crushing, tissue damage progresses in two phases: initially ischemia and ATP depletion occurs while tissue reperfusion follows thereafter. The second phase is characterized by increased vascular permeability with edema, inflammation and increased production of ROS. Prolonged ischemia and fluid loss inside the fascia are further complicated with the development of compartment syndrome, the management of which requires mechanical decompression with incision of the muscle fascia. [78]. Vigorous exercise [79], status epilepticus [80], tissue ischemia during ligation of large vessels intraoperatively [81] and prolonged postoperative recumbency or coma can cause rhabdomyolysis. Natural causes of rhabdomyolysis are lightning injuries [82] and extreme environmental temperatures (heat stroke or exposure to cold) [83] can also cause muscle injury (75).

b. Drug-induced rhabdomyolysis

The incidence of statin-induced rhabdomyolysis is approximately 0.04-0.2% (84). The underlying pathophysiology is unclear. Decreased cholesterol concentration in the sarcolemma [85] or decreased intracellular ATP after depletion of mevalonic acid and co-enzyme Q10 [86] may contribute to its development. Toxicity is dose-dependent and the risk is higher when a statin is co-administered with drugs that inhibit CYP3A4 system (macrolides, cyclosporine, fibrates) [87].

Other drugs that may cause rhabdomyolysis are corticosteroids [88], daptomycin [89], fibrates [90], SSRI [91], and propofol [92].

c. Toxin-induced rhabdomyolysis

Alcohol has a direct toxic effect in muscles, while factors such as hypokalemia, delirium tremens or alcoholic coma also contribute to muscle lesion[93].

The use of heroin, cocaine, ecstasy and amphetamines is etiologically connected with rhabdomyolysis [94]. Moreover, rhabdomyolysis has been reported after snakebites, spider venoms and bee sting [95-97].

d. Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a complication of antipsychotic agents (phenothiazines, haloperidol, lithium). It is caused due to dopaminergic block in the hypothalamus and is manifested clinically with hyperpyrexia, generalized seizures and rhabdomyolysis [98].

e. Malignant hyperthermia

Malignant hyperthermia may occur after administration of volatile anesthetics e.g. halothane or the neuromuscular blocker succinylcholine. A mutation of ryanodine receptor in the sarcolemma leads to intracellular accumulation of Ca^{2+} [99].

Other non-traumatic causes of rhabdomyolysis are infections [100], (viral, bacterial of fungal), electrolyte disturbances (hypokalemia [101]), hypothyroidism [102], hereditary [103] and immune disorders [104].

F. Heavy Metals

Cadmium forms a toxic complex with a protein named metallothionein in the proximal convoluted tubule. Its biological half life is >10 years. Chronic exposure to cadmium causes dysfunction of the proximal tubule, while ARF occurs after an acute exposure to high concentrations. Lead can cause injury of the proximal convoluted tubule, as well as nuclear inclusion formation. Acute intoxication is manifested with Fanconi syndrome or ARF [105]

Chemical compounds containing mercury can cause injury to the proximal convoluted tubule after binding the sulphhydryl groups in the lysosomes and phospholipids [106]. Accidental or intentional intoxication with HgCl₂ causes ATN.

Chromium intoxication and arsenic causes ATN. Lithium is a metal cation used in psychiatry for the treatment of bipolar disorder. Acute lithium nephropathy is manifested with diabetes insipidus [107]. Adenyl-cyclase inhibition results in decreased expression of AQP-2 water channels in the apical membrane of the collecting duct. The cellular damage is dose-dependent and reversible.

G. Ischemia-Reperfusion Injury

Ischemia-reperfusion injury plays a critical role in the pathogenesis of delayed graft function after renal transplantation. The incidence of this early complication is 25-30% [108], and is associated with high rates of acute rejection and reduction of the long-term graft survival [109]. Ischemia-reperfusion injury can also occur following major operation and especially in the ICU setting (see Prevention below). Reperfusion of kidney tissue after a period of ischemia leads to organic damage through the following mechanisms:

- Increased production of ROS [110] which results in lipid, protein and nucleic acid peroxidation, stimulation of the transcription factors NF-Kb and AP-1, expression of cytokine genes and adhesion molecules, as well as increased synthesis of arachidonic acid metabolites such as TXA₂ and LTB₄ which chemotactic activity [111]
- Activation of the complement cascade [112], through the alternative, as well as mannose-binding lectin pathway [113].

Factors C5a and C5b-9 stimulate the secretion of inflammatory mediators (pro-inflammatory cytokines, chemokines and adhesion molecules)

- Chemotaxis of WBC, and inflammation [112]

The WBC pass through the endothelial cells and reach the interstitium as follows:

- a. Loose adhesion of the WBC to the endothelium through selectin's binding to its receptor PSGL-1.
- b. Firm adhesion follows through binding of ICAM-1 to the integrins CD11a/CD18 and CD11b/CD18.
- c. Endothelial transmigration via the adhesion molecule PECAM-1.

In the intersitium the activated WBC release proteolytic enzymes and ROS, resulting in increased capillary permeability and edema, formation of microthrombi and cellular death.

There is growing evidence that lymphocytes participate in renal ischemia reperfusion injury not only by potentiating the inflammatory response but also through participating in the tissue healing response [114]

H. Acute Interstitial Nephritis (AIN)

Inflammatory damage of the kidney interstitium and tubules is a common cause of ARF that reaches 15-27% of histological samples from renal biopsies [115]. In more than 70% of cases it is drug-induced, while other causes of AIN are infections, systemic autoimmune diseases or idiopathic (Table 6). Although most cases have mild presentation, a 36% will eventually develop ESRD [116].

Table 6. Commonly causes of acute interstitial nephritis

1. Drugs	
–	antibiotics (β-lactams, sulfonamides, fluoroquinolones, rifampicin, vancomycin, erythromycin, minocycline)
–	NSAIDs and selective COX-2 inhibitors
–	5-Aminosalicylates (sulphasalazine, mesalazine, olsalazine)
–	proton pump inhibitors, histamine H ₂ receptor antagonists
–	diuretics
–	antiepileptics (Phenytoin, valproic acid, carbamazepine)
–	others (allopurinol, cyclosporine, anti-VEGF)
2. Infections	
–	viral (CMV, EBV, HIV, hantavirus, poliovirus)
–	bacterial (Legionella, Brucella, Streptococcus, Staphylococcus, Salmonella, Yersinia, E. Coli, Leptospira)
–	others (Mycoplasma, Mycobacterium tuberculosis, Schistosoma, Toxoplasma)
3. Systemic/autoimmune disorders	
–	SLE, Sjögren’s syndrome, Wegener’s granulomatosis, sarcoidosis
–	TINU syndrome
–	IGg ₄ immune complex with autoimmune pancreatitis
4. Idiopathic	

Abbreviations: NSAIDs, non steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; VEGF, vascular endothelial growth factor; CMV, Cytomegalovirus; EBV, Epstein- Barr virus; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus; TINU, tubulo-interstitial nephritis and uveitis.

Usually AIN is the result of a delayed-type hypersensitivity reaction (type IV) in which T-lymphocytes predominate. The antigen against which the immune response is directed may be exogenous or endogenous. When the antigen is of exogenous origin it is inoculated into the interstitial tissue, binding to a normal protein of the tubular basement membrane. In this case the exogenous antigen serves as a hapten. Alternatively, the antigen may present similar molecular structure with the tubular basement membrane. The immune response results in inflammatory infiltration of the tubulointerstitial tissue composed of lymphocytes, monocytes, eosinophils and plasmacytes. Hypersecretion of cytokines and growth factors stimulates production of extracellular matrix (collagen, laminin, fibronectin) and activation of fibroblasts. Consequently, interstitial fibrosis develops [117].

AIN is manifested with non oliguric AKI, proximal and distal tubular dysfunction and mild proteinuria. Hypersensitivity-associated signs and symptoms (fever, rash, arthralgias, arthritis, and myalgias) are present with various incidence. The classic triad of fever, rash and eosinophilia concerns only the 10-15% of cases [118]. Urine microscopy may show WBC, epithelial cells and eosinophils.

Diagnosis is made by renal biopsy which shows focal or diffused inflammation and interstitial edema as well as tubular inflammation. The presence of granulomas is rare in drug-induced AIN, being more commonly present in sarcoidosis and mycobacterial infections. Immunofluorescence is usually negative but granular or linear deposits can be found in systemic disorders. In NSAID-induced AIN electron microscopy reveals podocyte fusion resembling minimal change nephropathy.

Drug-Induced AIN

It is the most common cause of AIN representing an idiosyncratic allergic reaction. The list of the offending drugs is very long. However, the most common categories are the following:

1. **Antibiotics.** Beta lactams (penicillins, cephalosporins) are frequently implicated in hypersensitivity reactions with renal involvement. Methicillin-induced AIN is the historical prototype, evolving secondary to the formation of antibodies against tubular basement membrane. Fever, rash, or eosinophilia develop in >75% of cases and help to establish diagnosis [119]. Sulphonamides can cause hypersensitivity reaction and AIN when administered in patients with HIV infection or transplant recipients [120].
Among fluoroquinolones ciprofloxacin is the most commonly incriminated drug, although cases concerning other members of this antibiotic class have been reported [121]. Rifampicin can cause severe, dose-dependent AIN with oliguric ARF that commonly needs renal replacement therapy (RRT) [122].
2. **NSAIDs including COX-2 inhibitors.** NSAID-induced AIN has specific features [123]. It can occur even after 6-18 months of treatment. Usually it is not associated with fever, rash or eosinophilia but proteinuria of nephrotic type may be present. Renal biopsy shows mildly inflammatory changes of the tubules and interstitium, while electron microscopy may reveal podocyte changes similar to those observed in minimal change disease. Rare cases of granulomatous AIN have also been described [124]. Selective COX-2 inhibitors have been implicated for inducing AIN with similar clinical and histological features to NSAIDs [125].
3. **5-Aminosalicylates.** Sulfasalazine and the newest derivatives mesalazine and olsalazine used in the treatment of inflammatory bowel disease can cause AIN in 1:200-1:500 cases, most commonly during the first 12 months of treatment. Prognosis of the disease is favorable in case of a prompt diagnosis [126, 127].
4. **Protein-pump inhibitors.** They can cause mild renal injury. The classical hypersensitivity features (fever, rash, and eosinophilia) are usually absent [128].

Diseases of the Glomeruli and the Small Vessels

I. Glomerulonephritis

ARF is frequently the first clinical presentation of glomerulopathies characterized by extensive intracapillary or extracapillary hyperplasia e.g. post-streptococcal glomerulonephritis and rapidly progressive glomerulonephritis with crescent formation. Rapidly progressive glomerulonephritis is clinically characterized by rapid deterioration of renal function within weeks or months and histologically by formation of the crescents. It is classified into five types depending on the underlying pathogenetic mechanism (Table 7):

1. Type 1 [anti-GBM disease (Goodpasture's syndrome)]. It is caused due to anti-GBM antibody deposition along the inner zone of the GBM that targets α_3 chain of NC-1 (non collagen-1 domain of type IV collagen)
2. Type 2 (immune complex mediated crescentic glomerulonephritis). Deposition of immunocomplexes (circulating or formed in situ) and complement along GBM and/or the mesangium triggers the inflammatory response.
3. Type 3 (pauci-immune, ANCA positive). It is characterized by the lack of immune deposits on Immunofluorescence and the presence of circulating ANCA against MPO (p-ANCA) or against proteinase-3 (c-ANCA).
4. Type 4 (anti-GBM positive, ANCA positive)
5. Type 5 (anti-GBM negative, ANCA negative)

The characteristic histologic finding is the crescent formation. These structures consist of proliferating splachnic or parietal epithelial cells, inflammatory cells (polymorphonuclear lymphocytes, macrophages, T-lymphocytes), and fibroblasts [129]. Rupture of the GBM wall and Bowman's capsule results in fibrin insertion in the Bowman's space. Inflammatory cells are attracted into the space and immune response is initiated. Local production of cytokines (TNF α , IL-1), chemokines (MCP-1, MIF) and TGF β play a pivotal role [130]. Macrophages interact with parietal epithelial cells via integrins CD11/CD18 and VLA-4 and their ligands ICAM-1 and VCAM-1 [131]. During the course of disease the cellular crescents convert to fibrocellular and finally to fibrotic. In this process migration of myofibroblasts from the interstitium as well as collagen deposition play a central role [132].

Crescents may have focal or diffuse distribution, be segmental or circumferential and differentiate as cellular, fibrocellular or fibrotic. The extension and the characters are of prognostic value. Diffuse involvement (>50% of glomeruli) with circumferential, fibrocellular crescents has poor prognosis [133].

II. Thrombotic microangiopathies

In the congenital form TTP/HUS is caused due to deficiency of ADAMTS13 (A Disintegrin-like And Metalloprotease with ThromboSpondin type-1 repeats), a cleaving metalloprotease that degrades the large von Willebrand factor (vWF) multimers into normal size multimers [134-136]. It is characterized by very low activity in the plasma (2-7% of the normal levels) [137]. The result is the accumulation of large multimers of vWF., which induce platelet aggregation and clumping [138].

Table 7. Classification and common causes of crescentic glomerulonephritis

Type 1: Anti-GBM antibody mediated disease	1. Primary <ul style="list-style-type: none"> – renal- limited (without pulmonary hemorrhage) – Goodpasture’s disease (with pulmonary hemorrhage) – superimposed on another primary glomerulonephritis 2. Secondary <ul style="list-style-type: none"> – viral infection (HIV, influenza, hantavirus) – tumors (lymphoma, lung carcinoma) – volatile hydrocarbons – renal trauma (extra-corporeal shock wave lithotripsy)
Type 2: Immune complex mediated disease	1. Primary <ul style="list-style-type: none"> – renal-limited – superimposed on another primary glomerulonephritis (Ig A nephropathy) 2. Secondary <ul style="list-style-type: none"> – multisystem disease (SLE, purpura Henoch-Schönlein, cryoglobulinemia) – infection (post-streptococcal, HBV, HCV, endocarditis)
Type 3: ANCA-associated crescentic glomerulonephritis (pauci-immune necrotizing and crescentic glomerulonephritis)	1. Primary <ul style="list-style-type: none"> – renal-limited (renal-limited microscopic polyangiitis) 2. Secondary <ul style="list-style-type: none"> – multisystem disease (Wegener’s granulomatosis, systemic microscopic polyangiitis, Churg- Strauss syndrome) – drugs (propylthiouracyl, penicillimamine, minocycline) – environmental toxins (silica)
Type 4: Double antibody disease (anti- GBM antibody and ANCA positive)	Combination of types 1 and 3
Type 5: Idiopathic (anti- GBM antibody and ANCA negative)	Primary

Abbreviations: GBM, glomerular basement membrane; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus; HBV, hepatitis B virus; HCV, hepatitis C virus; ANCA, anti neutrophil cytoplasmic antibody.

HUS is divided into diarrheal and nondiarrhea-associated (atypical HUS, aHUS). In childhood most cases of HUS are due to *E. coli* O157:H7 which produces the Shiga-like toxin. This can be found in undercooked or partially cooked meat or beef, unpasteurized milk products or juices. Reaching the circulation Shiga-like toxin can cause red blood cell destruction. The released hemoglobin may cause tubular obstruction leading in ARF. The toxin also induces intravascular thrombogenesis and endothelial dysfunction through two mechanisms: inhibition of protein synthesis and necrosis or apoptosis of the endothelial cells. The endothelial damage itself promotes the formation of microthrombi and result in renal ischemia [139, 140].

Atypical HUS (aHUS) consists approximately 10% of HUS in children. There are congenital and acquired forms. Regarding the congenital form, numerous mutations on chromosome 9q34, containing the protease gene, have been identified [137]. A plethora of other pathogenetic mechanisms leading to the development of HUS have been implicated. These mechanisms include endothelial injury [141, 142], increased levels of plasminogen-

activator inhibitor type-1 (PAI-1) [143, 144], lack of a platelet inhibitor, mutations of complement regulation, and other osmotic factors. Conditions associated with HUS are cancer, chemotherapeutic agents (mitomycin C, cisplatin, gemcitabine), radiation therapy, high-dose chemotherapy and hematopoietic cell transplantation. Quinine which is a drug commonly used for treating malaria has also been related [145]. Atypical HUS is characterized by insidious onset and relapsing course, sometimes leading to severe AKI [146].

Table 8. Thrombotic microangiopathies

I. Idiopathic TTP/HUS	
–	genetic or immune-mediated abnormalities of ADAMTS13
–	genetic or immune-mediated deficiencies of complement’s proteins (factor H, membrane cofactor protein) (nondiarrhea-associated [atypical] HUS)
II. Secondary TTP/HUS	
1.	infections (<i>E. Coli</i> O157: H7, <i>S. pneumoniae</i> , HIV, CMV, <i>Aspergillus</i>) diarrhea-associated HUS
2.	Nondiarrhea-associated HUS (atypical HUS)
a.	drugs
–	chemotherapy (mitomycine C, bleomycin, tamoxifen, cisplatin)
–	other (ticlopidine, clopidogrel, quinine, calcineurin inhibitors, IFNa, OKT3)
b.	bone marrow transplant
c.	pregnancy, postpartum
III. Systemic disease-associated TMA	
–	antiphospholipid syndrome
–	scleroderma
–	malignant hypertension
–	malignancy
IV. Pregnancy-associated TMA	
–	HELLP syndrome

Abbreviations: TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; HIV, human immunodeficiency virus; CMV, cytomegalovirus; IFNa, interferon-a; TMA, thrombotic microangiopathy; HELLP, Hemolysis Elevated Liver enzymes and Low platelets.

Both disorders are characterized by fever, thrombocytopenia, microangiopathic hemolytic anemia, renal failure (HUS), and neurological abnormalities (TTP). Thrombotic microangiopathies are summarized in Table 8.

3. Post-Renal

Complete obstruction of the renal flow at any level along the renal excretory system leads to ARF within hours. Early management minimizes the risk of permanent kidney damage. Depending on the site of obstruction it is classified into intratubular, upper or lower urinary tract obstruction (Table 8). During the first six hours following an acute obstruction, intratubular hydrostatic pressure progressively increases. This rise is gradually transferred into the renal pelvis and renal parenchyma resulting in GFR reduction. Increased RBF is observed in the first hour due to the activation of the tubuloglomerular feedback mechanism

which and the stimulated production of vasodilating prostaglandins in the afferent arteriole. However, over the next hours release of local vasopressors (TXA₂, angiotensin II) as well as decreased synthesis of NO result in vasoconstriction and decline of GFR and RBF [147]. After the first six hours ureteric pressure declines due to distension and inhibited peristalsis. However, GFR and RBF continue to be low. Obstruction influences normal tubular function and as a result concentration disturbances, Type 1 renal tubular acidosis and potassium loss appear. Nevertheless, reduced GFR, acidosis and distal tubular resistance to aldosterone ameliorate potassium excretion. Relieve of obstruction is associated with post-obstructive polyuria with water and electrolyte loss (K⁺, Na⁺ and Mg²⁺).

Crystal-Induced Nephropathy

Crystal-induced nephropathy includes myeloma cast nephropathy, tumor lysis syndrome, drug-induced crystalluria and phosphate nephropathy.

Table 9. Common causes of postrenal acute renal failure

A. Intratubular obstruction

1. Crystal nephropathy
 - tumor lysis syndrome
 - drugs (acyclovir, methotrexate, indinavir, azatanavir, ciprofloxacin, foscarnet)
 - acute phosphate nephropathy
 - hypervitaminosis C
 - ethylene glycol intoxication
2. Cast nephropathy
 - myeloma kidney
 - heme pigments (hemoglobin, myoglobin)

B. Obstruction of the upper urinary tract

1. Intraluminal
 - stones, blood clots, papillary tissue
2. Intramural
 - tumors
 - pelvic-ureteral or vesicoureteral junction dysfunction
3. Extrinsic causes
 - reproductive system (tumors)
 - retroperitoneal space (fibrosis, lymph nodes, tumors, hematomas, radiation therapy)

C. Obstruction of the lower urinary tract

1. Prostatic causes
 - benign prostatic hyperplasia/prostatic carcinoma
 2. Urinary bladder causes
 - tumors, calculi
 - neurogenic bladder (spinal cord trauma, cerebrovascular accidents, diabetes, multiple sclerosis, Parkinson's disease)
 3. Urethral causes
 - strictures (trauma, postinstrumentation, infections)
-

1. Myeloma cast nephropathy

The presence of monoclonal light chains inside the renal tubules results in cast formation, giant cell reaction and interstitial fibrosis [148].

Light chains are normally filtered in the glomeruli and reabsorbed in the proximal convoluted tubule. After degradation by lysosomic enzymes they return to the circulation. Multiple myeloma is characterized by increased production of monoclonal light chains which exceeds the reabsorptive tubular capacity leading to light-chain proteinuria (Bence-Jones). Direct toxic effect of the abnormal proteins in the proximal convoluted tubule [149] as well as cast formation comprised of light chains and Tamm-Horsfall protein [150] contribute to renal injury. The risk increases with dehydration, low urine pH and increased tumor burden.

2. Tumor lysis syndrome

Lysis of tumor cells spontaneously or after treatment, leads in uric acid, potassium, phosphate, as well as cytokine release. It occurs in hematologic malignancies (non-Hodgkin lymphomas, leukemias) and manifests with ARF, convulsions, arrhythmias and sudden death [151].

The main mechanism of kidney injury is tubular obstruction by urate, calcium phosphate crystals and xanthine. Increased concentrations of these substances inside the tubular lumen favor the formation of crystals. Crystal solubility is influenced by urine pH, urine flow and hydration state of the patient [152].

Apart from the above mechanism uric acid causes renal damage through vasoconstriction, disturbances of renal autoregulation, oxidation and inflammation [153]. The massive cytokine release from cancer cells induce hypotension and inflammation [154]. The ARF is usually severe with anuria and dangerous electrolyte disturbances that require prompt and intensive management.

3. Drug-induced crystalluria

Acyclovir [155], methotrexate [156], the protease inhibitors indinavir [157], and atazanavir [158], as well as ciprofloxacin [159] promote crystal formation.

4. Phosphate nephropathy

Sodium phosphate-containing laxatives used for bowel preparation prior to colonoscopy may lead in calcium-phosphate crystal precipitation and ATN [160]. Most cases occur after oral administration. Absorption of large amounts of phosphate in conjunction with dehydration caused by diarrhea result to the release of huge amounts of calcium phosphate into the distal convoluted tubules and the collecting duct with subsequent formation of crystals. The ARF progresses into CKD.

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Chapter XI

Renal Failure: Prevention

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Abstract

The first step in the prevention of acute kidney injury (AKI) is to recognize people at risk. Advanced age, dehydration, diabetes mellitus, chronic kidney disease, heart failure and nephrotoxic substances are the most important risk factors. When the use of a nephrotoxic agent is absolutely necessary the exposure must be limited especially in patients at risk and renal function tests must be closely monitored. Moreover, adequate fluid intake is important in order to avoid dehydration and maintain normovolemia. One of the most commonly recognized nephrotoxins are the intravenous contrasts used for imaging. The prevention of contrast-induced AKI has been widely investigated and several measures have been tested: intravenous isotonic saline (0.9%) or bicarbonate infusion, hypotonic saline (0.45% or dextrose 5% in water), oral hydration, fluid restriction, mannitol, low- and iso-osmolar versus high-osmolality contrasts, theophylline, statins, N-acetylcysteine, and prophylactic hemofiltration. Isotonic saline and bicarbonate infusion have both shown clear benefit. N-acetylcysteine, although questioned by some investigators, has shown benefit in most studies. The use of iso- or low osmolality contrast agents is recommended in patients at risk of AKI, such as diabetics as well as patients with pre-existent kidney impairment. Prophylactic hemofiltration is expensive but has shown benefit. In perioperative situations, normovolemia pre- and post-surgery decrease the risk of AKI after surgery. In patients undergoing cardiopulmonary bypass surgery fenoldopam reduces the incidence of AKI. The earliest administration of isotonic saline and isotonic bicarbonate decrease the risk of AKI following rhabdomyolysis. Finally, the use of rasburicase plus intravenous saline hydration reduce the risk of tumor lysis syndrome and AKI in cancer patients undergoing chemotherapy. In recent years, investigators have focused on the discovery of serum or urine markers that can detect the development of AKI at an early stage. The studies have

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shown promising results, however questions still need to be answered before these markers can be safely used in the daily practice.

Introduction

Five percent of hospitalized people are diagnosed with AKI. In the ICU setting the incidence reaches 50% [1]. The prevalence of AKI has risen over the last years with no change in mortality that approximates 50-80% in the ICU patients who need renal replacement therapy [1].

Prevention is the best treatment of ARF and has three targets: first, to recognize risk factors and populations at risk (Table 1); second to avoid actions that pose individuals at risk of ARF and to initiate preventive treatment when this risk cannot be abolished; the third is the use of biomarkers that can predict ARF before its occurrence.

For this topic of the prevention of AKI we found very helpful the exhaustive review of the literature made by Kellum et al. [2]. We also complemented our search with reviews and randomized controlled trials (RCT) published on PubMed between 2008-December 2011.

1. Risk Factors

General risk factors of ARF are age, hypovolemia, hypotension, sepsis, pre-existing kidney, heart or liver disease, diabetes mellitus, administration of nephrotoxic agents such as aminoglycosides, amphotericin B (especially the deoxycholate form rather than the lipid formulations), immunosuppressive treatment, ACE inhibitors, NSAIDs, and intravenous contrast agents [3-6]. In the perioperative patients risk factors are prolonged aortic clamping, emergency surgery, intravenous contrast in quantities >100 ml, and previous renal impairment with creatinine clearance of <47 ml/min [4].

In a study of postoperative patients 152,244 operations were included and took place in the USA [9]. Risk factors for the development AKI after general surgical procedures were found to be the following: age ≥ 56 years, male sex, congestive heart failure, ascites, hypertension, emergency surgery, surgery in whom peritoneal cavity is opened, preoperative creatinine >106 $\mu\text{mol/l}$ and diabetes mellitus independent on oral or insulin treatment. It was found that patients with ≥ 6 factors had 10% incidence of AKI, while the hazard ratio compared with patients with <3 risk factors was 46.2. As stated previously, patients require ICU hospitalization are at higher risk to develop AKI. The same applies to patients that critical care is required postoperatively.

Additionally to the above risk factors others believe that female gender, COPD, peripheral vascular disease, prolonged aortic clamping (>2 hours) at surgery, and the need for intraaortic balloon pump preoperatively, and prolonged operating time pose patients at risk to develop AKI after surgery [10-12].

A recent retrospective study evaluated the incidence of AKI after radical nephrectomy for renal cell cancer [13]. This study included 519 adults (>40 years old) who had normal renal function prior to operation. Risk factors of AKI were advanced age [odds ratio (OR) 1.02, 95% confidence interval (CI) 1.00-1.05], male gender (OR 3.13, 95% CI 1.91-5.12), higher

BMI (OR 1.08, 95% CI 1.01-1.15), smaller tumor size (OR 0.87, 95% CI 0.81-0.93) and higher preoperative GFR (OR 1.04, 95% CI 1.03-1.06). Moreover, subjects who developed post-operative AKI had higher risk of CKD at 1 year and at 3 years post surgery.

Table 1. Risk factors of acute renal failure

Serious illness that requires ICU	Single kidney
Advanced age	Multiple myeloma
Dehydration	Nephrotoxic drugs
Diabetes mellitus	Crush injury
Chronic kidney disease	Renal transplantation [7]
Chronic liver failure	Hyperuricemia
Heart failure	Peripheral artery disease
Sepsis or shock	Proteinuria [8]
Systemic lupus erythematosus	

Adapted from <http://www.MayoClinic.com> and

<http://www.fpnotebook.com/renal/Failure/ActRnlFlrRisk.htm> both accessed on 18/04/2011.

Elderly people are prone to develop ARF because anatomical as well as functional changes occur with increasing age [14]. The aging kidney is characterized by lower renal blood flow and impairment of kidney autoregulation. These along with co-morbidities that are more prevalent in the elderly such as congestive heart failure and hypertension treated with ACE inhibitors and/or diuretics, osteoarthritis treated with NSAIDs make them more vulnerable to develop AKI. The use of aminoglycosides as well as radiocontrast agents are additional factors in these patients. In the hospitalized elderly 50% of the causes of ARF are intrinsic. Pre-renal accounts of approximately one third of causes of AKI. In the ICU setting, ATN accounts for 76% of the causes of ARF. However these numbers differ from study to study.

2. Prevention on AKI in Specific Situations

2.A. Drug-induced AKI

2.A.1. *Acyclovir*

Intravenous acyclovir can precipitate in the renal tubules resulting in AKI at 24-48 hours after initiation of treatment. Dehydration and pre-existent CKD are known risk factors. Intravenous hydration and occasionally dose reduction is recommended in order to reduce the risk of AKI [15].

2.A.2. *Aminoglycosides*

It is known that aminoglycosides can cause ATN in 10-20% of patients [16, 17]. There are several preventive measures that may decrease the incidence of aminoglycoside-induced AKI:

1. Use, if possible the least nephrotoxic aminoglycoside. The order is neomycin>gentamicin>tobramycin>amikacin>netilmicin>streptomycin with neomycin the most and streptomycin the least nephrotoxic [16].
2. Correct electrolyte disturbances hypokalemia and hypomagnesemia prior to initiation of treatment (Decker BS, Molitoris BA (Authors), Palevsky PM, Berns JS (Section Editor), Sheridan AM (Deputy Editor). Pathogenesis and prevention of aminoglycoside nephrotoxicity and ototoxicity. www.uptodate.com accessed 05/27/2011).
3. Correct dehydration.
4. Avoid, whenever possible their use in the elderly and in patients with reduced effective circulating blood volume (such as those with liver failure and ascites or congestive heart failure)[18]. Adjust dose for renal function [19].
5. Monitor blood levels and use a single-dose of aminoglycoside which is less nephrotoxic than multiple doses [18-25]. However, in patients with fever and neutropenia this is not true [26]. Furthermore, monitoring blood levels can not always prevent AKI [27].
6. Avoid prolonged treatment (>10 days) [19].
7. Avoid other nephrotoxic drugs (Decker BS, Molitoris BA (Authors), Palevsky PM, Berns JS (Section Editor), Sheridan AM (Deputy Editor). Pathogenesis and prevention of aminoglycoside nephrotoxicity and ototoxicity. www.uptodate.com accessed 05/27/2011).

Several substances have been tested for the prevention of aminoglycoside nephrotoxicity. None of them has been adopted yet by the clinical community for this indication.

The first compound is polyaspartic and polyglutamic acid [anionic polyamino acid (PAA)] [28-36]. Studies have shown that PAA interferes with the binding of the aminoglycoside to the proximal tubular cell membrane [34-36]. Moreover, PAA binds directly to aminoglycosides. In this fashion it displaces them from negatively charged lysosomes [37]. Thus, PAA may protect proximal tubules from exposure to the aminoglycoside or by displacing it from the lysosome and therefore by preventing its passage through the proximal tubular cell [37].

Other compounds tested in regards to their role in the prevention of aminoglycoside nephrotoxicity are the antioxidants deferrioxamine, methimazole, vitamin E, vitamin C, and selenium. Studies have shown that maybe effective in the prevention of gentamicin nephrotoxicity [29, 38, 39]. Finally, superoxide dismutase, lipoic acid, dimethyl-sulfoxide (DMSO), N-acetylcysteine, and melatonin have shown effect [38, 40-45].

A gentamicin congener in whom antimicrobial effect remains but lacks nephrotoxicity has been isolated. It is known that gentamicin used in clinical practice is not a homogeneous compound; rather, it consists of C1, C1a, C2, and C2a congeners in whom the nephrotoxic potential is different [46]. More specifically, the C2 congener has been shown to be bactericidal, but not toxic for the kidney [46].

2.A.3. Cisplatin

The most important measures to prevent cisplatin-induced nephrotoxicity is the administration of intravenous isotonic saline before and after infusion and the avoidance of its

use if creatinine clearance is <60 ml/min. Other measures consist of lower doses of cisplatin if possible or cisplatin analogues. Non platinum based chemotherapies are also an additional option when supported by clinical trials.

According to our experience IV of 1-2 L of saline infusion initiated the previous night from cisplatin administration, followed by 3-4 L of saline with dextrose for the next 24 hours in patients with creatinine clearance >60 ml/min worked very well and no patient experienced nephrotoxicity. Supplementation of KCl 20mEq/L and MgSO₄ on alternative bags is also prudent. Urine output monitoring to achieve 150 ml/hour especially for the first 6 hours after cisplatin infusion is very important. A loop diuretic during that time or mannitol was given if the urine output was less than desired. In the case of pre-existent renal dysfunction with creatinine clearance less than 60 ml/min platinum analogues such as carboplatin or non-platinum based chemotherapy regimes were preferred.

The protective effect of normal saline is supported also by others as we will describe below. All clinicians agree that the administration of intravenous saline to increase renal perfusion and diuresis significantly decreases the risk of nephrotoxicity [47]. Without preventive measures the incidence of nephrotoxicity after administration of cisplatin exceeds 50 % of cases [48, 49]. We recommend that all patients who receive cisplatin need intravenous administration of normal saline.

However the optimal hydration solution is not known because no comparative studies exist (Portilla D, Masin Safar A, Shannon MG, Penson RT (Authors), Palevsky PM (Section Editor), Sheridan AM (Deputy Editor). Cisplatin nephrotoxicity. www.uptodate.com accessed 05/28/2011).

The same authors suggest the following regimen: 1000 mL of isotonic saline plus 20 meq of KCl and 2 grams of MgSO₄ given IV over 2-3 hours prior to cisplatin administration, following by at least 500 ml over the two hours after cisplatin administration. The goal is to maintain a urine output of at least 100 mL/hour for 2 hours before and 2 hours after chemotherapy. If cisplatin is contraindicated, non-platinum based chemotherapeutic regimens should be considered.

Oftentimes mannitol is used to increase urine output; however this is not supported by evidence. The use of furosemide is required only in the case of fluid overload.

2.A.4. Methotrexate

Risk factors for methotrexate-induced AKI are high-dose of MTX and pre-existent CKD. When treatment with high doses is needed intravenous hydration and urine alkalization are recommended in order to prevent AKI [15].

2.A.5. NSAIDs

Treatment with NSAID should be avoided in individuals with CKD, DM, congestive heart failure or liver cirrhosis, and in the elderly as mentioned above [50, 51]. Concurrent use with ACE-I, ARB, beta-blockers are discouraged. Finally, NSAID treatment poses individuals at risk of CI-AKI. Therefore, it is recommended that NSAID or CO X-2 inhibitors to be discontinued 48 hours prior to contrast exposure [51].

2.B. Contrast-induced Nephropathy

Contrast-induced AKI is a well recognized complication of iodinated contrast agents and one of the few causes of ARF that can be predicted and therefore prevented. Post-contrast AKI is the third most common hospital-acquired cause of ARF in USA. Its prevalence approximates 11% [52]. Patients at risk to develop contrast-induced AKI are those with CKD [53, 54], Type 2 diabetes mellitus [55], especially when serum creatinine levels are at least 1.3 mg/ml [56]. Moreover, congestive heart failure, ejection fraction <40%, hypovolemia, reduction of effective circulating blood volume, cardiogenic shock, the use of intraaortic pump are considered risk factors [57].

The volume of contrast agent was traditionally considered an additional risk factor: as the volume of iodinated contrast agents increases, the risk of AKI increases too [58]. However, a large study of 5,256 patients who underwent a coronary artery angiogram showed the following paradoxical results: the incidence of post-contrast AKI after intravenous administration of different volumes of iodinated contrast was <110 ml, 16%, 115-160 ml, 14%, 161-225 ml, 8%, and >225 ml, 7%. The results were statistically significant and showed that the volume of contrast is probably not a risk factor for ARF [59].

Intravenous NaCl 0.9% versus Oral Hydration

In one RCT intravenous NaCl 0.9% was compared with oral hydration in 53 patients who underwent elective cardiac catheterization with a contrast agent that contained iodine [60]. The incidence of ARF defined as the increase in serum creatinine level by ≥ 0.5 mg/dl (44.2 $\mu\text{mol/l}$) at 48 hours was the primary efficacy endpoint. Intravenous sodium chloride was superior to oral fluids in the prevention of ARF [1/27 (4%) versus 9/26 (35%) respectively, 95% CI 0.015 to 0.79].

Intravenous NaCl 0.9% versus NaCl 0.45% in Dextrose 5%

One RCT compared isotonic saline infusion with half-saline infusion in dextrose in the prevention of post-contrast AKI [61]. In this study 1620 individuals who underwent coronary angiography participated. The primary efficacy endpoint was the elevation of serum creatinine >0.5 mg/dl (45 $\mu\text{mol/l}$) at 48 hours. Both regimes were initiated in the morning of the procedure. Isotonic sodium chloride was found to be superior to half-isotonic saline in the prevention of contrast-induced nephropathy (0.7% versus 2.0% respectively, $p=0.04$). Patient categories benefitted the most were women, diabetics and subjects who received >250 ml of contrast ($p=0.01$ for all).

Half-isotonic Saline versus Fluid Restriction

An RCT compared NaCl 0.45% with fluid restriction in the prevention of AKI after cardiac surgery [62]. In this study 45 patients with CKD (GFR <45 ml/min were included. Elevation of serum creatinine $>25\%$ from baseline was defined as ARF. Subjects received 0.45% of NaCl at a rate of 75 ml/hour for 12 hours prior to the operation or were fluid restricted. Half isotonic saline infusion was superior to fluid restriction in the prevention of AKI post-surgery [9/30 (30%) versus 8/15 (53%) respectively]. Furthermore NaCl 0.45% infusion reduced the need of dialysis after surgery [0/30 versus 4/15 (27%) respectively, $p<0.01$].

Inpatient versus Outpatient Treatment

An RCT compared inpatient intravenous NaCl 0.45% administration with outpatient oral fluids in the prevention of post-contrast ARF [63]. In this study 36 individuals with CKD underwent cardiac catheterization. They were divided into two groups. The first received intravenous infusion of half saline initiated 12 hours prior and continued for 12 hours after the procedure. The infusion rate was 75 ml/hour. The second received as an outpatient 1 L of clear fluids starting 10 hours before catheterization. This group subsequently received intravenous infusion for 6 hours starting just before catheterization. The primary efficacy endpoint was the incidence of contrast-induced AKI. No statistical difference was found in the two groups.

Sodium Chloride versus Sodium Bicarbonate Both in Dextrose

An RCT compared the pre-emptive infusion of normal saline in dextrose with sodium bicarbonate in dextrose to prevent contrast-induced AKI [64]. All individuals (119) had serum creatinine levels of at least 1.1 mg/dl (97.2 μ mol/l). Both regimes were given at an infusion rate of 3ml/kg/hour for 1 hour prior to the procedure, followed by a rate of 1 ml/kg/hour for 6 hours. Serum creatinine levels were measured prior to the intravenous contrast administration (iopamidol), and at 24 and 48 hours. Sodium bicarbonate was superior to sodium chloride in the prevention of contrast-induced AKI [1/60 (1.7%) versus 8/59 (13.6%) 95% CI 2.6% to 21.2%]. Interestingly, the bicarbonate group had higher baseline serum creatinine values.

Isotonic Sodium Chloride versus Isotonic Sodium Bicarbonate

Hafiz et al. compared sodium bicarbonate with sodium chloride infusion with or without N-acetylcysteine for the prevention of CI-AKI in patients with CKD undergoing cardiac catheterization [65]. A total of 320 individuals were included. Subjects were randomized to receive either IV dextrose 5% with 154 mEq/l of sodium bicarbonate or IV NaCl 0.9%. Sodium bicarbonate was given at an infusion rate of 3 ml/kg for 1 hour prior to the procedure and continued at 1 ml/kg/hour after the procedure. Sodium chloride was given at 1ml/kg/hour starting at 12 hours before the procedure and continued for 12 hours post-procedure. N-acetylcysteine was administered at a dose of 1200 mg 2-6 hours before and 6-12 hours after cardiac catheterization in 50% of patients in each group. A 25% increase of serum creatinine or an absolute elevation of 0.5 mg/dl was considered CI-AKI. The incidence of CI-AKI did not differ between the groups (NaHCO₃ 8.8% and NaCl 11.8%). Risk factors of CI-AKI were age ($p=0.001$), volume of IV contrast agent >3 ml/kg ($p=0.038$) and the administration of diuretics ($p=0.005$). NAC did not reduce the incidence of CI-AKI in both groups.

Another study evaluated the incidence of CI-AKI (defined as the 25% or 0.5 mg/dl increase of serum creatinine from baseline at 48 hours post-contrast) in 264 patients who underwent cardiovascular procedures [66]. All individuals had a baseline serum creatinine >1.2 mg/dl. Subjects were randomized to receive NaHCO₃ or NaCl 0.9% or NaCl 0.9% plus NAC. Sodium bicarbonate was superior to sodium chloride alone in the prevention of CI-AKI (4.5% vs 13.6% respectively, $p=0.036$). Furthermore, there was a trend towards significance compared with the NaCl plus NAC group ($p=0.059$). Although the superiority of sodium bicarbonate over sodium chloride is supported also from several meta-analyses [67-73], meta-analysis is not considered the right tool to assess heterogenous studies [74, 75]. However, The

European Society of Urogenital Radiology taking into account a recent meta-analysis lacking publication bias and heterogeneity suggested that sodium bicarbonate is equal or superior to sodium chloride in the prevention of CI-AKI [75, 76]. The committee advises that, when normal saline infusion is used the rate must be 1-1.5 ml/kg/hour starting at least 6 hours prior and continued 6 hours after contrast exposure. Moreover, in outpatients sodium bicarbonate infusion must be preferred at an infusion rate of 3 ml/kg/hour 1 hour prior, followed by a rate of 1 ml/kg/hour for 6 hours after contrast exposure [75].

Low -versus High-osmolality Contrast Agents

The largest RCT that compared non-ionic (second generation) with ionic (first generation) contrast agents was conducted in 1196 individuals [77]. Subjects were divided into four groups: CKD and DM both absent (n=364), CKD absent, DM present (n=318), CKD present, DM absent (n=298) and CKD present, DM present (n=216). Patients were randomized to receive iohexol or meglumin/sodium diatrizoate for cardiac angiography. Elevation of serum creatinine $>1\text{mg/dl}$ ($88\mu\text{mol/l}$) from baseline at 48-72 hours was defined as post-contrast AKI. The use of non-ionic, low osmolality contrast (iohexol) was associated with a 3.3 times risk reduction of post-contrast AKI compared with the ionic, high osmolality contrast agent (meglumin/sodium diatrizoate).

Apart from the above trial there are also other smaller studies which showed that low osmolality contrast agents are associated with less risk of AKI compared with high osmolality agents in individuals with impaired renal function [serum creatinine 1.4-2.4 mg/dl ($123\text{-}211\mu\text{mol/l}$)] [78-83].

Iso-osmolar versus Low-osmolality Contrast Agents

Iodixanol is the only available iso-osmolar non-ionic contrast agent thus far. A randomized clinical trial compared iodixanol with iohexol in 129 subjects with DM and CKD [mean serum creatinine 1.5 mg/dl ($133\mu\text{mol/l}$)] [84]. The study showed that iodixanol was associated with less nephrotoxicity [defined as elevation in serum creatinine $>0.5\text{ mg/dl}$ ($44\mu\text{mol/l}$)]. The results in numbers were 3% versus 26 %, respectively. However, other studies have not shown any benefit from the use of iso-osmolar compared with low-osmolality agents other than iohexol [85]. Thus, nephrotoxicity is probably a side effect of iohexol. With this in mind, ACC/AHA recommend that percutaneous coronary interventions must be performed using either a low-osmolality agent other than iohexol, an iso-osmolar or the ionic low-osmolality contrast ioxaglate [86].

N-acetylcysteine

There are several reviews and randomized controlled clinical trials on the use of N-acetylcysteine to prevent AKI after IV iodine contrast administration at various clinical settings [87-94]. These studies have different methodologies and conclusions vary from study to study regarding whether there is any benefit or not from its use. There are also slight differences in the inclusion and exclusion criteria from trial to trial. The dose of N-acetylcysteine is 600 mg twice daily orally starting on the day before contrast exposure for a total of two days. The largest meta-analysis was conducted by Kelly et al. [95] who included a total of 41 randomized controlled trials. The results showed that N-acetylcysteine reduced the incidence of post-contrast nephropathy compared with hydration alone (relative risk 0.62

(95% CI 0.44 to 0.88). The authors concluded that taking into account safety, low cost and reno-protective effect, N-acetylcysteine is recommended to individuals at high-risk of post-contrast nephropathy.

Briguori et al. compared the standard (600 mg orally twice daily) with the double dose (1200 mg orally twice daily) of N-acetylcysteine in a RCT where 224 individuals participated [96]. All subjects had renal impairment with serum creatinine levels at least 1.5 mg/dl (135 μ mol/l) or creatinine clearance <60 ml/min. Duration of treatment was two days starting the day before the exposure to the contrast agent for coronary, peripheral procedures or both. Non ionic, low-osmolality contrast agent was used in this study. Elevation of serum creatinine by at least 0.5 mg/dl at 48 hours was the primary efficacy endpoint. N-acetylcysteine at double dose was more reno-protective compared with the standard dose [4/114 (4%) versus 12/109 (11%) respectively, 95% CI 0.09 to 0.94]. The benefit was more pronounced in patients who received ≥ 140 ml of contrast.

Another study evaluated the renoprotective effect of N-acetylcysteine in 354 individuals who had a recent MI and a coronary angiogram [97]. Subjects were divided into three groups: the first received N-acetylcysteine 600 mg IV bolus prior to angiography, followed by 600 mg orally twice daily for 2 days. In the second group the drug was given at 1200 mg bolus prior to the procedure, followed by 1200 mg twice daily orally for 2 days). Finally, the third group received placebo. The incidence of post-contrast nephropathy defined as the elevation of serum creatinine at least 25% above baseline was the primary efficacy endpoint. This study showed that double dose was more reno-protective than conventional dose of N-acetylcysteine and placebo in this patient-population (incidence of AKI 15%, 8%, and 33%, respectively, $p < 0.001$).

Theophylline versus NaCl 0.9% in Patients Undergoing CABG

A RCT compared theophylline versus NaCl 0.9% in the prevention of CI-AKI in patients who underwent CABG [98]. Subjects were randomized to receive theophylline at a loading dose of 4 μ g/kg followed by an infusion of 0.2 μ g/kg/hour for a maximum of 96 hours or NaCl 0.9%. Theophylline did not reduce CI-AKI compared with NaCl 0.9%.

A meta-analysis of seven RCT evaluated the role of theophylline or aminophylline in the prevention of CI-AKI [99]. It was found that xanthines were associated with less increase in serum creatinine. Although a favorable effect of xanthines was demonstrated in these studies the clinical significance is unknown.

Statins in the Prevention of CI-AKI

Zhang et al. conducted a meta-analysis to evaluate whether statin pretreatment can prevent CI-AKI [100]. They included 4 RCT with a total of 751 individuals. They found that statin can not reduce the incidence of post-contrast nephropathy and the need for RRT compared with no treatment. However, statin pretreatment mildly reduced serum creatinine levels compared with no treatment (-0.06 mg/dl 95% CI -0.12 to 0.00, $p = 0.05$).

Hemofiltration in the Prevention of CI-AKI

Marenzi et al. evaluated the role of hemofiltration at prevention of radiocontrast nephropathy [101]. In this RCT 114 subjects were enrolled. All individuals had CKD with serum creatinine levels > 2 mg/dl (176.8 μ mol/l) and underwent coronary interventions.

Patients were randomized to receive hydration with isotonic saline infusion at a rate of 1ml/kg/hour (n=56) or hemofiltration (n=58) initiated 4-8 hours prior to contrast exposure and continued for 18-24 hours thereafter. Hemofiltration consisted of fluid replacement at a rate of 1000ml/h without a decrease of body-weight. Hemofiltration decreased the incidence of CI-AKI, the need for temporary RRT, the in-hospital and the one-year mortality (contrast nephropathy: hemofiltration 5%, isotonic saline 50%, $p<0.001$, temporary RRT: hemodialysis or hemofiltration 3%, isotonic saline 25%, $p<0.001$, in hospital mortality: hemofiltration 2%, isotonic saline 14%, $p=0.02$, one-year mortality: hemofiltration 10%, isotonic saline 30%, $p=0.01$).

2.C. AKI in Peri- and Post-operative Patients

The incidence of postoperative AKI varies between studies from 1.1-17% [3, 102]. Patients undergoing cardiac revascularization have an estimated risk of 8% to develop AKI after surgery [10]. This wide variation is due to the different types of operation and different definitions of ARF [103]. When RIFLE criteria are used, the risk of AKI after cardiac surgery is 15-20% [104, 105].

Risk factors for post-operative AKI are nephrotoxins (aminoglycosides, amphotericin B, intravenous contrast agents, NSAIDs), aortic surgery, cardiac surgery, CABG surgery, kidney and liver transplantation, surgery in a patient with obstructive jaundice and increased intraabdominal pressure [106].

Post operative risk factors are all the conditions characterized by low output such as MI, bleeding, need for IABP, congestive heart failure and requirement of >3 inotropic agents [10]. Postoperative AKI is associated with high mortality rate that exceed 50% in some studies and is dependent of the type of the operation [107]. According to others, patients who develop ARF after surgery have a 19% mortality rate, while in those with normal renal function mortality rate is only 1% [10, 108, 109]. Two thirds of the postoperative patients that need dialysis therapy will succumb while in hospital [110, 111].

The first step in the prevention of postoperative AKI is to recognize the risk factors. There are scoring systems for this purpose published in the literature [112-114].

Optimizing Hemodynamic Status

Cardiac function and fluid status need to be optimized before surgery to avoid hypovolemia or fluid overload. In the postoperative state hemodynamic, fluid status and blood glucose monitoring are important and, whenever possible inotropic support will be of value [10].

This preventive measure applies to every condition that poses individual at risk of post-ischemic ATN (after a major surgery, patient in sepsis and seriously ill conditions in the ICU).

Brienza et al. conducted a meta-analysis of 20 RCT studies [115]. They presumed that volume expansion, inotropic support, and adequate oxygen supplementation will be helpful in these settings since hypotension, hypovolemia and cardiac dysfunction are the most common causes of AKI in surgical patients. They included a total of 4420 participants. The authors found that careful hemodynamic monitoring, with the above measures resulted in significant (compared with controls) reduction of AKI, which is very common in these population.

Numerous studies have been performed to investigate whether pharmacological treatments can decrease the incidence of AKI in the ICU setting. The vast majority of these studies regard post-cardiac surgical patients. Unfortunately, there is no clear benefit from any agent, despite a few encouraging results as we will describe below.

Patel et al. (2011) made recently a systematic review on the pharmacological agents used at prophylaxis of AKI in cardiac surgical patients [116]. They identified studies examining the role of dopamine, fenoldopam, calcium channel blockers, natriuretic peptides, diuretics and N-acetylcysteine. Although these drugs did not reduce mortality, fenoldopam and Atrial Natriuretic Peptide (ANP) reduced the incidence of renal replacement therapy (fenoldopam 5%, NNT 20, 95% CI 11.3, 83.0, ANP 3.5%, NNT 29, 95% CI 17.1, 84.4). Furthermore, Brain Natriuretic Peptide decreased the incidence of RRT by 10% (NNT 11, 95% CI 6.2, 32.0). Contrarily, dopamine decreased creatinine clearance (-4.26 ml/min, 95% CI -7.14, -1.39). In the following we analyze the RCT evaluating various drugs in the prevention of AKI after cardiac surgery.

N-acetylcysteine

N-acetylcysteine was evaluated in two RCT in the prevention of AKI in the perioperative setting [117, 118]. The first was in patients undergoing elective aneurysm surgery. In this small RCT 42 subjects were randomized to receive either N-acetylcysteine 1200 mg orally twice daily the day before the operation, followed by 600 mg orally twice daily after the operation for two days, or placebo. The study showed no benefit with the use of N-acetylcysteine in this patient population. The second study included 296 high-risk individuals that underwent elective or urgent CABG. Patients randomized to receive two pre-operative and two post-operative doses of N-acetylcysteine at 600 mg each or placebo. The drug did not show any benefit in the prevention of post-operative AKI.

There are also seven RCT that evaluated the effect of NAC in the prevention of AKI after cardiac surgery [119-125]. In these studies NAC was compared with placebo (n=1060). NAC did not reduce the incidence of AKI post-surgery, did not reduce the need for RRT, and also did not affect creatinine clearance and mortality.

Diuretics

The role of furosemide or mannitol in the prevention of AKI after cardiac surgery was evaluated in five RCT [126-130]. Despite the heterogeneity and the small numbers there were important conclusions: forced diuresis did not influence mortality, did not alter creatinine clearance, increased the incidence of RRT, as well as the incidence of AKI. However, these effects were not statistically significant compared with placebo.

Dopamine

Eleven RCT were identified on the role of dopamine in the prevention of postoperative AKI [126, 127, 131-139]. The quality varied between studies and also the control group and the dose of dopamine (2-5 µg/kg/min). Dopamine reduced creatinine clearance (-4.26 ml/min, 95% CI -7.14, -1.39).

Enoximone

Two RCT evaluated the role of enoximone that is a phosphodiesterase III inhibitor in the prevention of AKI after cardiac surgery [140, 141]. The first study showed that enoximone was harmful by decreasing creatinine clearance at 24-48 hours (-30 ml/min, 95% CI -37.71, -22.29, n=42).

Prostaglandins

Prostaglandins PGE₁ or PGI₂ compared with no treatment in two RCT [142, 143]. The second study demonstrated that prostacyclin produced a significant increase in creatinine clearance (35 ml/min 95% CI 7.28, 62.72)) at 24-48 hours.

Fenoldopam

Fenoldopam is short-acting dopamine-1 receptor antagonist initially approved for the treatment of hypertensive emergencies in patients who have AKI or are at high risk. Its efficacy in the prevention of AKI after cardiac surgery was evaluated in an RCT conducted by Ranucci et al [144]. A total of 80 patients who underwent complex cardiac procedures were included in the study. Subjects were randomized to receive fenoldopam at an infusion rate of 0.1 µg/kg/min started at the initiation of cardiopulmonary bypass and continued for 12 hours thereafter or placebo that was isotonic saline at the same infusion rate and for the same duration as fenoldopam. There was a significant superiority of fenoldopam versus placebo in the prevention of AKI (0% vs 10%). Fenoldopam also reduced morbidity in the subgroup that inotropic support for at least 48 hours was needed. In this patient population, fenoldopam was superior to placebo in regards to renal hemodynamics, and peak blood lactate levels. The authors concluded that fenoldopam showed substantial benefit by improving renal function, morbidity and the incidence of AKI after cardiopulmonary bypass surgery.

There are also four RCT that evaluated the role of fenoldopam in cardiac surgical patients [145-148]. Placebo or dopamine served as control. Fenoldopam reduced the need for RRT by 70%. Regarding AKI there was a trend towards reduction of the incidence, although not statistically significant. Two RCT showed increase in creatinine clearance at 34-48 hours after surgery (26.04 ml/min, 95% CI 18.44, 33.15, n=353) [145, 147].

A RCT compared low dose dopamine with fenoldopam in patients who underwent liver transplantation [149]. Forty three patients were randomized to receive either a continuous dopamine infusion at 2µg/kg/min (n=21) or fenoldopam at 0.1 µg/kg/min (n=22). Both regimes were initiated at induction of anesthesia and continued for 48 hours. All patients had normal renal function preoperatively. The median increase in serum creatinine at Day 3 of surgery was 0.2mg/dl for fenoldopam and 0.5 mg/dl for dopamine (p=0.0004). Urine output and hemodynamics were similar in both groups. The need of diuretics was fewer in the fenoldopam group.

Calcium Channel Blockers

The efficacy of calcium channel blockers (CCB) (diltiazem or nifedipine) in the prevention of AKI after cardiac surgery was evaluated in six five RCT [133, 150-153]. The quality of these studies was questionable [116]. CCB did not show any beneficial effect on the prevention of post-operative AKI.

Natriuretic Peptides

The effect of synthetic natriuretic peptide in the prevention of AKI after cardiac surgery was estimated in eight RCT [154-161]. Apart from one RCT the others were of moderate or poor quality [116]. ANP reduced the need for RRT by 76% (OR 0.24, 95% CI 0.10, 0.56 NNT 29, n=853). However, ANP did not reduce creatinine clearance. This paradoxical phenomenon may be due to variable therapeutic strategies between studies and not a clear benefit of ANP [116].

The effect of nesiritide, a synthetic analogue of Brain Natriuretic Peptide (BNP) compared with placebo was evaluated in three RCT [162-164]. BNP reduced the incidence of AKI by 60% (OR 0.40, 95% CI 0.21, 0.76, NNT 11, n=373) compared with placebo.

Sodium Nitroprusside

One multicenter RCT evaluated the role of sodium nitroprusside in the prevention of AKI after cardiac surgery [165]. Sodium nitroprusside can improve creatinine clearance by 6.6 ml/min (95% CI 2.41, 10.79) at 24-48 hours but can not improve clinical outcome compared with placebo.

2.D. AKI after Hypotension-post-ischemic AKI

N-acetylcysteine

Despite its benefit in the prevention of post-contrast AKI, N-acetylcysteine did not show any effect in the reduction of AKI after hypotension. A RCT evaluated the potential role of N-acetylcysteine in the prevention of post-hypotension ARF [166]. One hundred and forty-two [142] patients with a hypotensive episode of at least 30 min within the last 12 hours were included. Individuals required vasopressors were also included. Subjects were randomized to receive either N-acetylcysteine or placebo for 7 days. The incidence of AKI (primary efficacy endpoint) defined as the increase in serum creatinine of at least 0.5 mg/dl (44 μ mol/l) from baseline did not differ between N-acetylcysteine and placebo (15.5% vs 16.9% respectively, p=0.82). The study had also secondary efficacy endpoints such as the incidence of a 50% rise in serum creatinine level, maximal elevation of the creatinine levels, recovery of renal function, duration of hospital stay (ICU or Ward), need of renal replacement treatment of any type, and mortality. N-acetylcysteine did not show any benefit in the secondary outcomes.

Fenoldopam in the Critically Ill

Fenoldopam has been used in the critically ill patients with AKI. Its role is not elucidated. There are two clinical studies one randomized controlled and a case control study. The first was conducted by Tumlin et al. [167]. This randomized, double-blind, placebo-controlled clinical trial included a total of 155 individuals. Eighty (80) subjects received low dose fenoldopam, while 75 received placebo. All patients had AKI defined as a >50% absolute increase in serum creatinine from baseline within 24 hours. The incidence of renal replacement therapy (RRT) did not differ between the groups (fenoldopam 13/80 (16.25%), placebo 19/75 (25.3%), p=0.163). Furthermore, there was no significant difference in mortality rates between the groups (fenoldopam 13.8%, placebo 25.3%, p=0.068). However, a secondary analysis in patient subpopulations fenoldopam was superior to placebo in non-

diabetics, as well as post-operative cardiothoracic patients ($p=0.048$ and $p=0.049$ respectively). The authors concluded that fenoldopam mesylate did not reduce the incidence of RRT and mortality in ICU patients with AKI due to ATN. Large RCTs are needed to confirm its benefit in non-diabetic patients and after cardiac surgery.

The second study performed by Roasio et al. evaluated the role of fenoldopam in the prevention of RRT in patients with AKI following cardiac surgery [168]. A total of 92 patients were included in this study, 46 in each group. Patients who developed oliguria or doubling creatinine levels after cardiac operation received continuous infusion of fenoldopam at a rate of $0.1\mu\text{g/kg/min}$ for 48 hours or supporting treatment. The standard treatment consisted of IV fluids and loop diuretics to maintain a MAP >60 mmHg and urine output >0.5 ml/kg/h. Indications of RRT were oligoanuria, elevation of serum creatinine $>4\text{mg/dl}$ or 3 times above baseline, hyperkalemia >6.5 mEq/l or severe acidosis ($\text{Ph}<7$). Fenoldopam reduced the need for renal replacement therapy compared to controls [8/46 (17%) versus 18/46 (39%), $p=0.037$].

2.E. AKI after Renal Transplantation

There is a moderate quality of evidence that isradipine reduced creatinine after live or cadaveric kidney transplantation. Calcium channel blockers if given in the perioperative period appear to prevent post-transplant AKI, but do not reduce the incidence of early allograft dysfunction. We identified one RCT evaluating the efficacy of isradipine in the prevention of AKI after living or cadaveric renal transplantation [169]. In this RCT 210 post-transplant patients participated. Isradipine significantly improved median serum creatinine levels at 3 and 12 months post surgery compared with placebo (3 months, isradipine mean serum creatinine $185\text{ }\mu\text{mol/l}$ (2.0 mg/dl), placebo $220\text{ }\mu\text{mol/l}$ (2.4 mg/dl), $p=0.002$), 12 months isradipine serum creatinine $141\text{ }\mu\text{mol/l}$ (1.4 mg/dl), placebo $158\text{ }\mu\text{mol/l}$ (1.6 mg/dl), $p=0.021$). However, isradipine did not reduce the incidence of delayed graft function or acute rejection compared with placebo.

2.F. Heme Pigment-induced AKI (Rhabdomyolysis-hemolysis)

It is known that AKI takes place in 33% of patients with rhabdomyolysis [170], more rare in hemolysis. Risk factors for rhabdomyolysis-associated AKI are hypovolemia, acidemia/aciduria, obstruction of renal tubules and high levels of myoglobin [171]. Myoglobin is less toxic to the kidney when hypovolemia and aciduria are both absent [171].

Apart from treating the underlying cause (rhabdomyolysis or hemolysis), the prevention of AKI requires prompt and aggressive fluid resuscitation. The aims of volume repletion are to maintain or increase renal perfusion, and to increase the urine output which will decrease intratubular cast formation, remove partially obstructing intratubular casts, and increase urinary potassium excretion (Eustace JA, Kinsella S (Authors), Palevsky PM (Section Editor), Sheridan AM (Deputy Editor) Prevention and treatment of heme pigment-induced acute kidney injury (acute renal failure). www.uptodate.com accessed 05/29/2011).

Intravenous saline infusion should be administered the earliest possible, and discontinued only if the muscle injury or hemolysis has resolved. Occasionally, large volumes such as 1.5

L/hour of IV normal saline are needed. It is commonly agreed that intravascular volume expansion with NaCl 0.9% and intravenous mannitol to maintain a urine output of 200-300 ml/h are preventive measures to reduce the incidence of AKI [171, 172].

In patients with hemolysis careful hemodynamic monitoring is required to avoid fluid overload and pulmonary edema. Overload is much less common in rhabdomyolysis, as they are more volume depleted (Eustace JA, Kinsella S (Authors), Palevsky PM (Section Editor), Sheridan AM (Deputy Editor) Prevention and treatment of heme pigment-induced acute kidney injury (acute renal failure). www.uptodate.com accessed 05/29/2011).

Urine alkalization with IV bicarbonate prevents the formation of myoglobin casts in the kidney tubules [172]. Bicarbonate solution is prepared by mixing 150 mL of 8.4% bicarbonate with 850 mL of dextrose 5% or water for injection and given at an infusion rate of 200 mL/hour. The goal is to maintain a urine pH >6.5. Intravenous bicarbonate must be discontinued if pH is constantly below 6.5 for 4 consecutive hours after initiation, arterial pH is >7.5, serum bicarbonate >30 mmol/L, or severe symptomatic hypocalcemia develops. In this case saline infusion should continue for volume resuscitation. Saline infusion should be continued CK levels decrease to <5000 U/L in the plasma and urine dipstick shows that hematuria is absent (Eustace JA, Kinsella S (Authors), Palevsky PM (Section Editor), Sheridan AM (Deputy Editor) Prevention and treatment of heme pigment-induced acute kidney injury (acute renal failure). www.uptodate.com accessed 05/29/2011). The risk of AKI increases when CK is above 5000 IU/L. In that case the above measures are required [173]. In patients with hemolysis hemoglobin and LDH should be monitored.

Ringer's lactated must be avoided because of the risk of hyperkalemia and lactic acidosis due to rhabdomyolysis [171].

2.G. Scleroderma Renal Crisis

Scleroderma renal crisis develops in approximately 10 to 20 % of patients with the diffuse form of systemic sclerosis [174-180]. It is much less common in the limited cutaneous form of systemic sclerosis. SRC is potentially a life-threatening condition. Several risk factors have been implicated. Among them, the most important is diffuse skin involvement [176, 178-181]. A series of 110 patients with SRC 78% of them had diffuse cutaneous scleroderma [179].

Another important risk factor for SRC is prior exposure to corticosteroids especially if the daily dose of prednisone (or equivalent) is ≥ 15 mg [179-184]. Other risk factors are autoantibodies directed against RNA polymerase [185], exposure to cyclosporine (a known renal vasoconstrictor) [186], large joint contractures, anemia not previously present, newly diagnosed heart failure, and pericardial effusion [176, 181]. To the contrary, pre-existent hypertension, and CKD, antibodies against topoisomerase-1 and abnormal urine microscopy are not predictive of SRC.

Data from retrospective or cohort studies have shown that ACE-i do not harm, but also do not protect from development of SRC [179, 181, 182]. In regards to glucocorticoids, if needed for the treatment of co-existing myositis the dose of prednisone (or its equivalent) must not exceed 15 mg/day.

2.H. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is the most common hematological emergency in children and adults [187-190]. Calcium phosphate, xanthine, as well as urate crystals may precipitate in the kidney or cause renal vasoconstriction leading to AKI [191-196]. Destroyed tumor cells also release cytokines that induce systemic inflammatory response and multiorgan failure leading to death. Finally, TLS can cause fatal arrhythmias, and seizures.

Patients at risk of TLS are those suffering from high-grade non-Hodgkin lymphoma or acute leukemia; however, it has been also described in subjects with tumors not usually associated with this complication [197-200]. High tumor burden, dehydration, oliguria, low urine pH, pre-existent CKD, and high levels of solutes (calcium phosphate, uric acid, xanthine). Laboratory tests that pose patients at high risk to develop TLS-associated AKI are lactate dehydrogenase >2 times the upper limit of normal and elevated uric acid levels at presentation [191].

The mainstay of prevention of AKI in TLS is IV saline infusion (2500-3000 ml/m² of body surface area) plus bicarbonate, and in some cases loop diuretics. The goal is to increase renal perfusion, glomerular filtration and urine pH to make urate crystals more soluble. The target is urine output ≥ 2 ml/kg/hour [191].

Reduction of serum uric acid levels with allopurinol or rasburicase is important to improve or at least preserve renal function [191]. These agents have also a beneficial effect by reducing phosphate levels [191, 201]. Allopurinol inhibits xanthine oxidase. Thus, hypoxanthine and xanthine do not convert to uric acid, but they accumulate in the blood and this may cause renal failure. Allopurinol cannot catabolize the already existing uric acid which remains to be toxic to the kidney. Two days are needed in order to decrease uric acid levels.

Contrarily, rasburicase catabolizes uric acid to allantoin that is highly soluble [191]. Because xanthine does not accumulate and uric acid is degraded, rasburicase is superior to allopurinol in the prevention of TLS-associated AKI [191].

A multicentre RCT compared rasburicase with allopurinol on the prevention of TLS in 52 high-risk children with leukemia or lymphoma [202]. Patients randomized to rasburicase ($n=27$) 0.20 mg/kg IV over 30 minutes or oral allopurinol 300 mg/m² (or 10 mg/kg) divided into three doses every 8 hours. Duration of treatment was 5-7 days. Intravenous bicarbonate 20-40 mEq/l was allowed accordingly as well as IV hydration with 3000 ml/m²/day. The total duration of the study was 14 days.

Uric acid levels the first 5 days of treatment and more specifically the area under the plasma uric acid concentration from days 0 to 4 (AUC_{0-96}), was the primary end point of this study. The relative reduction of uric acid levels at 4 hours after the first dose of treatment was defined as secondary end point.

Rasburicase caused more rapid decline in serum uric acid compared with allopurinol (AUC_{0-96} 128 \pm 70 mg/dl versus 329 \pm 129 mg/dl, respectively, $p<0.0001$). Rasburicase reduced serum uric acid levels more markedly compared with allopurinol at 4 hours (86% versus 12% respectively, $p<0.0001$). The group that received rasburicase had a baseline serum creatinine 144% of their age/sex matched normal values, while the allopurinol group had 132%. After 96 hours of treatment serum creatinine levels were 102% and 147% for rasburicase and allopurinol respectively. The last observation indicates that rasburicase not only preserved but improved renal function. Finally, rasburicase was well tolerated.

3. Future Perspectives in the Prevention of AKI

3. Biomarkers in the Prevention of AKI

Since serum creatinine is not reliable in predicting AKI [1], an effort to discover markers like the troponin in MI has been done. During the last few years multiple studies on biomarkers of AKI have been published in the literature. Among them, the Acute Kidney Injury Network (AKIN) has listed seven: urinary KIM-1, urinary NGAL, urinary IL-18, plasma IL-6, urine and plasma cystatin C, and urinary L-FABP [203]. Among them NGAL is probably the most promising [204]. This is a prolific field of extensive research. AKI appears to be very complex and the various causes and pathophysiologic mechanisms makes it more complex to be predicted by a single biomarker. Furthermore, other biomarkers are non-specific for AKI and for others there are no standardized tests [1]. We do not know whether the use of more than one would be useful in the prevention of AKI in high risk patients. Finally, it is not known once elevated, if interventions will decrease the incidence of AKI, morbidity and mortality.

Neutrophil Gelatinase-associated Lipocalin

Neutrophil gelatinase-associated lipocalin is expressed in various tissues of the body (kidney, prostate, respiratory and gastrointestinal epithelium [205]. It appears to be very sensitive but not specific marker of AKI, since it is also elevated in CKD and sepsis [1]. NGAL is an acute phase protein raised in various inflammatory conditions as well as in cancers [206]. After nephrotoxic and ischemic insult accumulates into cortical tubules, blood and urine [207]. Due to its small size and resistance to degradation, NGAL is easily detectable in urine [1]. NGAL promotes re-epithelization and inhibits apoptosis of the tubular epithelial cells which means that exerts a protective effect for the kidney [208, 209].

ELISA is used to measure serum as well as urine levels of NGAL [1]. Both assays are easy and the results are available in 15 and 35 minutes respectively. The urine levels can be done at the bedside and require only a few amount of urine sample. ELISA is correlated well with the initially used Western Blot technique [210].

Plasma NGAL values >150ng/ml is measured 2h after CABG with an AUC of 0.96 have 84% sensitivity and 94% specificity to predict AKI [1]. When measured in the urine 2 hours after CABG values >100 mg/ml with AUC 0.95 have 82% sensitivity and 90% specificity to predict AKI [1]. However, as mentioned earlier NGAL is not specific marker in AKI. It is also elevated in hypertensive and diabetic individuals [211, 212]. Due to the absence of comorbidities NGAL is more specific in children [1]. Finally, it increases with age [213].

Prevention of Ischemia-reperfusion AKI

It is known that ROS play an important role in the ischemia-reperfusion ATN. During this process, increased mitochondrial membrane permeability leads in depolarization, decreased synthesis of ATP and increased production of ROS after ischemia. SS-31 is a mitochondria-targeted tetrapeptide which can scavenge ROS and inhibit mitochondrial depolarization. In rat models SS-31 appears to protect mitochondria from depolarization, accelerates ATP recovery, and reduces apoptosis and necrosis of tubular cells as well as tubular dysfunction. Moreover, it accelerates the proliferation of tubular cells that survived

from ischemic insult. The results are promising and may offer a new target of pharmacologic intervention to prevent ischemia-reperfusion AKI [214].

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Chapter XII

Acute Renal Failure: Treatment

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Abstract

Since almost all AKI develops outside of the renal unit the most appropriate facility for care will depend on the presence or absence of non-renal organ failure, the need for renal support and the need for renal specialist input. The latter will be determined, in part, by the likelihood that AKI will be transient and self-limiting, and by its aetiology, particularly if an esoteric diagnosis is possible.

Successful management requires early diagnosis, investigation of the causes, management of complications, timely renal replacement therapy, prevention of ongoing kidney injury, aggressive supportive care, and correction of the primary disorders.

There is currently no evidence to support the use of a specific pharmacological therapy in the treatment of AKI secondary to hypoperfusion injury and/or sepsis since most interventional therapeutic trials in experimental animals have failed in humans.

In many cases AKI can be effectively treated and resolved by adequate volume replacement. The goal is to achieve and maintain euvolemia while restoring effective circulating volume to allow adequate tissue and kidney perfusion. Diuretics may be useful in volume overload. Loop diuretics have also been used to convert patients with oliguric to non-oliguric AKI, to facilitate the management of fluid and electrolyte disturbances and reduce the requirement for renal replacement therapy.

In severe cases it is important to remember that the underlying medical conditions (e.g. sepsis, haemorrhage) and complications such as coagulation disorders and infections should be adequately treated while the intrinsic forms of AKI will require specific therapy. Although pre-renal AKI responds well to conservative treatment in AKI, in the presence of complications such as hypervolemia eg, acute pulmonary edema or large cumulative positive fluid balance, hyperkalemia, metabolic acidosis and uremic symptoms dialysis should be considered the treatment of choice. Historic data suggest that “early” initiation of renal replacement therapy is associated with improved survival, but the evidence is not robust to allow specific recommendations. Thus, the choice to initiate or not, the kind and the optimal dosing of renal replacement therapy still remain a clinical decision.

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Introduction

Once the diagnosis of ARF is established, immediate treatment is required. The physician has to face three main challenges.

- 1) The treatment of life threatening complications that accompany the renal impairment.
- 2) Identify and treat the underlying cause.
- 3) Take the appropriate supportive measures should be taken in order to keep euvolemia and electrolyte and acid-basis balance as well as to prevent further renal insults.

Attention should also be paid in the complications that often occur in patients with ARF, such as coagulation disorders and infections. When conservative measures fail to be effective, or when the physician considers that as urgent, renal replacement therapy should be performed. The steps followed for the treatment of acute AKI are summarized in Table 1.

A. Treatment of Life Threatening Complications

1. Hyperkalemia

Hyperkalemia, defined as plasma potassium greater than 5.5 mmol/l, is a common and life-threatening electrolyte abnormality in patients with ARF [1].

Table 1. Management of AKI

A. Treatment of life-threatening complications
1. Hyperkalemia
2. Pulmonary Edema
3. Acidosis
B. Treatment of the underlying cause
1. Pre-renal Azotemia
2. Acute Tubular Necrosis
3. Post-renal Azotemia
4. AKI in special situations
C. Supportive Measures
1. Bleeding
2. Nutrition - Dietary management
D. Renal Replacement Therapy
1. Indications
2. Modality
3. Timing
4. Adequacy
5. Plasma Therapies and Adsorption Techniques
E. Future Therapies
1. Bioartificial kidney
2. Stem cell therapy

The main cause of hyperkalemia in these patients is the reduced renal potassium excretion as significant reduction in GFR occurs. Uremic acidosis, cell necrosis, which accompanies some causes of ARF (rhabdomyolysis, hemolysis, tumor lysis) and medicines, often used by these patients, such as NSAIDs, ACE-I, ARBs, potassium sparing diuretics, trimethoprim and calcineurin inhibitors, are contributing factors in the development of hyperkalemia. [2-5].

The diagnosis is based mainly on the laboratory data in conjunction with the medical history, whereas symptoms are nonspecific (generalized fatigue, weakness, paresthesia) [1, 6]. Electrocardiographic changes are also one indication of hyperkalemia, there are, however, not always present. The classic changes are narrow-based peaked T waves, widened QRS complex and prolonged PR interval ($>6,5$ mmol/l) (Figure 1), absence of P and widened QRS complex-similar to ventricular tachycardia (>8 mmol/l), sine wave, ventricular fibrillation and asystole (>10 mmol/l).

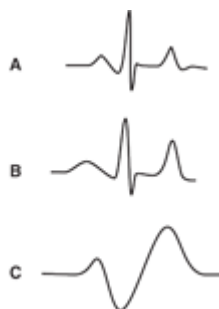


Figure 1. Classic ECG changes in hyperkalemia: peaked T waves, fluttering of the P wave, widened QRS complex.

Pseudomyocardial infarction pattern, sinus tachycardia and bradycardia, idioventricular rhythm, and 1st-, 2nd-, and 3rd-degree heart block have also been described. [2, 7-9]. According to the serum potassium levels, hyperkalemia can be classified into mild (5,5-6,5 mmol/l), moderate (6,5-7,5 mmol/l) and severe ($>7,5$ mmol/l). [1]. Emergent treatment should be initiated in moderate and severe hyperkalemia or if any ECG changes are present. [10, 11].

The treatment of hyperkalaemia can be divided into 4 steps (Table 4):

Step 1. Stabilisation of Cardiac Membranes

Calcium balances the changes caused by hyperkalemia in the membrane potential. A bolus of 10 ml of 10% calcium gluconate is given intravenously over two to five minutes. The effect is expected within 2-3 minutes but last for only 30 to 60 minutes. [6]. If ECG abnormalities persist calcium gluconate can be repeated every 10-20 min to a maximum dose of 50 ml calcium gluconate.

Attention is needed in patients taking digitalis, as hypercalcemia can induce digitalis toxicity. [12]. In this situation, slow infusion (in 100 ml of dextrose 5% infused over 30 minutes) is recommended. [6].

Step 2. Potassium Shift from Extra- to Intracellular Space

The next and the most effective way to manage a hyperkalemia is the lowering of plasma potassium by shifting it into the cells. There are three ways to achieve this.

Insulin with Glucose

Insulin stimulates cell membrane $\text{Na}^+/\text{K}^+-\text{ATPase}$ driving potassium into cells [4]. Ten units of short acting (soluble) insulin should be added to 50 ml of 50% dextrose and infused over 10–20 minutes. [13].

A decrease in serum potassium of 0.6-1 mmol/l is expected after 10-20 minutes [10, 14, 15].

The administration of this infusion can be repeated after 4h. Insulin alone can be given to hyperglycemic patients (blood glucose >14 mmol/l) as the infusion of further glucose can worsen hyperkalemia secondary to its osmotic effect. [5]. The need for rapidly attained supraphysiological insulin levels to produce a hypokalemic effect, explain the inadequacy of glucose infusion alone as treatment for hyperkalemia. [16].

Hypoglycemia is the most common side effect and therefore blood glucose should be monitored closely [2].

β_2 Adrenergic Agonists

Salbutamol stimulates indirectly the $\text{Na}^+/\text{K}^+-\text{ATPase}$ shifting potassium into cells [10, 17]. It can be administered intravenously (0.5mg) or via nebulizer (10-20 mg). [13]

A decrease of 1.6-1.7 mmol/l in 2h when administered IV and an immediate decrease of 0.62-0.98 mmol/l lasted for 1-2h when administered as inhalation can be expected. [18, 19]. Tachycardia is the most common side effect and it should therefore be avoided in patients at risk. [13].

Sodium Bicarbonate

Sodium bicarbonate decreases serum potassium by increasing the blood pH.

A 50-100 ml solution of 8.4% can be administered over 30 minutes via central line or 500 ml 1.26% peripherally.

However, routine bicarbonate therapy should be avoided, unless severe acidemia is present, since little benefit has been proven to have in reducing plasma potassium [6, 20-23].

Moreover, rapid correction of acidosis can aggravate hypocalcemia.

A combined therapy with insulin and dextrose plus salbutamol and sodium bicarbonate has been proven to be more effective than either treatment alone or any other combination. [24].

Step 3. Reduction of Total Body Potassium

While the above measures protect from the severe effects of high plasma potassium levels, they do not affect the total body potassium. This can be achieved by increasing the potassium loss through the urinary or gastrointestinal system or through hemodialysis, when conservative measures fail.

Loop Diuretics

Loop diuretics (furosemide) blockade the Na-K-2Cl co-transporter channels in the thick ascending limb of the Loop of Henle. [25].

A slow intravenous bolus of furosemide 40-120 mg or an infusion of 10-40 mg/h to a maximum of 1000 mg/day is recommended. The effect depends on the onset of diuresis. Substantial amounts of potassium can be lost over 24h with urine output $> 2\text{L/day}$ [26].

Ion Exchange Resins

Calcium or Sodium Polystyrene Sulphate induces loss of potassium from the body by exchanging calcium or sodium with potassium in the gastrointestinal tract. They can be administered orally (15g up to qds) or rectally (15-30g suspended in 2% methylcellulose and 100mL water rectally up to qds, retained for at least 2h) [13, 27]. A decrease of 1 mmol/l in serum potassium over 24h can be expected. [27]. Side effects include hypercalcemia and salt/water overload (with calcium and sodium containing resins respectively), and hypomagnesaemia. [13].

Haemodialysis

Haemodialysis is the most effective way to reduce potassium in patients with ARF [14].

It provides a removal of 50-80 mmol K⁺ in a 4h session. [1, 28]. However, it is an invasive method, and should therefore be chosen when conservative methods have been proved ineffective.

Step 4. Prevention of Further Potassium Accumulation

This can be achieved avoiding potassium rich foods (Table 2) and all drugs that might cause hyperkalemia (Table 3)

2. Pulmonary Edema

Pulmonary edema is a life threatening complication of salt and water overload in oligoanuric patients with ARF, which should be immediately recognized and treated. Dyspnea, cyanosis, tachycardia, widespread wheeze or crepitations in the chest, arterial hypoxemia and widespread shadowing on the chest radiograph confirm the diagnosis.

The foremost step in the initial management of pulmonary edema is the upright positioning of the patient and the oxygen administration in as high concentration as possible.

The second step is to offload the decompensated heart using, accordingly to the needs diuretics and/or intravenous opioids and/or nitrates. Furosemide, in a bolus dose of 40-80 mg IV alone or in combination with bumetanide 2-4 mg may not be effective in patients with renal failure.

Table 2. Common foods with high level of potassium

GRAINS	Whole-grain breads, wheat bran
SNACK FOODS/SWEETS	Nuts or seeds, chocolate
FRUITS	Bamboo shoots, baked or refried beans, broccoli, Brussels sprouts, carrots, olives, mushrooms, onions, potatoes, pickles, sauerkraut, spinach, tomato, tomato sauce,/tomato juice, and vegetable juice
VEGETABLES	Bamboo shoots, baked or refried beans, broccoli, Brussels sprouts, carrots, olives, mushrooms, onions, potatoes, pickles, sauerkraut, spinach, tomato, tomato sauce,/tomato juice, and vegetable juice
DAIRY PRODUCTS	Milk and milk products, buttermilk, yogurt
CONDIMENTS	Imitation bacon bits, light salt or salt substitutes

Table 3. Common used drugs inducing hyperkalemia

ACE inhibitors
Angiotensin-II receptor antagonists
NSAIDs
Amiloride
Spironolactone
Cyclosporine
Tacrolimus
Trimetoprim
Heparin

Table 4. Treatment of Hyperkalemia

STEP 1	Stabilisation of cardiac membranes	10 ml of 10% calcium gluconate IV over 2-5 min
STEP 2	Potassium shift to intracellular space	50 ml of 50% dextrose IV over 10-20 min Salbutamol 0,5 mg IV or 10-20 mg via nebulizer 50-100 ml of 4,2% solution IV over 10 min (if pH<7.2)
STEP 3	Reduction of total body potassium	Furosemide 40-120 mg IV bolus Calcium or Sodium Polystyrene Sulphate p.o 15g up to qds or rectally (15-30g suspended in 2% methylcellulose and 100mL water rectally up to qds, retained for 2h) Hemodialysis
STEP 4	Prevention of further potassium accumulation	Low potassium diet Avoidance of drugs causing hyperkalemia

In these cases a larger dose of 250 mg in 50 ml 0.9% saline over one hour IV is recommended. [29-32]. Diamorphine, 2,5-5 mg IV (administered with metoclopramide 10 mg IV) can release symptoms rapidly and can be repeated, if needed and if tolerated.

Finally, an intravenous infusion of a venodilator, for instance glyceryl trinitrate 50 mg in 50 ml 0.9% saline, at a rate of 2–20 ml/h, should only be given if blood pressure is higher than 95 mmHg. In case patient's blood pressure is less than 95 mmHg, dopamine (up to 10-20 µg/kg/min) and inotropic agents should be administered initially. Renal replacement therapy in most cases is the last or the only effective treatment.

Hemodialysis and hemofiltration has proven to have the same effectiveness, whereas peritoneal dialysis is less effective as emergency treatment. [13].

3. Acidosis

Metabolic acidosis is a common complication of acute renal failure due to accumulation of anions as kidneys fail to maintain homoeostasis. Most of the times is mild to moderate and demands no specific treatment is required. However, when severe acidosis is present

(pH<7.2), certain measures should be taken, as it can have a negative effect on the function of cardiovascular and nervous system.

Alkaline solution - 100 ml of 8.4% sodium bicarbonate via central line or 500 ml 1.26 % peripherally over 15-30 minutes can be administered although its benefit has not been proven. Side effects include hypernatremia, volume overload, worsening of intracellular acidosis and hypocalcemia. [33]. Hemodialysis or hemofiltration may be needed if severe acidosis persists in oligoanuric patients. Finally, dietary protein restriction is recommended for further control of the acidosis.

B. Treatment of the Underlying Cause

Once dealing with the life threatening complications of ARF, the next challenge for the physician is to identify and treat the main cause that led to renal failure. Unless this is not cured, renal function is expected to deteriorate.

Causes of ARF are divided into three categories, according to the pathophysiology way responsible for the renal function impairment. This division is a helpful guide to choose the appropriate therapy.

1. Pre-Renal Azotemia

Treatment of the underlying cause (e.g. hemorrhage, congestive heart failure, sepsis) and maintenance of euvolemia are the main goals of the treatment of renal failure caused by hypoperfusion.

The best way to monitor the adequacy of fluid replacement therapy is a clinical examination of extracellular fluid volume status (postural hypotension, Jugular Venous Pressure, JVP), urine output, and daily weights.

Fluid replacement should be according to the nature and tonicity of fluid losses and to the electrolyte abnormalities presented.

Which is the optimal resuscitation fluid is still debated. The Saline versus Albumin Fluid Evaluation (SAFE) trial compared the use of either 4% albumin or normal saline for fluid resuscitation in ICU patients [34, 35]. At 28 days, there was no significant difference between the two groups in respect to the primary outcome of death or secondary outcomes of organ failure, need for RRT, or duration of hospitalization.

Normally, a 0.9% saline solution can be used in most of the cases whereas for urinary losses a 0.45% saline solution is considered as the most appropriate.

As renal function starts to recover, a positive balance of 500 ml/day (hourly input equal to previous hourly's output plus 25 ml) should be kept.

It is important to monitor the patient's volume status throughout the episode of AKI [36]. This remains an essential part of patient management in the recovery phase. Patients may develop a polyuric phase during which they are at increased risk of developing a negative fluid balance and electrolyte disturbance including hypernatremia and hypokalemia. On the other hand if the patient is considered euvolemic replacement should be adjusted to avoid pulmonary edema [37].

Careful consideration is needed concerning the re-introduction of medications such as antihypertensives and diuretics. [38].

Packed red blood cells should be administered in hypoperfusion due to hemorrhage, with a generally accepted goal of a mean value of hemoglobin of 9-10 g/dl.

In most cases renal injury is reversible. However, if treatment is delayed, ischemic acute tubular necrosis may occur.

2. Acute Tubular Necrosis

The management of established ischemic acute tubular necrosis is based on the maintenance of adequate renal perfusion and the prevention of further renal injury. Specific pharmacological agents, discussed below, are commonly used, although there is no evidence for their benefit.

Diuretics

The aim of using loop diuretics attempted by many physicians in ischemic ATN is to increase diuresis and convert oliguric to non-oliguric AKI. The rationale behind the use of loop diuretics was based on their putative ability to reduce the energy requirements of the cells of the ascending limb of Henle and therefore ameliorate the resultant ischemic damage as [39]. Additionally loop diuretics by inhibiting prostaglandin dehydrogenase prevent the breakdown of renal vasodilator PGE₂ and maintaining adequate urine output flush out debris from renal tubules [40].

However, despite the effect on renal output, high doses of IV or oral furosemide have not demonstrated a beneficial effect on renal and patient survival [41]. Additionally furosemide given in this setting increases the risk of ototoxicity which may be permanent.

We found five studies (three of them were RCT [42-44]) evaluating the role of furosemide in post-ischemic ATN [30, 31, 42-44]. Cantarovich et al. compared high doses of IV furosemide with placebo in 338 patients with established renal disease [42]. Subjects were randomly assigned to IV furosemide 25 mg/kg/day (maximum daily dose 2 g), IV furosemide 35 mg/kg/day (maximum daily dose 2.5 g) or placebo. The trial had survival as a primary and total number of dialysis sessions required as a secondary endpoint. Furosemide was associated with shorter time to >2L diuresis/day compared with placebo (5.7 versus 7.8 days respectively, $p=0.004$). Moreover, furosemide resulted in increased likelihood to produce polyuria compared with placebo (57% versus 33% respectively, $p<0.001$).

Although these favorable effects furosemide did not improve patient survival (primary endpoint) and did not reduce the number of dialysis sessions required (secondary endpoint).

Finally, furosemide did not increase renal recovery rate and did not decrease the time on dialysis.

Another study evaluated different furosemide regimes in 58 subjects with established acute renal failure after trauma of surgery [43]. The parameters tested were urine output, number of dialysis sessions required, duration of kidney injury and mortality. Individuals were randomized to IV furosemide 1 g single dose, or furosemide 3 g IV or PO to achieve a hourly urine output of at least 200 ml or decrease in serum creatinine below 300 $\mu\text{mol/l}$. Oliguria reversed in 24 out of 28 patients given sustained furosemide but in only two given a

single injection. There were no differences between different furosemide modalities in the tested parameters. Two patients developed deafness, one was permanent.

It seems reasonable to use diuretics only in non dehydrated oliguric patients, at a dose suitable to the degree of renal impairment (250 mg furosemide intravenously over one hour is a standard regimen), and to stop diuretic treatment if oliguria persists. Such use should not postpone the initiation of dialysis if required [32].

Mannitol

Mannitol is an intravascular volume expander and may function as a free radical scavenger as well as an osmotic diuretic [45].

However the available retrospective series, most of which are uncontrolled, report conflicting results regarding its effectiveness [46].

The interpretation of these findings is hampered by the lack of reporting of other elements of treatment, such as adequacy of volume resuscitation, presence of other factors contributing to AKI (eg, drugs, sepsis, hypotension), timing of interventions, and relatively low rate of severe AKI (eg, requiring dialysis).

Moreover unless the patient is carefully monitored and losses replaced when appropriate, mannitol can lead to volume depletion, hyperosmolarity syndrome and hyponatremia.

The increase in plasma osmolality can also cause passive movement of potassium out of cells and raise the plasma potassium concentration [47]

Vasodilator Agents

Dopamine

It is known that dopamine increases natriuresis at low doses. It has been proposed that dopamine may potentially reduce ischaemic cell injury in patients with AKI by improving renal blood flow and reducing oxygen consumption through inhibition of sodium transport [48].

However, low-dose dopamine does not appear to have any beneficial effect in the treatment of post-ischemic ATN [Sanoff S, Okusa MD (Authors), Palevsky PM (Section Editor), Sheridan AM (Deputy Editor). Possible prevention and therapy of postischemic acute tubular necrosis: treatment. www.uptodate.com accessed 05/25/2011)] [49].

The best study which demonstrated that dopamine is ineffective in the treatment of established AKI was a meta-analysis of 61 clinical trials [50]. A total of 3359 individuals with or at risk of AKI were randomly assigned to receive either low-dose dopamine (<5 µg/kg/min) or placebo or no treatment. Dopamine did not reduce mortality, the need for renal replacement therapy, or adverse effects. However, the drug induced non significant decrease in serum creatinine, increased creatinine clearance and increased urine output by 24% on Day 1. The authors concluded that dopamine, although improves the parameters of renal physiology, does not offer any substantial clinical benefit in patients with or at risk of AKI.

The failure of dopamine to function as a prophylactic agent may be caused by the divergent effects of specific dopamine receptors in the kidney. Activation of dopamine A-1 receptors increases renal blood flow in normal and diseased kidneys, whereas dopamine A-2 receptor activation leads to prolonged vasoconstriction [51].

Fenoldopam

Fenoldopam, is a selective dopamine A-1 receptor agonist acting by increasing renal blood flow to both the cortex and medullary regions in the kidney [52].

Current studies indicate that fenoldopam reduces the need for renal replacement therapy, whereas it seems to have no effect on the mortality in patients with ATN [53].

One prospective, multi-center RCT in critically ill patients with incipient renal dysfunction randomized patients to receive 2 µg/kg/min dopamine or 0.1 µg/kg/min fenoldopam mesylate as continuous infusion over a 4-day period [54]. This study suggests that in the setting of acute early renal dysfunction, and before severe renal failure occurs, the attempt to reverse renal hypoperfusion with fenoldopam is more effective than with low-dose dopamine [36].

Such results highlight the need for large multi-center randomized controlled trials to be performed to establish the use of fenoldopam for this purpose.

Atrial- Brain Natriuretic Peptides

ANP and BNP are systemic and renal vasodilators. They inhibit renal tubular sodium reabsorption, attenuate the activation of the renin–angiotensin–aldosterone system and lower the oxygen requirements in several nephron segments [36].

Although there are evidences that low dose of human ANP (50 ng/kg per min) decreases the need of dialysis [55], a large, multicenter study showed no benefit according to the need of dialysis after administration of high doses of synthetic Atrium Natriuretic Peptide (anaritide, 200 ng/kg per min) [56]. However, it seems that oliguric patients had a better outcome. [57]. Thus, large studies are required to confirm this result. [58].

Regarding recombinant BNP (nesiritide) there is not adequate evidence and its benefit remains to be proved in AKI associated with heart failure and cardiac surgery [36, 59].

Vasopressor Agents

During an episode of AKI, autoregulation of the kidneys is compromised and renal blood flow decreases rapidly, leading to renal ischemia. Vasopressors may therefore play a critical role in the management of AKI by restoring the mean arterial pressure and urine output. [60].

Norepinephrine

There are many metabolic changes, such as significant nitric oxide release, down-regulation of α -adrenergic receptor responsiveness, endothelial damage and loss of vascular smooth muscle tone that accompany AKI which may explain the effectiveness of norepinephrine. [61]. Although the exact pathophysiological paths of its action remain to be elucidated, its use in patients with AKI could play a role when maintenance of mean blood pressure is required. [60].

Vasopressin

Vasopressin, a peptide hormone released in acute shock, increases mean arterial pressure and decreases cardiac output by stimulating V1 receptors. [60]. Since its levels progressively decrease exogenous administration has been considered. [62]. Low dose vasopressin infusion has shown to improve arterial blood pressure. Although its use in conjunction with norepinephrine may allow a decrease in norepinephrine dose [63], a recent study suggests that

vasopressin plus low-dose norepinephrine is not more effective than epinephrine alone in patients with septic shock. [62].

Growth Factors

Experimental studies suggest that growth factors may provide a benefit in patients with ATN by accelerating tubular regeneration and functional recovery in established post-ischemic ATN [Sanoff S, Okusa MD (Authors), Palevsky PM (Section Editor), Sheridan AM (Deputy Editor). Possible prevention and therapy of postischemic acute tubular necrosis: treatment. www.uptodate.com accessed 05/25/2011]. Regenerated tubular cells appear to be mostly derived from dedifferentiated cells (kidney-derived stem cells) that have survived the ischemic insult [64, 65], and to lesser extent from migrating bone marrow stem cells [Sanoff S, Okusa MD (Authors), Palevsky PM (Section Editor), Sheridan AM (Deputy Editor). Possible prevention and therapy of postischemic acute tubular necrosis: treatment. www.uptodate.com accessed 05/25/2011]. During this phase, growth factors, including insulin-like growth factor-I (IGF-I), epidermal growth factor (EGF), and hepatocyte growth factor, are required [66-69].

Animal studies suggest that the exogenous administration of these agents provide a benefit, according to the raise of plasma creatinine, the extend of tubular injury and the time of recovery [70].

However, clinical studies fail to find a benefit in patients treated with IGF-1 [71] Several barriers, including heterogeneous and complex patient factors, lack of a standardized definition of acute renal failure and diagnostic criteria, and the lack of clear and specific endpoints for the clinical trials may contribute to the negative results [Sanoff S, Okusa MD (Authors), Palevsky PM (Section Editor), Sheridan AM (Deputy Editor). Possible prevention and therapy of post-ischemic acute tubular necrosis: treatment. www.uptodate.com accessed 05/25/2011].

3. Post-Renal Azotemia

Obstruction of urine outflow of both kidneys or in a single functioning kidney may arise anywhere from renal pelvis to urethra. Treatment is dictated by the location of the obstruction, the underlying cause and the degree of renal impairment and usually a close collaboration between nephrologists, urologists and radiologists is required.

Bladder catheterization is the only treatment required in most cases. On the other hand, complete bilateral ureteral obstruction presenting as AKI requires prompt urologic intervention to save renal function. Percutaneous nephrostomy, cystoscopy and retrograde ureteral catheterisation may be needed. In most of the cases, the urologic intervention results in a rapid improvement of renal function and limit renal lesion but the longer the delay the more the long term damage. Even in case of acute tubular necrosis, renal function will gradually recover in most of the cases. In this phase, general supportive measures including optimization of the hemodynamic status by appropriate fluid and diuretic therapy, administration of vasopressors and/or inotropes and, eventually treatment of any underlying sepsis is recommended [72]. In the recovery phase the maintainance of euvolemia and electrolyte balance is of primary importance, since post-obstructive polyuria, due to tubular concentration dysfunction may happen. Moreover, obstruction may result in an impaired

distal tubular response to aldosterone, resulting in a paradoxical hyperkalemic renal tubular acidosis when relieved. This usually resolves spontaneously. A small number of patients will develop permanent tubular damage and thus a persistent salt wasting nephropathy [73].

Dialysis should rarely be required in AKI due to obstruction unless treatment of life-threatening hyperkalemia and/or severe fluid overload occurs till the appropriate procedures take place.

4. AKI in Special Clinical Situations

A) Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is defined as acute renal failure in patients with advanced cirrhotic liver disease due to fulminant hepatic failure from any cause.

Increased production or activity of vasodilators, mainly in the splanchnic circulation, and nitric oxide production from the endothelium appears to play a central role [74-78].

There is a gradual decline in renal function as the liver disease progresses. In this initial stage the intravenous administration of the sympatholytic agent clonidine may lower the renal sympathetic tone and renal vascular resistance and raise the GFR by as much as 25 % [79]. However, despite a persistent reduction in sympathetic activity, this benefit does not appear to be sustained with chronic oral therapy [80].

Restoration of renal function may be achieved with the improvement of hepatic function due to partial resolution of the primary disease, e.g. abstinence from alcohol in alcoholic cirrhosis, lamivudine in hepatitis B. However, in most of the cases, HRS is a fatal complication, and the only definitive treatment currently available is liver or liver-kidney transplantation [81].

A number of other treatment modalities have been tested for the management of HRS, but most evidence is derived from small no controlled studies. The primary role of these treatment options is to provide a bridge to liver transplantation. Treatment may also provide acute reversal of renal failure and some symptomatic relief, but relapse is a common occurrence.

Alpha-Adrenergic Agonists

The combination of octreotide (somatostatin analogue) at a dose of 0.1-0.2 mg tid plus midodrine (a-adrenergic agonist) .7.5-12.5 mg tid is a commonly used treatment for HRS. The goal is to increase Mean Arterial Pressure by ≥ 15 mmHg. Although its impact on splanchnic circulation in patients with cirrhosis is unknown midodrine can cause systemic vasoconstriction. Octreotide inhibits secretion of glucagon, which may play a role in the vasodilatation associated with cirrhosis. To notice that neither compound appears to have single agent activity [82, 83].

Clinical trial experience evaluating octreotide/midodrine in HRS is relatively limited, with a total of two prospective pilot studies using different dosing regimens and two retrospective series. [82, 84-86].

In one prospective, non-randomized study of patients with type 1 HRS, Angeli and colleagues examined a group of five patients treated with oral midodrine and parenteral

octreotide plus 20% albumin solution versus eight patients treated with intravenous dopamine plus the same amount of albumin.

All patients receiving octreotide/midodrine/albumin survived the two-day treatment period, whereas seven of eight patients in the dopamine/albumin group died within 12 days of the study period [82].

The other study, conducted by Wong et al., [86] was a single-arm trial of 14 patients treated with oral midodrine, a bolus injection of octreotide followed by intravenous octreotide, and 50 g/day of intravenous albumin. A total of 10 patients had a gradual reduction of SCr levels and were considered responders, while four patients were considered non responders.

In a retrospective study of 53 patients administered octreotide and midodrine and 21 concurrent (but nonrandomized) control subjects, treatment was associated with a significant reduction in mortality (49 versus 67 % in the control group) and a significantly higher incidence of a reduction in serum creatinine concentration (30 versus 14 %) [84].

Thus, midodrine when used in combination with octreotide appears to be a potentially useful agent for treating HRS. It may improve length of survival and transplantation rates, particularly in patients with type 2 HRS. Its oral administration makes it an intriguing option for patients who need long-term therapy or those being treated outside the intensive care unit.

Noradrenalin

Noradrenalin has been studied in three relatively small pilot studies in HRS. In the first study, its combination with albumin and furosemide reversed HRS in 10 of 12 patients with type 1 disease; however, ischemic episodes were reported in two of them [87, 88]. Two more recent small, prospective, randomized trials have examined the use of noradrenalin plus albumin in type 1 HRS, compared (n=10 and n=20, respectively) with terlipressin plus albumin (n=12 and n=20, respectively) [89, 90].

Although these results appear encouraging, larger randomized, controlled studies are required to elucidate the role of noradrenalin in the treatment of HRS.

Vasopressin Analogs

Vasopressin analogs have been shown to have a substantial effect on splanchnic circulation. [91].

Although ornipressin and vasopressin appear to be efficacious in HRS causing effective circulating volume expansion with increase in glomerular filtration rate [92, 93], they also exert substantial ischemic adverse effects in the splanchnic, muscular, and coronary circulations and were therefore abandoned [92, 93].

The newer agent terlipressin was developed in order to obtain the same efficacy results with other vasopressin analogs but with less toxicity, and it is currently the most studied agent in type 1 HRS.

A systemic analysis of three small trials involving a total of 51 patients, with co-interventions that included albumin, fresh frozen plasma, and cimetidine, suggested that terlipressin significantly lowered mortality rates (risk difference -0.34, 95% CI -0.56 to -0.12) and improved renal function (as assessed by creatinine clearance, serum creatinine levels, and urine output) [94].

Two meta-analyses of clinical trials on terlipressin were published in 2006 [94, 95]. One of them included data from 154 unique patients from 10 trials. The study found that terlipressin offers substantial improvement in HRS outcomes although there was a relatively high recurrence rate after terlipressin withdrawal (56%).

A Cochrane review that analyzed data from four trials in a total of 48 patients reached similar conclusions, that terlipressin reduced mortality by 34%. Mortality in the control was 65% [94]. Terlipressin also improved renal function, SCr, and urine output.

Although these data are very promising, further studies are needed to better define its risks and benefits in the hepatorenal syndrome, particularly whether the drug's salutary effect on renal function outweighs its ischemic complications.

Other Agents

Dopamine agonists, endothelin antagonists, misoprostol, N-acetylcysteine, and angiotensin converting enzyme (ACE) inhibitors have been tested alone or in combination but the benefit is conflicting [96-99]. For this reason their use in the treatment of hepatorenal syndrome cannot be recommended.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS can lower portal hypertension, improve renal function, and prolong survival in patients with advanced cirrhosis and ascites. [100, 101].

It appears to be a feasible option for patients with either type 1 or type 2 HRS. Insertion of the shunt within 4–6 weeks of the onset of HRS has shown improvement of renal function, and survival. [102]. Improvement in renal function after TIPS may not occur immediately, but several weeks later [92, 102, 103]. Placement of TIPS is not without risk, and careful patient selection may optimize safety and efficacy in patients with HRS.

A model scoring system based upon the survival of 231 patients who underwent elective TIPS was devised to predict survival after the procedure [104]. Such patients have a median survival of three months or less following the procedure.

Overall, these results suggest that, in selected patients with hepatorenal syndrome, TIPS may provide a short-term benefit. Given the risks associated with this procedure (particularly the high incidence of encephalopathy), it should be considered only as a last resort in patients who are not a candidate for or are awaiting liver transplantation

Renal Replacement Therapy

The use of continuous or intermittent RRTs provides an opportunity to support renal function in patients with HRS. However, few studies have evaluated RRT for the treatment of HRS.

A retrospective analysis of 26 patients with HRS demonstrated that 7 (44%) of 16 patients receiving hemodialysis survived versus 1 (10%) of 10 patients who did not receive hemodialysis. [105]. A more recent prospective observational study evaluated the predictive factors for overall and 30-day survival during RRT. Eight (27%) out of 30 patients were alive at 30 days (median survival 21 days). Only three patients who received a liver transplant lived longer than 1 year [106].

Another dialysis technique, termed ascites reinfusion dialysis, has been associated with some success in a very limited number of patients with refractory ascites and acute renal

failure [107]. With this approach, ascites is conveyed via an infusion pump into the arterial inlet of a hemodialysis apparatus. This results in an ascites/blood mixture of 5 % ascites/95 % blood, which is pumped through the dialysis membrane. This mix is then reinfused back into the patient. Survival on dialysis is generally limited by the severity of the hepatic failure, as well as concurrent respiratory failure. Moreover renal replacement therapy is frequently difficult to perform in patients with hepatorenal syndrome since decompensated hepatic function is associated with hemodynamic instability [106]. Thus, although the use of RRT has been proven that prolongs survival in patients with HRS, at this time its use can be recommended only in those who have some other accepted indication for RRT (e.g., overt uremia, hyperkalemia) and are candidates for liver transplantation.

Artificial Hepatic Support

Several hepatic support systems have been evaluated for the treatment of combined liver and kidney failure. These support systems include the Molecular Adsorbent Recirculating System (MARS; Gambro AB, Stockholm, Sweden), the Fractionated Plasma Separation, Adsorption and Dialysis system (Prometheus; Fresenius Medical Care, Bad Hamburg, Germany), single-pass albumin dialysis (SPAD), and single-pass albumin extended dialysis (SPAED) [108-111].

These systems are intriguing because they can remove water-soluble and albumin-bound toxins and provide combined hepatic and renal support [112, 113]. Although they have demonstrated the ability to improve relative laboratory values; more research is needed to determine the clinical impact of these artificial liver support therapies.

Hypotension during extracorporeal hepatic support treatment, cost, and the need for an additional secondary albumin dialysis circuit should be considered before initiating therapy. Continued advances in circuit functionality, plasma separation techniques, and adsorption column and filter capabilities could provide a novel approach to the treatment of cirrhosis and HRS.

B) Sepsis

Although AKI in sepsis and septic shock was traditionally thought to result from renal ischemia secondary to inadequate renal blood flow recent studies in both humans and animals demonstrate that sepsis-associated AKI results from the host response to infection and not solely from decreased renal perfusion with ischemia. This implies the release of a vast array of inflammatory cytokines, arachidonic acid metabolites, vasoactive substances and thrombogenic agents. These biologically active mediators lead to apoptotic cell death of glomerular endothelial and proximal tubular cells [114, 115] and after a chain of reactions assembly of iNOS protein which culminates in the formation of NO with systemic vasodilatation [116, 117].

Therefore, since the pathophysiological mechanisms in sepsis induced AKI are shifting from vasoconstriction and ischemia to vasodilatation and hyperemia and from acute tubular necrosis to acute tubular apoptosis our therapeutic approaches need to be altered accordingly [118-120]

Prevention measures and therapeutic strategies common with other ischemic or nephrotoxic ATNs (hydration, loop diuretics, dopamine and fenoldopam administration, maintenance of mean arterial pressure ≥ 60 mmHg and avoidance of non-ionic contrast agents

and nephrotoxic drugs) as well as renal replacement therapy are reviewed in the corresponded chapters. [119]

In the following we will discuss two emerging and encouraging new treatment concepts specific for sepsis-induced AKI.

Activated Protein C

Acquired protein C deficiency is common in severe sepsis and is associated with a higher incidence of AKI and mortality, potentially as a result of decreased generation of endogenous aPC. Endogenous aPC plays a fundamental role in a coordinated system for controlling thrombosis, modulate endothelial dysfunction by blocking cytokine signaling, adhesion molecule expression, vascular permeability, apoptosis and leucocyte migration [121].

The administration of aPC appears to improve renal perfusion, decrease leukocyte-endothelial interactions, downregulate iNOS mRNA production, and improve renal function in a variety of animal models of AKI, including endotoxin and polymicrobial sepsis.

A retrospective analysis of the PROWESS trial [122] revealed that therapy with activated drotrecogin alfa was associated with improved renal function compared to placebo in patients who had severe protein C deficiency. Treatment with activated protein C (APC) reduced progression to renal failure as well as the need for renal replacement therapy.

Notwithstanding, at a clinical level, there has been much controversy about the efficacy of APC [123]. Such controversy has led to calls for more randomized, controlled studies of patients with sepsis. On 10/25/2011 Eli Lilly and Company announced withdrawal of drotrecogin alfa from the worldwide market, since the recent study PROWESS-SHOCK did not show a substantial survival benefit in patients with sepsis and septic shock.

Caspase Inhibitors

Caspases are enzymes that are believed to play a key role in apoptosis. Du et al. [124, 125], in a series of experiments in murine tubular epithelial cells, demonstrated the central role of caspase-8 in mediating apoptosis in response to exogenous nitric oxide or cytokine-induced nitric oxide synthesis.

Although epithelial cell apoptosis could be blocked by caspase-8 inhibition using z-IETD-fmk and Caspase inhibitors have been developed as antiapoptotic agents later Cauwels et al. [126] demonstrated that in a model of TNF-induced shock in mice, caspase inhibition was in fact associated with enhanced oxidative stress, mitochondrial damage, hyperacute hemodynamic collapse, kidney failure, and death.

Nonetheless, despite our limited understanding of the complex biology of apoptosis in sepsis, some promising results have emerged from the use of an endogenous phospholipid growth factor (lysophosphatidic acid) with antiapoptotic properties [127].

C) Acute Interstitial Nephritis (AIN)

Most cases of drug-induced AIN were due to methicillin. The drug has been withdrawn from the market since it was found that the incidence of AIN is 17% if given more than 10 days [128, 129]. For this reason we will not refer to studies pertinent to methicillin-induced AIN.

Discontinuation of the offending drug is the most important measure leading in recovery of renal function in most cases. It is considered that decreased likelihood of recovery have

individuals with prolonged renal failure (>3 weeks duration), AIN secondary to NSAIDs, as well as specific histologic findings on kidney biopsy like interstitial granulomas, interstitial fibrosis and tubular atrophy [130].

Should renal failure persists, high dose of prednisolone at 1 mg/kg/day orally is recommended. However, treatment with glucocorticoids is debated by many clinicians since RCT do not exist and data are conflicting.

Buysen et al. evaluated 27 subjects with idiopathic AIN or secondary to ampicillin, NSAIDs, cimetidine, and infection [131]. Ten patients did not show any improvement after drug discontinuation or treatment of infection. Intravenous methylprednisolone 1 g for 3 days followed by oral prednisone 40-60 mg for 3-4 weeks resulted in 60% complete response and 40% partial response.

A retrospective, multicenter study compared glucocorticoids with no treatment in subjects with biopsy-proven drug-induced AIN [132]. Steroid treatment resulted in decreased requirements of renal replacement therapy at 18 months (4 versus 44%), and improved serum creatinine levels compared with no treatment (2.1 versus 3.7 mg/dl). When treatment was initiated ≤ 7 days of drug discontinuation the likelihood of renal recovery was higher.

However, other studies showed no benefit from treatment with glucocorticoids in individuals with AIN [128, 130, 133-135]. More specifically, in one study of 42 subjects with biopsy-proven AIN, 26 received glucocorticoids [133]. These patients received IV methylprednisolone for 3 days followed by oral prednisolone 0.75 mg/kg tapered over 3-6 weeks. The study showed no benefit in reducing serum creatinine at 1, 6, and 12 months with steroids compared with no treatment.

There are two possible explanations for these negative results; the first is the severity of AKI in those series; the second is that many patients had NSAID-induced AIN which does not usually respond to glucocorticoids [128, 133, 136].

Recently we published a case of sulfasalazine-induced AIN [137]. When we reviewed the literature we found that most patients who did not respond to treatment with corticosteroids were those who developed AKI more than 12 months after the initiation of sulfasalazine.

In general, if we take into account that short-term treatment with glucocorticoids is relatively safe, it is recommended to be given if renal function does not improve in 3-7 days after discontinuation of the offending drug.

In that occasion renal biopsy should be prudent in order to exclude histologic types which do not respond to immunosuppressive treatment. Prednisone at an initial dose of 1 mg/kg/day (40-60 mg) for at least 1-2 weeks and subsequently tapered over 2-3 months will improve renal function in most cases. The improvement is expected in 1-2 weeks after initiation. Intravenous methylprednisolone 0.5-1 g/day for 3 days is recommended in severe cases.

In glucocorticoid-dependent or -resistant patients mycophenolate mofetil at a daily dose of 1-2 g for at least 12 months should be given [138].

If the above measures fail and the patients meet the criteria for renal replacement therapy [134, 135, 139], this will be most of the time short-term and 90% of patients will be dialysis-independent [133, 140, 141].

D) Cardiorenal Syndrome

In general reduced GFR in patients with CHF in the acute phase or in the long term is an adverse prognostic sign. More specifically, for every reduction of GFR by 10 ml/min, mortality increases by 15% [142]. Given in absolute creatinine values, in patients hospitalized

for acute decompensated heart failure (ADHF), an abrupt increase in serum creatinine level >0.3 mg/dL (>26.5 μ mol/L) from baseline is associated with increased mortality [143]. Other consequences are longer hospital stays, and more frequent readmissions. This acute increase occurs in the 21%-45% of hospitalizations for ADHF, putting the magnitude of the problem [144-147].

As long as GFR is an important prognostic sign in CRS, attempts should be aimed to improve renal function. However, there is no medical treatment that can improve renal function. Moreover, even in that case we would not know if the improvement of renal function will improve survival. There is supporting evidence that improvement in cardiac function can improve by its turn renal function in both types 1 and 2 CRS [148-150]

Loop diuretics are the first line treatment of both types of CRS (acute and chronic). It is interest that while, as expected, serum creatinine levels should be increased or, at least remain stable after treatment, some patients have improvement of renal function. An explanation of this at a first glance paradoxical effect, it is considered to be due to reduction of the intraabdominal pressure along with a reduction in right ventricular dilatation. However, even in the case that renal function deteriorates, aggressive fluid removal in overload states, results in improved survival [151].

Angiotensin converting enzyme inhibitors as well as angiotensin receptor blockers is an important part of the treatment of systolic HF because it improves symptoms, reduces hospitalizations and increases survival. Of course the survival benefit is not due to increase of GFR, since it is known that these agents may moderately worsen renal function.

Intravenous vasodilators such as nitroglycerine, nitroprusside and nesiritide are indicated in acute decompensation manifested with pulmonary edema.

The dose of nesiritide is 2 μ g/kg bolus IV followed by a continuous infusion of 0.01 microg/kg per min [152, 153]. Nesiritide may decrease GFR that is due at least in part to the fall of blood pressure.

Administration of inotropes other than digoxin are warranted only in the case of acute decompensation with cardiogenic shock. Otherwise, dobutamine, dopamine and milrinone may increase mortality if given for other indications.

Tolvaptan, an oral vasopressin (V_2 -receptor) antagonist may provide benefit in patients with cardiorenal syndrome that is resistance to high dose diuretics. It produces electrolyte-free water diuresis. However, it is only approved for use in patients who have hyponatremia [154].

In ultrafiltration isotonic fluid from the venous compartment is removed by plasma filtration of plasma through a semi permeable membrane. It is the last resort in patients with acute decompensation and diuretic resistance. This does not necessarily mean that the patient has advanced kidney disease. In that case the failed heart cannot manage the overload by increasing its workload and fails. The patient becomes oliguric due to the decreased renal perfusion. There are two RCT (UNLOAD and RAPID-HF) that evaluated the ultrafiltration in comparison with aggressive diuretic treatment [155, 156]. In the first study a total of 200 individuals with HF and ≥ 2 signs of fluid overload participated. Patients were randomized to undergo continuous veno-venous ultrafiltration or to receive diuretics. Ultrafiltration resulted in better body weight reduction, fluid removal and reduced the need of re-hospitalization within 90 days.

The second study conducted earlier evaluated the efficacy of ultrafiltration in acute decompensated HF with fluid overload. Although it resulted in not significant weight loss

compared with diuretics, the study opened the green light for the use of ultrafiltration for this indication.

It is known that adenosine reduces GFR because of the afferent arteriole constriction. This effect is produced by its action on the adenosine -1 receptor [157]. Therefore a drug that blocks selectively adenosine-1 receptor could theoretically increase GFR and increase diuresis [158].

The PROTECT trial which was a prospective, phase III, double-blind, placebo controlled study, compared the experimental selective A1 adenosine receptor antagonist rollophylline with placebo in 2033 hospitalized patients with HF and kidney dysfunction [159]. Subjects were randomized in a 2:1 ratio to receive either rollophylline 30 mg IV for up to 3 days or placebo. Primary endpoint was the success rate defined as symptom improvement. Rollophylline did not improve symptoms compared with placebo. In regards to renal dysfunction there was not any significant difference in deterioration of renal function between the groups. Finally, death from cardiac or renal cause and readmission rate within 60 days was similar between the groups. The authors concluded that the results do not encourage its use in patients with cardiac and renal failure.

E) Rhabdomyolysis

As mentioned earlier in the prevention section, management of the underlying cause as well as fluid resuscitation is the best measure once a patient presents with rhabdomyolysis.

Metabolic complications include hyperkalemia, hypocalcemia, hyperphosphatemia, and hyperuricemia.

Calcium supplementation for hypocalcemia is needed only in symptomatic hypocalcemia or for the management of severe hyperkalemia.

Hyperkalemia should be expected and may happen even in the absence of severe renal failure due to potassium release for injured muscles. Treatment of hyperkalemia must be aggressive with calcium gluconate, dextrose with insulin, and bicarbonates. Dialysis may be required for refractory hyperkalemia, especially if the patient is oliguric or anuric.

Hyperuricemia must be treated with allopurinol 300 mg/day if serum uric acid levels exceed 8 mg/dL (476 μ mol/L). Others believe that the same dose must be given if there is a 25 % increase from baseline.

In established AKI, careful monitoring of fluid and electrolyte balance is needed. Indications for renal replacement therapy are fluid overload, hyperkalemia, severe acidemia, and uremia.

Rhabdomyolysis-induced AKI generally has favourable prognosis. Most patients will be dialysis-independent and with normal or near normal renal function [160].

F) Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP)

Thrombocytopenia with microangiopathic hemolytic anemia when acute renal failure is the dominant feature the condition is called HUS. If symptoms from CNS predominate, the diagnosis is TTP. However, there are patients with renal disease as well as focal neurological signs [161-164].

TTP-HUS if left without treatment results in irreversible kidney failure, progressive neurologic deterioration, cardiac ischemia, and the end result is death [161, 165]. Without

plasma exchange mortality approximates 90 percent [161, 165, 166], and reaches 20 % with plasma exchange. This is the most effective treatment available for this condition [166-169]. Plasma therapy must be initiated even if diagnosis is not certain. The reason is that patient's condition may deteriorate very quickly and lead to death [170-175]. Plasma exchange acts by reversing the platelet consumption that causes thrombosis and all the clinical picture which characterizes HUS-TTP [167, 170, 176-181].

During plasma exchange patient's plasma is replaced by normal plasma. This has two implications 1) the circulating antibody against ADAMTS13 is removed together with the very high molecular weight von Willebrand factor (VWF) multimers. 2) Normal plasma contains ADAMTS13 which is the missing protease.

Treatment with oral prednisone 1 mg/kg/day or IV methylprednisolone 125 mg twice daily is warranted in idiopathic TTP/HUS, when renal failure is not severe and in patients that low platelet count does not respond to plasma exchange [163, 171]. Patients in whom thrombocytopenia recurs when plasma therapy is discontinued have also indication for treatment with glucocorticoids [182].

These patients with mild disease and not severe kidney dysfunction plasma exchange may be initiated if platelet count does not rise 48 hours after initiation of glucocorticoids [163].

Regarding the choice of plasma therapy, plasma exchange appears to be superior than plasma infusion as deduced from two RCT in whom 210 individuals participated [167, 178].

In the first study of 102 subjects with TTP/HUS remission and survival rate at 6 months were as follows: plasma exchange remission 78%, survival 78%, plasma infusion remission 38%, survival 50% [167]. The superior benefit from plasma exchange is due to infusion of more plasma rather than the removal of the circulating antibody against ADAMTS13 and of the very high molecular weight von Willebrand factor (VWF) multimers [183].

Although inferior to plasma exchange high dose plasma infusion (25 to 30 ml/kg per day) is recommended in emergency situations as initial treatment when plasma exchange cannot be promptly commenced [184, 185].

The atypical HUS (aHUS) is a condition considered to be due to defective complement regulation in approximately 50% of cases [186-190]. Plasma infusion or plasma exchange is the mainstay of treatment. However, even with plasma therapy, many times renal function continues to deteriorate resulting in ESRD.

There is supporting evidence that patients with aHUS can have genetic defects which lead in excessive activation of the alternative complement cascade [172, 191]. These individuals could be with agents that act on the membrane attack complex (MAC) composed of C5b-9 [190]. In general treatment of resistant cases is challenging. Eculizumab, a humanized monoclonal antibody against C5, has recently been shown to be an effective treatment in aHUS [191-195] when plasma therapy fails to halt progression of renal dysfunction [190].

G) Rapidly Progressive Glomerulonephritis (RPGN)

RPGN if not treated quickly evolves into ESRD requiring RRT over a period of weeks to months.

Treatment of RPGN generally consists of pulse corticosteroids, oral corticosteroids, cyclophosphamide and plasmapheresis. Azathioprine also has a role in the treatment of this condition. These treatments were established from old studies when the full categorization of

RPGN was not yet known. However, it was known that prednisolone alone or in combination with azathioprine add little benefit [196].

Intravenous methylprednisolone 0.5-1 g/day for 3 days is recommended in all patients presented with RPGN before histologic or serologic diagnosis is available. Plasmapheresis should be initiated if the patient has hemoptysis at presentation. Renal biopsy must be performed at the earliest possible. Pulse methylprednisolone will not alter the histologic findings on renal biopsy. After the empiric treatment with methyl prednisolone± plasmapheresis, further therapy will be guided according to the histologic findings.

We will describe the treatment of all four forms of RPGN:

- 1 Type 1: anti-GBM (Goodpasture's) disease
- 2 Type 2: immune complex (IgA, post-infectious, lupus nephritis, mixed cryoglobulinemia)
- 3 Type 3: pauci-immune (Wegener's, microscopic polyangitis)
- 4 Type 4: double antibody with features of both type 1 and type 3
- 5 Idiopathic immune complex (type 2) and ANCA negative (type 3)

1. Treatment of Anti-GBM Disease

Plasmapheresis and immunosuppressive treatment with cyclophosphamide is the treatment of choice for anti-GBM disease [197-200]. The aim of immunosuppressive treatment is to prevent formation of autoantibodies, while plasmapheresis removes the already existing in the blood. Moreover, plasmapheresis removes other inflammatory mediators such as complement.

Pulse intravenous methylprednisole 15-30 mg/kg/day for 3 days (maximum of 1 g/day), followed by oral prednisone 1 mg/kg/day (maximum 60-80 mg/day) tapered off after remission is achieved (most of the time within 3 weeks) to 20 mg/day. This dose is continued for 6 weeks with slow tapering over 6-9 months.

Cyclophosphamide is given orally at 2 mg/kg for 2 months initially.

Plasmapheresis is performed daily or alternative day 4 L exchanges for 2-3 weeks and albumin is administered to replace losses from the procedure [197, 198, 201]. In the case of pulmonary hemorrhage or recent (on the previous 3 days) kidney biopsy, 1-2 L of fresh frozen plasma instead of albumin is used for substitution at the end of the exchange to replete coagulation factors [202, 203].

The total duration of treatment is judged by the fact that autoantibody formation ceases at 6-9 months [199, 204].

Plasma anti-GBM antibody levels must be monitored every 1-2 weeks until they are negative for two consecutive times, but not less than 6 months from presentation. Re-appearance of anti-GBM antibodies warrants restarting plasma exchange.

When anti-GBM antibodies are detected in plasma at 2 months, cyclophosphamide must be continued for 2 more months. If antibodies still present, then oral azathioprine at 1-2 mg/kg must substitute for cyclophosphamide for a total of 6-9 months. Prophylaxis against *Pneumocystis jiroveci* pneumonia with trimethoprim-sulfamethoxazole one single-strength tablet every day or one double-strength tablet three times a week is recommended as long as the patient receives. When trimethoprim-sulfamethoxazole is contra-indicated, atovaquone 1500 mg daily or dapsone 100 mg daily can be used instead [205]. Prophylaxis against

corticosteroid-induced osteoporosis may also be needed with calcium plus vitamin D, plus bisphosphonates.

Prognosis

Levy et al. reviewed 71 cases of anti-GBM disease [198]. The mean age was 40 years (range 17-76 years). Sixty two percent (62%) presented with pulmonary hemorrhage. Thirty nine patients (55%) required dialysis and 13 (18%) presented with serum creatinine levels ≥ 500 $\mu\text{mol/l}$ on presentation, but did not require dialysis in the first 72 hours. The median follow up was 90 months (range 12-289 months). Treatment consisted of oral prednisolone 1 mg/kg/day (maximum 60 mg/day) and oral cyclophosphamide 2-3 mg/kg/day. Subjects >55 years old received reduced dose of cyclophosphamide. Duration of treatment was 6-9 months for prednisolone and 2-3 months for cyclophosphamide. A few patients received oral azathioprine 1-2 mg/kg/day for 8 weeks. Plasma exchange 50 ml/kg (maximum 4l) was performed for 14 days or until anti-GBM antibody was not detectable in plasma. Substitution of Human Albumin (5%) with the addition of calcium and potassium was used to replace removal. Individuals who underwent recent (in the last 3 days) surgery or had pulmonary hemorrhage, 150-200 ml of fresh frozen plasma at the end of the exchange was administered.

Patient and renal prognosis were better when serum creatinine level was less than 500 $\mu\text{mol/l}$ at presentation, and worse in subjects who needed prompt dialysis. Patient and renal survival at 1 and 5 years is summarized in Table 5.

2. Type 2: Immune Complex (IgA, Post-Infectious, Lupus Nephritis, Mixed Cryoglobulinemia)

IgA Nephropathy

When disease is rapidly progressive and/or crescent formation on kidney biopsy, combined immunosuppressive treatment is indicated. There are uncontrolled studies evaluating patients with crescentic, rapidly progressive glomerulonephritis supporting the use of intravenous pulse methylprednisolone followed by oral prednisone, intravenous or oral cyclophosphamide, and/or plasmapheresis [206-210].

Glucocorticoids probably reduce the injury due to the acute inflammation but do not correct the underlying abnormality that is responsible for the IgA production [211].

Rocatello et al. evaluated the efficacy of combined immunosuppressive treatment with methylprednisolone, oral CYC and plasmapheresis in six patients with crescentic glomerulonephritis secondary to IgA nephropathy [208]. All subjects received IV pulse methylprednisolone 15 mg/kg/day for 3 days followed by oral prednisone 1 mg/kg/day for 4 weeks and then, 0.75 mg/kg for additional 4 weeks. CYC was given at 2.5 mg/kg/day for 8 weeks. The patient finally, underwent plasmapheresis. The authors reported substantial clinical improvement at two months, decrease in serum creatinine, as well as proteinuria.

Another study evaluated 12 patients with crescentic proliferative IgA nephropathy, plasma creatinine concentration of 2.7 mg/dL (240 $\mu\text{mol/L}$) and 4g/24h protein excretion at presentation (210). Patients received pulse methylprednisolone (15 mg/kg per day for three days) IV followed by oral prednisolone 1 mg/kg per day for 60 days, then 0.6 mg/kg per day for 60 days. Subsequently the dose was reduced to 0.3 mg/kg per day for 60 days, and all

patients were on 10 mg/day when a repeat biopsy was performed. Moreover, intravenous CYC 0.5 g/m² was administered for 6 months.

Table 5. Patient and renal survival of patients with anti-GBM disease

	Serum creatinine <500 μ mol/l (n=19)	Serum creatinine \geq 500 μ mol/l, dialysis not required in the first 72 hours (n=13)	Serum creatinine \geq 500 μ mol/l, dialysis required in the first 72 hours (n=39)
1 year			
Patient survival	100%	83%	65%
Renal survival	94%	82%	8%
5 years			
Patient survival	94%	80%	44%
Renal survival	94%	50%	5%
Patient survival at last follow up	84%	62%	37%

Treatment resulted in significant reduction of serum creatinine concentration (from 2.7 to 1.5 mg/dL [240 to 133 μ mol/L]) and in proteinuria 1.4 g/day. Moreover, the repeat biopsy at that time demonstrated no cellular crescents and endocapillary proliferation in all patients. Treatment with prednisone 0.15 mg/kg/day continued for 3 years. Comparisons were made with historic controls who received no treatment. The incidence of ESRD at 3 years was significantly lower in the group that received treatment compared with the controls [1/12 (8%) versus 5/12 (42%) respectively].

Data do not support the use of cyclosporine for this indication [207, 212].

Lupus Nephritis

Patients presented with acute renal failure, or florid crescentic glomerulonephritis, need treatment with CYC 500 mg IV every 2 weeks for 3 months (a total of six doses=3g cumulative dose along with, pulse IV methylprednisolone at 500 to 1000 mg daily given over 30 minutes daily for three days to attain a rapid immunosuppressive effect. This is due to the fact that conventional doses of oral prednisolone may be ineffective and 10-14 days are needed for IV CYC to work. Alternatively, IV CYC can be given monthly at 0.5-1 g/m² for a total of 4-7 doses. Monitoring of WBC count as well as renal function tests is required at least every 2 weeks. Dose adjustment maybe needed. In the case that leukocyte nadir is <4000/ μ L and/or the neutrophil count < 1500/ μ L, the dose must be reduced by 0.25 g/m² of BSA or temporarily withheld. Contrarily, if WBC nadir is > 4000/ μ L, the neutrophils are > 1500/ μ L, or there is no improvement, the next dose may be increased by 0.25 g/m² of BSA. However, in any case the maximum dose should not exceed 1.0 g/m² of BSA.

The IV pulse methylprednisolone is followed by oral prednisolone 0.5 mg/kg/day for four weeks, which is subsequently tapered to low dose maintenance therapy (0.1-0.2 mg/kg of prednisone per day).

Azathioprine (AZA) or mycophenolate mofetil (MMF) for maintenance immunosuppression appear to be superior to CYC and glucocorticoids. This observation is

based on a RCT of 59 patients with severe lupus nephropathy (46 had diffuse proliferative, 12 focal proliferative, and 1 membranous lupus) [213]. Forty three patients were black or Hispanic that is known to respond less well to CYC and generally have worse prognosis than whites. These individuals after an induction therapy with 4-7 monthly cycles of intravenous pulse cyclophosphamide and glucocorticoids were randomly assigned to receive maintenance therapy with one of the following plus low-dose oral prednisone (0.1 to 0.2 mg/kg/day): MMF (500 to 3000 mg/day), AZA (1 to 3 mg/kg per day), or IV CYC (0.5 to 1.0 g/m² every three months). The median duration of treatment was 24 (CYC), 29 (MMF), and 30 months (AZA).

Patient and renal survival at 6 years of follow up were the primary efficacy end points of this clinical trial. The event-free survival rate regarding patient and renal survival was significantly higher with MMF and AZA compared with CYC (90 and 80 versus 45 percent). CYC was also associated with more infections and a higher incidence of amenorrhea. Among patients who experienced a renal relapse the numbers for MMF, AZA and CYC were three, six and eight patients respectively. The difference between MMF and CYC was statistically significant.

Plasmapheresis is generally not supported from RCT since it offers no additional benefit [214, 215]. Moreover, cytotoxic therapy combined with plasmapheresis appears to be associated with higher rates of infection and death in this patient population [216].

However, plasmapheresis may have a role in selected patients with AKI, such as those with severe crescentic LN that require renal replacement therapy (especially if there is concomitant ANCA, as deduced from the MEPEX clinical study of patients with Wegener's granulomatosis) or those with proliferative lupus nephritis and thrombotic thrombocytopenic purpura with antiphospholipid antibodies.

Mixed Cryoglobulinemia

Aggressive therapy with plasmapheresis and immunosuppression is required in patients with idiopathic mixed cryoglobulinemia and acute severe disease manifested with rapidly progressive renal failure.

Plasmapheresis serves to remove cryoglobulins from circulation, while immune-suppressive treatment prevents formation of new. Immunosuppressive treatment consists of methylprednisolone 1000 mg daily intravenously for three days, followed by oral prednisone 1 mg/kg and cyclophosphamide [200, 217-219].

As deduced from uncontrolled studies, combination treatment leads to a response rate of 55-87% of individuals (200, 220). Although renal function improves or stabilizes with treatment, patient may succumb from extrarenal causes [218]. Finally, there are other concerns when a patient with mixed cryoglobulinemia initiates combination treatment: the profound immunosuppression can exacerbate HCV infection or low-grade non-Hodgkin lymphoma [218, 221].

Plasmapheresis. Most of the time the prescription includes one plasma volume exchange three times weekly for two to three weeks. The replacement fluid needs to be warmed 5% human albumin, otherwise circulating cryoglobulins may precipitate [222].

3. Type 3: [Pauci-Immune (Wegener's, Microscopic Polyangitis)]

In Wegener's granulomatosis (WG) and microscopic polyangitis (MPA) immunosuppressive treatment must be initiated in patients with active disease. The Birmingham Vasculitis Activity Score is used for this purpose (BVAS/WG) [223-225]. According to BVAS/WG score any major item that is organ or life threatening such as gangrene, scleritis, retinal exudates/hemorrhage, sensorineural deafness, mesenteric ischemia, alveolar hemorrhage, respiratory failure, RBC casts on urine microscopy and a rise in creatinine >30% or reduced eGFR by >25% warrant prompt initiation of combination therapy with glucocorticoids plus Cyclophosphamide (CYC). Patients who refuse or cannot take CYC, rituximab is another option. Occasionally, methotrexate can be given in mild disease with minimal or no renal involvement. Finally, patients with severe disease will benefit from plasmapheresis.

Cyclophosphamide (CYC) can be given either orally or intravenously in WG or MPA. Clinical studies have shown similar remission rates. Oral CYC is associated with fewer relapses but higher rates of leucopenia, and possibly infection [226-230].

Oral CYC is given at 1.5-2 mg/kg daily. Duration of treatment is usually 3-6 months or until a stable remission is attained. White blood cell (WBC) count is monitored at least every two weeks and must be >3000/ μ l with neutrophils >1500/ μ l. Dose reduction or temporal withholding is required when leucopenia develops. The expectant lymphopenia is not an indication to withhold or reduce the dose. Furthermore, in renal failure dose reduction is also required but doses less than 1 mg/kg/day do not seem to work well.

The initial dose of pulse IV CYC is 750 mg-1 g/m² of Body Surface Area (BSA). In the obese, elderly or patients with renal dysfunction (eGFR <40ml/min) the dose must be reduced to 500mg/m² of BSA.

The subsequent doses will be adjusted according to the WBC and neutrophil counts as well as patient's response. Monitoring of WBC is needed as mentioned earlier. WBC < 3000/ μ l, and/or neutrophils <1500/ μ l warrant dose reduction by 250 mg/m². Contrarily, if WBC is >4000/ μ l and patient does not respond to treatment the dose of CYC may increase by 250 mg/m².

In most occasions treatment is continued monthly for a total of 6 months, then every 3 months for 18 months (total duration of treatment 24 months).

Glucocorticoids

Regarding glucocorticoids disagreement between experts exists on whether all patients need to start IV pulse methylprednisolone at 7-15 mg/kg/day (maximum 0.5-1 g/day) for 3 consecutive days or only those with severe respiratory disease or crescentic glomerulonephritis.

Oral glucocorticoids consist of prednisone 1 mg/kg/day (maximum 60-80 mg/day) for 2-4 weeks. If there is significant improvement the dose can be gradually decreased to 20 mg/day by the end of 2 months. Subsequently, the dose can be gradually tapered off to zero to complete a total of 6-9 months. This treatment can be employed only if no persistent symptoms exist [231, 232]. Alternative day glucocorticoid therapy is not generally recommended.

Immunosuppressive treatment aims at induction of complete remission defined as the absence of active disease (BVAS/WG score 0). In regards to renal remission, disappearance

of hematuria or red cell casts is considered complete renal remission. Of course, hematuria may be due to other causes such as CYC toxicity. In that case red cells are not dysmorphic and hematuria resolves within 3-4 weeks from the last dose of the drug. Persistence of hematuria after that time should raise the suspicion of transitional cell carcinoma of the bladder.

It is important to stress out that complete remission means the absence of active disease and not absence of disease [233]. There are many patients with complete remission but also irreversible tissue damage when the disease was active. More specifically for renal involvement absence of hematuria and red cell casts but persistent proteinuria or slowly progressive CRF is considered complete response. These patients may benefit from ACE inhibitors. Partial remission in the kidneys means persistence of dysmorphic red cells in urine with or without red cell casts, but improvement or stable renal function and remission of extrarenal manifestations. These patients require additional treatment.

Regarding prognosis clinical trials have shown that combination treatment with oral CYC plus glucocorticoids lead in 80% survival rate, and significant clinical improvement is attained in > 90% of cases with WG/MPA. Complete remission is observed in 75% of patients [226, 227, 231, 233-239]. Most remissions are achieved within 2-6 months.

Patients who cannot tolerate or do not wish to receive CYC, rituximab (RTX) appears to be an effective alternative.

A multicenter RCT (RAVE trial) compared CYC 2 mg/kg daily orally with RTX 375 mg/m² of BSA weekly for 4 weeks. Fifty one percent of patients had relapsing disease. Individuals received IV pulse methylprednisolone 1 g, followed by oral prednisone 1 mg/kg/day. In patients who were newly diagnosed with WG, RTX was non-inferior to CYC in attaining remission within 6 months (64% versus 53% respectively). However, patients with relapsing disease responded better to RTX (remission rate RTX 67%, CYC 42%). Side effects did not differ between the groups. [240].

The second RCT called RITUXVAS included 44 patients with ANCA-associated renal vasculitis diagnosed recently [241]. Patients were randomized to a 3:1 ratio to receive methylprednisolone 1 g/day IV for 3 days, followed by oral methylprednisolone 1 mg/kg/day with tapering to 5 mg by the end of 6 months plus, either rituximab 375 mg/m² of BSA weekly for 4 weeks with two IV CYC pulses at 15 mg/kg or IV CYC monthly for 3-6 months and oral azathioprine thereafter. In the RTX group a third dose of CYC 15 mg/kg IV was given if there was progressive disease in the first 6 months. The study showed no significant differences in remission rates between the RTX and CYC only group at 12 months (76% versus 82% respectively). Side effect profile was similar between groups.

Plasma exchange is indicated in patients with severe kidney disease, concurrent anti-GBM disease or severe pulmonary hemorrhage. Contrarily, patients with mild disease can receive methotrexate 15 mg orally weekly increased to 25 mg by 12 weeks until month 10 and slow tapering to zero by 12 months [205, 242].

The patients while on immunosuppressive treatment must receive prophylaxis against *Pneumocystis jiroveci* pneumonia. Trimethoprim-sulfamethoxazole one single strength tablet every day or one double-strength tablet 3 times a week is the first option. In the case of allergy or other contra-indication (use of methotrexate) alternative options are atovaquone 1500 mg orally daily or dapsone 100 mg orally daily.

Scleroderma Renal Crisis

Scleroderma renal crisis (SRC) without treatment may evolve into ESRD in 1-2 months and death in the first year of diagnosis [243]. Effective and prompt blood pressure control is the cornerstone of treatment in SRC. With treatment renal function improves or stabilizes in approximately 70% of cases and survival approximates 80% in 1 year.

As compared with other classes of antihypertensives, ACE-I appear to be more effective in reducing blood pressure and also in improving survival in this patient population [244, 245]. The most experience is of the use of captopril; however, other ACE-I such as enalapril or ramipril may be equally effective. Moreover, captopril has rapid onset and short duration of action thus, providing an advantage, especially during the first days of the treatment. The initial dose of captopril must be 6.25 to 12.5 mg 3-4 times daily orally (or through a nasogastric tube in severe cases) and titrated according to response (maximum daily dose 300-450 mg). The goal is BP to return to the baseline within 72 hours. Since blood pressure elevation is acute, there is no risk of rapid control. However, some clinicians recommend reduction of the SBP by 20 mmHg per day.

Because SRC is characterized by bilateral intrarenal artery stenosis, daily monitoring of serum creatinine levels are recommended, especially during the first days after initiation of treatment. Initial worsening of renal function should not discourage continuation of treatment, since it is transient.

Monitoring FBC, FDP, haptoglobin, LDH and blood smear are recommended, because resolving of microangiopathic hemolysis is an indication of improvement.

Maintenance treatment with other ACE-I is continued indefinitely at low doses.

Some centers in Europe (including our) use intravenous iloprost along with ACE-I in the acute setting. The use of NSAIDs, IV contrasts and other nephrotoxins must be strictly avoided [246]. If BP control cannot be achieved with captopril, calcium channel blockers such as amlodipine or vasodilators (minoxidil) may be used. Beta-blockers are contraindicated since this condition is associated with Raynaud's phenomenon.

Other measures that may be of benefit are ARBs [247], epoprostenol and fish oil.

Even if with the optimal treatment 20-50% of patients will progress to ESRD requiring hemodialysis or peritoneal dialysis [245, 248, 249]. However, not all will remain dialysis-dependent [245].

Mortality of SRC is still high despite the optimal management and is related to the need of renal replacement therapy which is an adverse prognostic sign. In a review of 110 patients with SRC 76% survived at 1 year with ACE-I [248]. However, most of the patients died within three months had myocardial involvement [248].

C. Supportive Measures

1. Bleeding

Intracranial, gastrointestinal or bleeding from disseminated intravascular coagulopathy may contribute in the morbidity and mortality in patients with acute renal failure. Abnormalities in platelet adhesivity and aggregability are the main recognized causes.

Treatment of bleeding in AKI is directed to amelioration of the primary disorder. Although usually renal replacement therapy in chronic renal failure leads in dramatic improvement in coagulation this is not the case in acute renal failure, since the primary stimulus for AKI may also be primary instigator of the bleeding disorder. [250].

In the search for pharmacological agents that could improve hemostasis in uremia, despite the fact that factor VIII and vWF are normal in uremic patients, intravenous desmopressin was considered. In a study by Mannucci et al. the postinfusion bleeding time became normal in about 75% of them, and returned to baseline values after approximately 8 hours. [251].

Conjugated estrogens are a long-acting alternative to desmopressin, because they shorten the bleeding time with a more sustained effect lasting for 10 to 15 days. [252]. The two products can be given together, exploiting the different timings of their maximal effects.)

Cryoprecipitate infusion, ddAVP and plasmapheresis have been reported to improve the hemorrhagic tendency in thrombotic thrombocyte purpura (TTP) and haemolytic uremic syndrome (HUS).

2. Nutrition

Malnutrition has been identified as an independent contributing factor of in-hospital mortality for patients with AKI [253, 254]. Renal failure is associated with significant metabolic and immunologic disturbances along with the induction of a pro-inflammatory state which is exacerbated by malnutrition [255].

Nutritional support is, therefore, an important part of the management in these patients [254] and should be administered as early as possible, when needed.

However, during the acute phase of ARF (the first 24 hours after trauma or surgery) nutritional support should be avoided because decreased utilization of nutrients during this phase may lead to an increase of oxygen requirements, and aggravate tissue injury and renal dysfunction. [256].

Although, the optimal administration of nutrients in ARF patients has not yet been defined [257], maintenance of protein stores and correction of pre-existing or disease-related deficits in lean body mass remain the main goals of the treatment [256].

Moreover, there are complex metabolic abnormalities that affect not only proteins, but also carbohydrates and lipids, which should be taken into account before administration of the appropriate nutritional therapy [256].

Nutritional regimens for ARF have been progressively lowered, and this is in agreement with what is currently being suggested for critically ill patients [258].

Protein Metabolism

Protein catabolism and negative nitrogenous balance that accompany ARF are mainly caused by increased insulin resistance. Impairment of protein synthesis in the kidneys, acidosis, inflammatory mediators, as well as renal replacement therapy contribute to protein breakdown [256].

It is generally accepted that the optimal intake of protein or amino acids is affected mainly by the nature of the underlying cause of ARF and the extent of protein catabolism as well as the type and frequency of dialysis [256].

The recommended nutritional regimen for patients with ARF may include a protein intake of 1.5–1.8 g/kg/day [38, 259–261].

In non hypercatabolic patients, during the polyuric phase of ARF protein intake of just 0.97 g/kg body weight per day seems to be adequate [262], whereas in the polyuric recovery phase in patients with sepsis-induced ARF, a nitrogen intake of 1.3 g/kg body weight per day is required [263].

Glucose Metabolism

Hyperglycaemia may occur due to insulin resistance [264], decreased glucose uptake by skeletal muscle and accelerated hepatic gluconeogenesis [265].

Carbohydrates are considered the main source of energy in patients with ARF. Glucose, not exceeding 5 g/kg body weight/day is recommended. [254].

Lipid Metabolism

Hypertriglyceridaemia, especially low-density lipoprotein is increased, and high-density lipoprotein is decreased as a result of impaired lipolysis [266].

Recommended prescription for fat is approximately 0.5–1 g/kg body weight/day [254].

Electrolytes and Micronutrients

Electrolyte, vitamin and trace element disturbances are common in AKI and therefore special care is required when nutrition dilemma presents.

Levels of water-soluble vitamins are usually low and requirements increase, if renal replacement therapy is performed or if any hypercatabolic situation is the underlying cause of AKI. Depletion of thiamine (vitamin B1), which may occur during continuous hemofiltration, resulting to lactic acidosis and heart failure, can be prevented with administration of 600 mg thiamine [256, 267], whereas, supplementation of vitamin C should be avoided due to the risk of developing secondary oxalosis [256].

Fat soluble vitamins, vitamin A and E are reduced, while vitamin K levels are normal or even elevated [268].

It is generally accepted that most commercial multivitamin preparations for parenteral infusions contain the recommended daily allowances of vitamins and can safely be used in ARF patients [269].

Regarding to phosphate, although hyperphosphatemia is expected, and thus a parenteral nutrition with low phosphate content should be administered, some patients may present with hypophosphatemia. In this case, supplementation of 5 mmol per day is required to maintain normal plasma phosphate concentrations [256].

Metabolic Impact of Renal Replacement Therapy

Renal replacement therapy results in loss of both macronutrients and micronutrients which must therefore be supplemented in accordance to the method utilized and its intensity.

Generally, RRT results to an increase of protein breakdown as well as to loss of several nutrients with low protein binding and/or small molecular weight, such as vitamins or amino acids. A total daily loss of 10–15 g amino acids and 5–10 g protein has been reported along with significant losses of water-soluble vitamins [270].

Moreover, heat loss (350 to 700 kcal per day) is expected during continuous hemofiltration due to infusion of cooled substitution fluids and the oxidation of lactate anions that these fluids may contain [256].

Protein intake should be increased to compensate for the protein and amino acid losses during RRT of about 0.2 g/kg/day, taking into account also that about 10–15% of infused amino acids in parenteral nutrition during RRT are lost in the dialysate/ultrafiltrate [271].

Energy Requirements

The optimal nutritional regimen for patients with ARF may include a relatively low (as compared to the past) energy content (25–35 kcal/kg/day) [259–261]. A recent study suggest that energy intake of 40 kcal per kg of body weight per day, in contrast to 30 kcal, does not substantially improve estimated nitrogen balance, and did not ameliorate protein catabolism in critically ill patients with ARF. Rather, the increased energy provision appears to enhance the risk of artificial nutrition-related side effects. (hyperglycaemia, hypertriglyceridaemia and fluid overload) [257].

Energy supply should comply with a mixture of glucose and lipids in the ratio of 60/40 or 50/50. [254].

Enteral Vs Parenteral Nutrition

Enteral nutrition is the recommended form of nutritional support for patients with AKI. The provision of nutrients via the gut lumen helps maintain gut integrity, decreases gut atrophy and decreases bacterial and endotoxin translocation. If oral feeding is not possible then enteral feeding (tube feeding) may be necessary to meet nutritional requirements [272].

Taking everything into account, nutritional support should be adjusted to patient's metabolic status, the underlying disease as well as the patient's ability to cover the nutritional requirements by eating. [256].

Physicians should first identify the patients with AKI that require nutritional support and then administer the appropriate therapy according to the metabolic changes mentioned above.

There are several artificial enteral and parenteral formulas as well as prepared amino acids solutions that are used in clinical routine.

D. Renal Replacement Therapy

Patients with acute kidney injury (AKI) and most likely those with underlying chronic kidney disease (CKD) [273], often require initiation of renal replacement therapy (RRT). The potential impact of RRT on clinical outcomes in patients with AKI has been a subject of intensive investigation. The key issues to consider in RRT include indication, modality, timing of initiation, frequency and adequacy of the therapy. The link between these interconnected RRT-related variables and clinical outcomes has remained to be determined.

1. Indications

Currently, there is wide variation worldwide on the indications for and timing of initiation and discontinuation of RRT for AKI. Various parameters are used as a guide without any standards in this field. Generally, the decision to start RRT is influenced strongly by held physician beliefs in addition to patient characteristics and logistical or organizational aspects of a given institution.

There are some absolute indications (Table 6 [274, 275]), however it is clear that patients should be treated as a whole and indications for and timing of RRT must be viewed within the context of the patient's entire clinical condition. [274].

Table 6. Absolute indications for renal replacement therapy in patients with AKI

1. Fluid overload with pulmonary oedema
2. Refractory hyperkalemia >6.5 mEq/L with ECG abnormalities
3. Acidosis, pH< 7.1
4. BUN>100 mg/dl (35.7 mmol/L) or complications of severe uremia (encephalopathy, pericarditis, neuropathy/myopathy)
5. Uremic symptoms such as pericarditis, neuropathy or a general decline not otherwise explained
6. Hypermagnesemia>8 mEq/L (4 mmol/L) with anuria and absent deep tendon reflexes
7. Lactic acidosis related to metformin use
8. Drug overdose with a dialyzable toxin

2. Modality

Renal replacement therapy is delivered as hemodialysis (HD), and continuous renal replacement therapy (CRRT).The proliferation of modalities of CRRT in the last few years has provided an increasing selection of options for managing renal support.

RRT can be provided as intermittent hemodialysis (HD) or continuous (CRRT) hemofiltration (HF), alone or in combination (HDF) and newer “hybrid” therapies such as extended duration dialysis (EDD), sustained low-efficiency dialysis (SLED) [276]. Moreover, although continuous renal replacement therapies were historically delivered via an arteriovenous circuit today techniques based on venous access alone are almost exclusively used. The same is valid for the peritoneal dialysis which may still have a role only where anticoagulation is not possible or vascular access not feasible [277].

The medical literature is brimming with studies designed to demonstrate superiority of one regimen over the others, but whether the selection of treatment modality impact on patient and renal survival remain to be determined.

Although it is widely perceived that CRRT is superior to HD in hemodynamically unstable critically ill patients, prospective randomized clinical trials have failed to confirm this supposition. Several studies designed to compare the effects of CRRT and HD on systemic hemodynamics, splachnic perfusion and mortality rates [278, 279]. In a US multi-centre trial of 166 patients with AKI, Mehta and colleagues reported intensive care unit and hospital mortality rates of 59.5% and 65.5%, respectively, in patients randomized to CRRT as compared to 41.5% and 47.6%, respectively, in patients randomized to HD (p<0.02). After

covariate adjustment, there was no difference in mortality attributable to a specific modality of RRT [280]. In addition in this study there was a high rate of crossover between the treatment modalities. A US single-centre trial, randomized 80 patients to either CRRT or HD, and although greater hemodynamic stability and fluid removal rates were reported with the former, there was no difference in survival [281].

More recently, the results of the Hemodiafe Study, the largest prospective randomized controlled study comparing CRRT and HD have been reported [282]. This study enrolled 360 patients in 21 ICUs in France. There was no difference in the primary study endpoint of 60-day survival between treatment groups (31.5% in HD versus 32.6% in HDF; $p = 0.98$). Treatment modality also had no significant effect on length of stay, rate, and time to recovery of kidney function or frequency of adverse events. Interestingly, despite the hemodynamically unstable population (vasopressors were used in greater than 85% of patients), HD was not associated with increased frequency of hypotension, a finding the Hemodiafe study group ascribed to standardized use of synthetic membranes, bicarbonate buffers and adherence to strict guidelines including gradual ultrafiltration, and use of cool dialysate with a high sodium concentration.

Multiple meta-analyses comparing outcomes with HD and CRRT have been published. A 2002 metanalysis by Kellum et al. [283] that included 13 studies (of which only three were RCTs) suggested that CRRT might be associated with a lower relative mortality risk after adjustment for severity of illness and study quality. In contrast, Tonelli et al. [284] concluded that CRRT does not seem to offer any survival advantage over HD, restricting their meta-analysis to RCTs. A Cochrane review in 2007 analyzed 15 RCTs and found that mortality, renal recovery, and episodes of hypotension did not differ between modalities although mean arterial pressures were higher in patients on CRRT [285]. A meta-analysis by Bagshaw et al. [286] included nine RCTs and again showed no differences in mortality or recovery of kidney function, although CRRT was associated with less hemodynamic instability and greater volume removal.

Comparative studies of continuous and hybrid techniques are limited. A small trial randomized 39 patients to either CVVH or 12 hour, extended dialysis using a single-pass batch system and found equivalent cardiovascular tolerability and urea clearances but faster correction of acidosis and lower heparin requirements with the latter [287].

With regard to solute removal, hemofiltration relies on convective solute clearance, dialysis provides primarily diffusive clearance whereas hemodiafiltration employs a variable combination of both mechanisms. Convection provides better clearance of middle molecules or solutes with molecular weights above 500–1000 Da while HD for the small molecules such as urea and creatinine. It was proposed also that convective modalities (continuous hemofiltration and hemodiafiltration) modulate the immune response by clearing the cytokines that promote and perpetuate the systemic inflammatory response syndrome (SIRS) [288]. Indeed, CVVH was associated with lower levels of plasma tumor necrosis factor- α (TNF- α) when compared with CVVHD in patients with severe AKI and SIRS, but other cytokine levels, including interleukin IL-6 and IL-10, were not affected. It has been argued, also that cytokine clearance during hemofiltration is inconsequential in comparison to their endogenous production [289]. Thus, in the absence of outcome data, no recommendations can be made to favor either convective or diffusive modalities.

In the last years, bicarbonate has become the primary buffer for both replacement and dialysate fluids in CRRT replacing the previous used lactate and acetate. Evidence of benefit

over lactate-based solutions is inconsistent with some studies showing no substantive differences in metabolic parameters, pH, or hemodynamic status [290] whilst others have shown improved haemodynamic stability [291] and more rapid control of systemic acidosis¹⁴. Despite these conflicting data, the likelihood of benefit, especially in the sickest patients, and the ready availability of commercially-prepared bicarbonate fluid, seems to justify its use in CRRT.

In summary, the available currently published studies do not allow evidence-based guidelines for the selection of RRT modality for the treatment of AKI. Usually, the preferred modality to choose is intermittent hemodialysis for cardiovascularly stable patients, and continuous or hybrid therapies for those with cardiovascular compromise and multi-organ failure [292, 293]. The method chosen should therefore be guided by the individual patient's clinical status, local medical and nursing expertise, and the availability of RRT modality (Table 7).

3. Timing

“Timing” refers to the time in which RRT is initiated in patients with AKI. In patients with ARF, the goal of RRT is to attain solute clearance and fluid balance while waiting for kidney function to recover. Timely institution of RRT is fundamental to achieving this goal.

Table 7. Advantages and disadvantages of different RRT modalities in AKI

Modality	Use in hemodynamically unstable patients	Solute clearance	Volume control	Anti-coagulation
Peritoneal dialysis	Yes	Moderate	Moderate	No
Hemodialysis	No	High	Moderate	Possible without
Hybrid techniques	Possible	High	Good	Possible without
CVVHF	Yes	Moderate/High	Good	Possible without
CVVHD	Yes	Moderate/High	Good	Possible without
CVVHDF	Yes	High	Good	Possible without

CVV:continuous veno-venous.

HF:hemo-filtration, HD:hemo-dialysis, HDF:hemo-dia-filtration.

Current indisputable indications initiating RRT include persistent hyperkalemia, severe acidosis, and hypervolemia that are unresponsive to conservative measures; uremic serositis; bleeding diathesis; and severe encephalopathy.

Prophylactic RRT was a term used to describe the initiation of dialysis therapy before nitrogenous waste products reached some arbitrary predefined “critical” blood value, irrespective of clinical indications. Although retrospective and observational studies have

suggested improved survival with very early initiation of continuous RRT, interpretation of these studies is confounded by their failure to include patients with AKI who recover renal function or die without ever receiving RRT [294].

It has also been argued that a strategy of early initiation of dialysis might subject patients to the risks of hemodialysis who would recover renal function with conservative therapy alone and that exposure to hemodialysis might delay recovery of renal function and adversely impact patient survival [295].

A single study has attempted to address the timing of CRRT prospectively. Bouman and colleagues [296] randomized 106 critically ill patients with AKI at two centers to three groups: early high-volume CVVH ($n = 35$), early low-volume CVVH ($n = 35$) and late low-volume CVVH ($n = 36$). Treatment was initiated in the two early groups within 12 hours of meeting study inclusion criteria, which included the presence of oliguria for more than 6 hours despite hemodynamic optimization or a measured creatinine clearance of less than 20 ml/minute on a 3 hour timed urine collection. In the late group, renal support was not initiated until the BUN was more than 112 mg/dl, potassium was more than 6.5 mEq/l, or pulmonary edema was present. No significant differences in survival were observed between the three groups.

Thus, current data remain inadequate to answer the question of appropriate indications and timing of initiation of CRRT in AKI. [297-300]. Since the evidence to date is inconclusive because held on the basis of heterogeneous poorly designed studies, this potentially clinically important treatment strategy cannot be recommended at the present time.

On the other hand, it is common practice to start RRT at an early stage in patients with multiorgan failure because of their potential for further deterioration and the benefits that RRT may bring [301, 302].

4. Adequacy

Dosing and intensity of continuous renal replacement therapy (CRRT) are generally defined in terms of urea clearance and volume management.

It is recognized that using urea as a marker of intensity or dose of RRT has a number of limitations particularly in critically ill patients. Urea generation rates will differ between patients, due to patient specific factors (age, sex and race etc), due to disease specific factors (the catabolic rate, the presence of muscle injury and/or breakdown, sepsis and liver disease) and due to medical therapy such as nutritional support and steroid treatment. However given the current absence of any other more suitable marker urea clearance is accepted as the best way to compare intensity or dose of RRT [303].

Moreover the dose of RRT delivered to patients not only includes small solute clearances but also larger “middle” molecules whose clearance is affected not only by the frequency and duration of therapy, but also by the modality used. In addition to solute clearances, the prescription and delivery of renal support to patients with AKI also includes other key aspects of medical management, including sodium and water balance and correction of acid-base imbalance [304]. Extrapolation of urea kinetic modeling (Kt/V) to critically ill patients with AKI is difficult because of a non steady state, leading to a variable increase in urea generation rate, alterations in total body water and its compartmental distribution, and a changing renal excretory capacity that is not easily quantified.

Additional challenges are imposed when dosage is considered for different modalities of dialysis that vary in operational characteristics (diffusion, convection, and adsorption), duration (intermittent and continuous), and frequency. Consequently, two broad approaches have emerged for quantifying dosage. In intermittent hemodialysis, a consensus panel convened by the multinational Acute Dialysis Quality Initiative (ADQI) recommended that patients with AKI receive at least the minimum dose (Kt/V 1.2) that is considered appropriate for patients with established renal failure [305]. In contrast, in continuous therapies, the amount of effluent (ultrafiltrate-dialysate) per kilogram of body weight per unit of time is currently proposed as a measure of dialysis dosage. Regarding the amount of the latter the ATN study showed no beneficial patient outcome with a delivered CVVHDF dose (pre-dilution) of 35 ml/kg/h compared to 20 ml/kg/h [292]. Additionally the RENAL trial failed to demonstrate any survival benefit from receiving post dilution CVVHDF at a dose of 40 ml/kg/hr versus 25 ml/kg/hr [306]. These studies have now provided evidence that there is no survival benefit in critically ill patients receiving ultrafiltration doses > 25 ml/kg/hr. This suggests that a minimum delivered dose of 25 ml/kg/h is required, and to allow for circuit clotting, a higher dose should be prescribed, particularly for the critically ill patient.

Lastly only one study has evaluated the effect of daily and alternate day HD on the outcome among patients with AKI [307]. This reported both lower mortality (28% v. 46%, $p=0.01$) and shorter duration of AKI (9 ± 2 v. 16 ± 6 days, $p=0.001$) in the daily HD group. However the dose of haemodialysis delivered to the alternate day group was low (mean delivered Kt/V of 0.94 ± 0.11).

5. Plasma Therapies and Adsorption Techniques

Coupled plasma filtration adsorption (CPFA) a technique involving plasma separation followed by an adsorptive step over activated charcoal sorbent or plasmapheresis alone, or in combination with hemodiafiltration, as well use of polymyxin B hemoperfusion, allowing nonspecific removal of inflammatory mediators, are being actively investigated for AKI associated with sepsis or multiorgan dysfunction.

The feasibility of this concept has been investigated in animal experiments [308].

Although concentrations of various septic mediators decrease, results indicating survival are mixed and clear indications for use of these therapies require results from large randomized trials [309]. Similarly, hemoadsorption techniques using charcoal 110 and polymyxin B beads [310, 311] in small trials have suggested improved monocyte responsiveness, decrease in plasma tumor necrosis factor levels, and decreased proapoptotic activity of filtered plasma from septic patients when tested on cultured renal cells [312].

Larger clinical trials using this methodology are needed to clarify its role in the AKI patients with sepsis or multiorgan failure.

E. Future Therapies

1. Bioartificial Kidney

Treatment with an artificial kidney is the most widely applied therapy for kidney failure. Substantial improvements have been made in artificial kidney technology during the past decades, according to membrane technology, dialysate composition, and medication to address side effects. Despite these improvements, the high rates of mortality of critically ill patients with AKI did not change for several decades [313-317]. Thus it would definitely be useful to further improve artificial kidney technology [318, 319].

As kidney's complex functions cannot be completely replaced by the currently used artificial kidney it was suggested that renal cells could be included in the devices. The concept of bioartificial kidneys (BAKs) was first developed by Aebischer and co-workers in 1987 [320-324].

Bioartificial kidney or renal tubule assist device (RAD) combines a conventional hemofilter in series with a bioreactor unit containing renal epithelial cells. The epithelial cells derived from the renal tubule should provide transport, metabolic, endocrinologic and immunomodulatory functions.

Proximal tubular cells, proved to have stem cell – like characteristics, are isolated from diseased donor kidneys and cultured for intergration into a filtration device. [325].

Clinical trials with BAKs have been performed by the group of H. David Humes and coworkers. [326-328]. A Phase I/II clinical trial, which performed with 10 critically ill patients with AKI, had shown that the device was sufficiently safe. The levels of granulocyte colony-stimulating factor, interleukin-6 and interleukin-10 were significantly reduced in a subset of patients.

However, after 23 years of BAK research, many challenges including the problem of cell sourcing and the costs associated with in-center BAK treatment remain to be addressed, giving a call to larger clinical studies in order to clarify the role of BAK in the treatment of AKI. [326, 329].

2. Stem Cell Therapy

Studies have showed that intrarenal cells are primarily responsible for the regeneration in kidney injury [64, 330]. Hematopoietic stem cells have been also shown to locate to the injured kidney when renal injury is induced in animal models [331, 332]. This evidence suggests the use of dedifferentiated cells to repair renal injury once occurred. The possibility of deriving pluripotent embryonic stem-like cells from cultured somatic cells is also being investigated. [333].

However, further research in this field is required to justify the role of stem-cell therapy in AKI.

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Index

A

- Abraham, 137, 139, 264
- access, vii, 56, 58, 60, 62, 63, 64, 68, 69, 73, 78, 79, 85, 89, 90, 91, 93, 94, 96, 97, 98, 99, 100, 101, 105, 106, 107, 108, 109, 110, 111, 112, 113, 251
- accommodation, 68
- accounting, 18
- acetylcholine, 54
- acid, 38, 40, 44, 45, 53, 132, 133, 145, 150, 159, 168, 171, 172, 173, 174, 192, 204, 207, 208, 218, 222, 235, 236, 254, 263
- acidosis, 166, 168, 179, 202, 223, 224, 226, 227, 231, 248, 251, 252, 253, 256, 272
- activation state, 3
- active centers, 43
- acute interstitial nephritis, 174, 186, 263, 264
- acute kidney failure, 184, 271
- acute kidney injury, vii, 127, 129, 139, 141, 152, 153, 154, 156, 157, 163, 170, 181, 182, 183, 188, 189, 202, 203, 206, 210, 213, 218, 250, 257, 258, 259, 263, 272, 273, 274
- acute leukemia, 204, 218
- acute tubular necrosis, 37, 159, 165, 216, 228, 229, 231, 235, 258, 259, 260
- adaptation(s), 24, 39, 166
- adenosine, 26, 34, 38, 50, 161, 166, 170, 184, 239, 265
- adenosine triphosphate, 38
- ADH, 161, 163, 164
- adhesion, 3, 151, 173, 236
- adjustment, 22, 24, 25, 93, 94, 117, 121, 145, 148, 149, 151, 243, 251, 252
- adrenaline, 257
- adsorption, 235, 254, 255, 274
- adults, 155, 190, 204, 207, 218, 273
- adventitia, 92
- adverse effects, 62, 229, 233
- adverse event, 77, 251
- advocacy, 78
- aetiology, 18, 24, 143, 221
- afferent nerve, 26
- African-American, 64
- age, 18, 57, 59, 63, 68, 77, 93, 94, 97, 122, 126, 144, 145, 167, 168, 189, 190, 191, 195, 204, 205, 219, 242, 254, 264
- agencies, 63
- aggregation, 46, 132
- aging population, 71
- agonist, 146, 229, 232, 259
- agranulocytosis, 187
- AIDS, 153
- Air Force, 68
- albumin, 4, 5, 12, 40, 145, 150, 153, 154, 227, 232, 233, 235, 241, 244, 258, 261, 262
- albuminuria, 10
- alcoholic cirrhosis, 232, 260
- aldehydes, 40
- aldolase, 171
- aldosterone, 19, 20, 23, 24, 31, 32, 157, 161, 163, 179, 230, 231
- algorithm, 129, 133
- allergic reaction, 175
- allergy, 246
- alteplase, 103, 113
- alters, 93, 130, 169
- amanita phalloides, 165
- amenorrhea, 244
- American Heart Association, 29, 211
- amines, 166
- amino, 39, 42, 132, 138, 168, 248, 249, 250, 271, 272
- amino acid(s), 39, 138, 168, 248, 249, 250, 271, 272
- aminoglycosides, 165, 168, 183, 190, 191, 192, 198, 207, 208

- amphetamines, 172
 amyloid deposits, 133
 amyloidosis, 127, 128, 130, 131, 133, 134, 137, 138, 139, 140
 anaphylactic shock, 162
 anaphylaxis, 162
 anastomosis, 93
 anemia, 87, 203
 anesthetics, 162, 172
 aneurysm, 199, 213
 angina, 23
 angiogenesis, 14, 117, 120, 121, 123
 angiogram, 194, 197
 angiography, 21, 30, 156, 170, 184, 194, 196, 197, 209, 211, 212
 angioplasty, 99, 111, 212
 angiotensin converting enzyme, 162, 234, 270
 angiotensin II, 20, 23, 25, 26, 165, 166, 179
 angiotensin receptor blockers, 148, 238
 annual rate, 39
 antagonism, 265
 antibiotic, 104, 114, 175
 antibody, 27, 129, 176, 177, 240, 241, 242, 267, 269, 270
 anticoagulant, 102, 123, 125
 anticoagulation, 102, 123, 125, 251
 antidepressants, 171
 antigen, 4, 5, 174
 antihypertensive drugs, 162
 anti-inflammatory drugs, 162, 174, 182, 186, 209
 antioxidant, 28, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 54, 272
 antiphospholipid antibodies, 244
 antiphospholipid syndrome, 178
 antipsychotic, 172
 anuria, 82, 160, 180, 251
 aorta, 21, 23, 118
 aortic valve, 21, 118
 apathy, 64
 APC, 236
 apoptosis, 5, 11, 12, 25, 42, 44, 46, 52, 54, 166, 169, 177, 182, 205, 235, 236, 262, 263
 apoptotic pathways, 132
 arginine, 271
 arrest, 12
 arrhythmia(s), 18, 20, 27, 180
 arsenic, 165, 173
 arterial hypertension, 39
 arterial vessels, 22
 arteries, 23, 92, 93
 arterioles, 23, 38
 arteriovenous fistula, 68, 82, 89, 97, 105, 106, 107, 108, 110, 111
 arteriovenous shunt, 68
 artery, 21, 23, 30, 37, 41, 90, 92, 93, 96, 106, 107, 119, 147, 170, 191, 194, 214, 216, 247
 arthritis, 175
 ascites, 145, 163, 164, 181, 190, 192, 234, 260, 261, 262
 ascorbic acid, 208
 aseptic, 104
 Asia, 61
 aspartic acid, 207
 aspirate, 103
 assessment, 25, 55, 92, 95, 97, 98, 99, 100, 107, 130, 132, 134, 136, 138, 155, 206, 208
 asthma, 51
 asymptomatic, 29, 98, 139
 atherogenesis, 35
 atherosclerosis, 19, 20, 23, 28, 162
 ATP, 38, 44, 166, 172, 205, 219
 atrial fibrillation, 122, 125
 atrial septal defect, 144
 atrophy, 5, 7, 236, 250
 attitudes, 58, 59, 60, 81
 auscultation, 98
 autoantibodies, 203, 241, 270, 217
 autoimmune disease(s), 174, 217, 270
 autoimmune hemolytic anemia, 170
 autonomic nervous system, 26, 33, 34
 autonomy, 67, 80
 autopsy, 101, 123
 avoidance, 94, 143, 151, 192, 218, 235
 awareness, 56, 59, 60, 62, 64, 77, 124
 Azathioprine, 240, 244
 azotemia, 162

B

- bacteremia, 96, 114
 bacteria, 104
 bacterial infection, 164
 barbiturates, 171
 baroreceptor, 34
 barriers, 60, 67, 77, 79, 80, 85, 127, 231
 base, 63, 101, 118, 123, 145, 159, 254, 258
 basement membrane, 7, 11, 39, 40, 134, 166, 174, 175, 177, 267
 beneficial effect, 26, 47, 48, 148, 149, 200, 204, 228, 229
 benefits, 69, 73, 77, 79, 80, 97, 148, 149, 234, 254
 benign, 179
 bias, 59, 76, 78, 95, 196
 bicarbonate, 69, 83, 149, 150, 153, 189, 195, 203, 204, 209, 210, 224, 227, 252, 257, 273
 bile, 44

biochemistry, 53
 biocompatibility, 69, 84
 biomarkers, 34, 40, 48, 51, 161, 182, 190, 205, 206, 219
 biopsy, 1, 6, 132, 133, 134, 135, 142, 169, 175, 236, 237, 241, 242, 243
 bipolar disorder, 173
 birefringence, 133
 bismuth, 104
 bleeding, 96, 98, 102, 162, 198, 247, 248, 253, 271
 bleeding time, 248, 271
 blood clot, 179
 blood cultures, 104
 blood flow, 37, 39, 43, 46, 90, 91, 92, 93, 98, 99, 100, 101, 102, 103, 106, 110, 111, 113, 146, 149, 150, 154, 166, 167, 181, 191, 229, 230, 235, 258
 blood pressure, 22, 26, 27, 31, 34, 73, 83, 87, 93, 146, 154, 166, 181, 226, 230, 238, 247
 blood smear, 247
 blood stream, 68
 blood transfusion(s), 68
 blood vessels, 29, 45, 134
 bloodstream, 101, 123
 body mass index (BMI), 149, 191
 body size, 57
 body weight, 168, 238, 249, 250, 254
 bonds, 39, 40
 bone, vii, 6, 17, 19, 22, 23, 25, 28, 30, 124, 130, 167, 169, 178, 185, 231, 259, 276
 bone marrow, 6, 130, 167, 178, 231, 259, 276
 bone marrow transplant, 178
 bowel, 180
 bradycardia, 223
 brain, 29, 32, 57, 71, 123, 125, 161
 breakdown, 26, 228, 248, 249, 254
 bronchial epithelial cells, 50
 burn, 37

C

cadmium, 165, 173
 caffeine, 171
 Cairo, 218
 calcification(s), 19, 20, 21, 22, 23, 25, 30, 31, 33, 73, 117, 121, 122, 123, 124, 125, 126
 calcinosis, 84, 122, 123, 126
 calcium, 2, 9, 21, 22, 25, 31, 33, 44, 57, 81, 85, 117, 120, 121, 122, 123, 125, 126, 143, 148, 150, 166, 169, 180, 182, 199, 200, 204, 215, 223, 225, 226, 239, 242, 247
 calcium channel blocker, 143, 148, 199, 200, 247
 caliber, 24
 campaigns, 63

canals, 101
 cancer, 6, 14, 51, 79, 178, 180, 189, 190, 218, 266
 cancer cells, 180
 cancer progression, 14
 candidates, 95, 235
 capillary, 3, 10, 15, 21, 23, 39, 120, 121, 123, 124, 137, 173
 capsule, 38, 48, 123, 176
 carbamazepine, 174
 carbohydrates, 248
 carbon, 50, 53, 80
 carbon dioxide, 53
 carbon tetrachloride, 50
 carcinoma, 177, 179, 218
 cardiac arrest, 29, 32, 256
 cardiac arrhythmia, 34
 cardiac catheterization, 194, 195, 209, 219
 cardiac output, 145, 149, 161, 162, 230
 cardiac risk, 17, 28
 cardiac surgery, 144, 146, 148, 151, 152, 156, 167, 183, 194, 198, 199, 200, 201, 202, 209, 212, 213, 214, 215, 216, 217, 219, 230, 259
 cardiogenic shock, 194, 238
 cardiologist, 118
 cardiomyopathy, 18, 19, 20, 25, 30, 32, 162
 cardiopulmonary bypass, 189, 200, 214, 215
 cardiotonic, 20, 25, 32
 cardiovascular disease(s), vii, 2, 9, 17, 18, 19, 28, 29, 31, 35, 55, 61, 62, 71, 94
 cardiovascular risk, vii, 17, 18, 24, 28, 29, 30, 61, 71, 218
 cardiovascular system, 124
 case study(s), 73, 210, 211
 catabolism, 248, 250, 271
 catecholamines, 23, 27, 33, 34
 categorization, 240
 category a, 160
 catheter, 70, 94, 96, 97, 100, 101, 102, 103, 104, 111, 112, 113, 114
 cation, 168, 169, 173, 183, 257
 cefazolin, 104
 cell culture, 45
 cell cycle, 5, 12
 cell death, 38, 50, 168, 235, 262
 cell fate, 12
 cell membranes, 40, 45
 census, 55
 cerebral arteries, 122
 challenges, 2, 8, 70, 89, 92, 222, 254, 256, 276
 channel blocker, 202
 chemokine receptor, 15, 54
 chemokines, 5, 8, 12, 166, 169, 173, 176
 chemotherapeutic agent, 178, 188

- chemotherapy, 135, 136, 137, 138, 141, 142, 150, 178, 189, 193
- childhood, 177, 257
- children, 113, 177, 204, 205, 218
- cholestasis, 261
- cholesterol, 51, 168, 172
- chromium, 165
- chromosome, 177
- chronic hypoxia, 7, 15
- chronic kidney disease (CKD), vii, 1, 2, 3, 6, 7, 8, 9, 10, 13, 14, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 35, 55, 56, 59, 61, 62, 63, 64, 83, 85, 87, 97, 130, 138, 144, 145, 151, 152, 156, 165, 167, 168, 170, 180, 184, 189, 191, 193, 194, 195, 196, 197, 203, 204, 205, 206, 209, 211, 219, 250, 272
- chronic obstructive pulmonary disease (COPD), 144, 167, 190
- chronic renal failure (CRF), 9, 15, 30, 33, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 47, 48, 49, 50, 68, 81, 85, 123, 126, 213, 246, 247
- cigarette smoking, 122
- cimetidine, 233, 237
- circulation, 81, 100, 102, 112, 128, 143, 149, 151, 170, 177, 180, 232, 233, 244, 260, 261
- cirrhosis, 144, 150, 162, 163, 181, 232, 234, 235, 260, 261, 262
- city, 37
- classes, 247
- classification, 86, 136, 212, 267, 275
- cleavage, 8
- clinical application, 68, 82
- clinical examination, 227
- clinical presentation, 131, 176, 184
- clinical syndrome, 159
- clinical trials, 5, 146, 155, 193, 211, 229, 231, 233, 246, 251, 255, 265
- clonality, 128, 130
- clone, 132, 135
- clustering, 156
- CNS, 44, 239
- coagulopathy, 247
- cocaine, 171, 172
- coenzyme, 185
- collaboration, 62, 132, 231
- collagen, 5, 6, 7, 13, 14, 20, 22, 25, 32, 174, 176, 187
- colon, 218
- colonization, 104, 114
- colonoscopy, 180
- coma, 171, 172
- combination therapy, 140, 245
- commercial, 60, 249
- community(s), 28, 55, 56, 60, 62, 63, 64, 65, 76, 89, 192, 274
- comorbidity, 86, 97
- compartment syndrome, 162, 172, 185
- compatibility, 57, 58
- compensation, 181
- competition, 168
- complement, 5, 12, 164, 173, 176, 178, 186, 240, 241, 263, 267
- complexity, 56, 167
- compliance, 20, 23, 73, 79, 129, 150
- complications, vii, 37, 68, 73, 90, 97, 104, 134, 136, 138, 143, 144, 146, 154, 218, 221, 222, 227, 234, 239, 251, 262, 271
- composition, 255
- compounds, 40, 54, 173, 192
- compression, 93
- computed tomography, 119
- computer, 107
- conditioning, 42
- conduction, 20
- conference, 157, 274
- configuration, 90, 107
- confounding variables, 75, 93
- congestive heart failure (CHF), 75, 122, 144, 145, 167, 182, 190, 191, 192, 193, 194, 198, 227, 237, 264, 265
- congo, 133
- congress, 82, 139
- conjugation, 53
- connective tissue, 1
- consensus, 79, 91, 96, 135, 139, 141, 150, 157, 160, 181, 218, 254, 274
- consent, 63
- consolidation, 118
- constrictive pericarditis, 162
- construction, 93, 97, 107
- consumption, 44, 240
- control group, 42, 43, 44, 45, 46, 48, 99, 136, 199, 233
- controlled studies, 232, 233, 236
- controlled trials, 22, 26, 31, 98, 99, 100, 103, 136, 148, 149, 156, 190, 196, 210, 211, 212, 230, 258
- controversial, 2, 6, 257
- coronary angioplasty, 153, 209
- coronary arteries, 21, 23
- coronary artery bypass graft, 143, 144, 154, 157, 215, 216
- coronary artery disease, 18, 20, 94, 219
- coronary bypass surgery, 206, 215, 274
- coronary heart disease, 30, 122
- correlation(s), 6, 21, 27, 77, 107, 131, 264, 270
- cortex, 4, 9, 165, 208, 229

- corticosteroid therapy, 186, 263
 corticosteroids, 171, 172, 186, 203, 217, 237, 240, 264, 271
 cost, 39, 55, 68, 70, 79, 80, 81, 83, 85, 97, 98, 101, 109, 197, 235
 cost benefits, 79
 cost effectiveness, 55, 80
 cost saving, 70, 80
 counsel, 145
 covering, 121
 creatinine, 47, 48, 144, 145, 146, 160, 161, 163, 164, 165, 167, 170, 184, 190, 193, 194, 195, 196, 197, 199, 200, 201, 202, 204, 205, 209, 214, 228, 229, 231, 233, 237, 238, 242, 243, 245, 247, 252, 253, 264
 crescentic glomerulonephritis, 10, 176, 177, 187, 242, 243, 245, 270
 critically ill patient, vii, 143, 146, 148, 151, 154, 155, 182, 201, 212, 229, 248, 250, 251, 253, 254, 255, 256, 258, 259, 273, 274, 275
 criticism, 60
 cross sectional study, 56
 cross-validation, 206
 CRP, 72
 crystalline, 44
 crystalluria, 179, 180
 crystals, 22, 150, 169, 180, 204
 CT scan, 170
 Cuba, 37, 39, 40, 49, 50, 52, 54
 cultural differences, 60
 culture, 81, 118
 cyanosis, 225
 cycles, 244
 cyclooxygenase, 162, 174
 cyclophosphamide, 240, 241, 242, 244, 268, 269, 270
 cyclosporine, 165, 170, 172, 174, 203, 243
 cysteine, 8
 cystoscopy, 231
 cytokines, 3, 5, 8, 12, 27, 38, 49, 132, 164, 166, 167, 169, 173, 174, 176, 204, 235, 252, 262
 cytomegalovirus, 58, 153, 171, 178
 cytoplasm, 44, 168
 cytoskeleton, 47, 166, 169, 182
 deaths, 18, 117
 defects, 271
 deficiency(s), 170, 171, 176, 178, 236, 263, 272
 degradation, 8, 45, 169, 180, 205
 dehydration, 132, 164, 165, 167, 168, 170, 171, 180, 189, 192, 204
 delirium, 172
 delirium tremens, 172
 demographic factors, 20, 21, 22, 24, 25, 82
 dendritic cell, 3, 11, 12
 depolarization, 205
 deposition, 3, 5, 6, 8, 20, 30, 102, 117, 120, 122, 123, 127, 128, 133, 139, 149, 150, 171, 176
 deposits, 120, 121, 122, 123, 133, 134, 175, 176
 deprivation, 57, 78, 82
 depth, 71, 258
 derivatives, 45, 175
 dermatomyositis, 171
 destruction, 1, 39, 150, 177
 detachment, 7, 40, 166
 detectable, 205, 242
 detection, 98, 99, 110, 128, 129, 130, 133, 134, 137
 diabetes, 18, 20, 23, 39, 50, 55, 56, 58, 61, 62, 64, 71, 94, 108, 122, 144, 145, 148, 162, 167, 168, 169, 170, 173, 179, 184, 186, 189, 190, 194, 209
 diabetes insipidus, 162, 169, 173, 186
 diabetic nephropathy, 118
 diabetic patients, 56, 202, 219
 diagnostic criteria, 181, 231
 diarrhea, 162, 178, 180, 267
 diastole, 23
 diastolic blood pressure, 19, 23
 diet, 73, 226
 differential diagnosis, 124
 diffusion, 21, 60, 67, 254
 digestion, 91
 digitalis toxicity, 223
 dilated cardiomyopathy, 33
 dilation, 166
 directives, 95
 discontinuity, 47
 disease model, 4
 disease progression, 8, 15, 134
 diseases, 15, 29, 37, 55, 128, 187, 218, 268
 disorder, 23, 133, 163, 247
 displacement, 101
 dissociation, 49
 distribution, 8, 34, 57, 81, 154, 176, 182, 254
 diuretic, 154, 162, 164, 193, 228, 229, 231, 238
 diversity, 10
 DNA, 44, 49, 169, 207
 DNA repair, 49
 dogs, 27, 32, 257, 272

D

- damages, 45
 data collection, 79
 data set, 152
 database, 61, 102
 David Hume, 255
 death rate, 71, 84

donations, 63
 donors, 57, 58, 59, 60, 62, 63, 65, 71
 dopamine, 27, 146, 147, 154, 155, 199, 200, 214,
 226, 229, 232, 235, 238, 258, 259, 261
 dopaminergic, 172
 doppler, 99
 dosage, 254
 dosing, 207, 221, 232
 double bonds, 40
 down-regulation, 230
 drug abuse, 185
 drug interaction, 185
 drug toxicity, 183, 209
 drugs, 39, 40, 73, 129, 131, 143, 145, 148, 151, 154,
 162, 165, 167, 170, 171, 172, 175, 177, 178, 179,
 185, 191, 199, 208, 212, 217, 225, 226, 229, 264,
 271
 dyes, 129
 dyscrasia, 128, 131, 133
 dystonia, 171

E

earthquakes, 172
 East Asia, 61
 echocardiogram, 118, 122
 ECM, 3, 5, 7
 economic consequences, 69, 79
 economic evaluation, 85
 economic status, 57
 ecstasy, 171, 172
 edema, 40, 164, 169, 172, 173, 175, 225
 education, 60, 63, 65, 77, 78, 83, 84, 97, 139
 educators, 97
 effluent, 254
 elastin, 22, 23
 electrolyte, 147, 159, 167, 168, 169, 172, 179, 180,
 192, 221, 222, 227, 231, 238, 239
 electron, 175
 electron microscopy, 175
 electrophoresis, 127, 128, 129, 133, 137
 ELISA, 205
 elongation, 102
 emboli, 121, 123, 125, 126
 embolism, 41, 118, 123, 124, 125
 emergency, 98, 101, 118, 125, 138, 144, 145, 187,
 190, 204, 226, 240, 256
 employment, 79, 80, 83
 employment status, 83
 ENA-78, 167
 encephalopathy, 234, 251, 253, 270
 encouragement, 62
 end stage renal disease (ESRD), 8, 28, 30, 70, 71, 73,
 76, 77, 78, 79, 84, 86, 109, 124, 160, 162, 170,
 174, 177
 endocarditis, 118, 124, 162, 177
 endocardium, 117, 123, 124
 endothelial cells, 3, 43, 46, 91, 106, 166, 173, 177,
 262
 endothelial dysfunction, 38, 71, 92, 164, 166, 177,
 236
 endothelium, 14, 15, 38, 46, 48, 106, 173, 182, 232
 endotoxemia, 163
 end-stage renal disease, 18, 21, 22, 24, 26, 27, 29,
 30, 31, 33, 34, 55, 64, 82, 84, 86, 106, 109, 122,
 123, 124, 257, 275
 energy, 166, 167, 168, 170, 228, 249, 250, 271
 England, 78, 82, 85
 enlargement, 106
 enrollment, 21
 environment, 106
 environmental factors, 56, 62, 167
 environmental stimuli, 5
 environmental temperatures, 172
 enzyme(s), 28, 39, 40, 42, 43, 44, 45, 46, 47, 48, 50,
 54, 103, 148, 157, 169, 171, 172, 178, 180, 236,
 238
 enzyme inhibitors, 157, 238
 eosinophilia, 175
 eosinophils, 174, 175
 epidemic, 68, 266
 epidemiologic, 87
 epidemiology, 29, 31, 56
 epinephrine, 27, 162, 230
 epithelial cells, 3, 5, 6, 12, 14, 43, 52, 138, 166, 167,
 168, 175, 176, 182, 205, 236, 255, 263, 275, 276
 epithelium, 13, 38, 45, 46, 48, 166, 167, 171, 205
 equilibrium, 38, 48, 69, 85
 equipment, 69, 78, 99
 ERA, 82
 erosion, 123
 ERS, 157
 erythrocytes, 44, 53
 erythropoietin, 143, 148, 156
 ethnic groups, 56, 60, 61
 ethnic minority, 55, 60, 62
 ethnicity, 55, 56, 57, 61, 64, 65
 ethylene, 171, 179
 ethylene glycol, 171, 179
 etiology, 37, 117, 121, 161, 167, 170
 Europe, 59, 81, 84, 103, 247
 evacuation, 150
 evolution, 20, 67, 164, 211, 268
 excision, 122
 excitation, 27

exclusion, 164, 196
 excretion, 24, 47, 129, 149, 179, 202, 223, 242
 exercise, 53, 171, 172
 experimental condition, 44, 45, 47, 48
 expertise, 253
 exploitation, 60
 exposure, 28, 77, 78, 97, 170, 172, 173, 189, 192,
 193, 196, 197, 198, 203, 253
 external validation, 94
 extracellular matrix, 3, 5, 7, 8, 15, 25, 91, 174, 187
 extrusion, 123

F

faith, 59
 false positive, 127, 129
 families, 8
 family income, 69
 family support, 79
 fantasy, 12
 fascia, 172
 fat, 249
 fatal arrhythmia, 204
 fatty acids, 38, 108
 fear, 62, 79
 feelings, 58
 ferritin, 171
 fever, 175, 178, 192
 fiber, 275
 fibrin, 101, 103, 113, 114, 117, 120, 121, 123, 176
 fibrinolytic, 11, 164
 fibroblast growth factor, 3
 fibroblasts, 3, 5, 6, 7, 8, 12, 13, 14, 132, 174, 176,
 276
 fibrocytes, 6, 11, 13
 fibrogenesis, 4, 9
 fibrosis, vii, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,
 15, 20, 21, 23, 25, 30, 32, 54, 125, 132, 165, 169,
 174, 179, 180, 236
 fibrous tissue, 123
 filtration, 21, 24, 38, 39, 46, 130, 144, 146, 154, 161,
 164, 165, 168, 171, 204, 206, 233, 238, 255, 265,
 274
 financial, 69, 78, 80
 financial incentives, 80
 fine tuning, 7
 first generation, 101, 196
 fish, 96, 108, 247
 fish oil, 96, 108, 247
 fistulas, 90, 91, 92, 94, 95, 96, 100, 105, 106, 107,
 108
 fitness, 61
 flexibility, 69, 76

fluid, 20, 24, 31, 32, 83, 145, 146, 147, 149, 150,
 151, 153, 154, 159, 162, 163, 164, 167, 170, 172,
 181, 182, 189, 193, 194, 198, 202, 203, 221, 227,
 231, 238, 239, 244, 250, 251, 252, 253, 258
 fluid balance, 150, 221, 227, 253
 fluoroquinolones, 175
 focal segmental glomerulosclerosis, 58
 force, 38, 118, 119
 formation, 1, 3, 20, 39, 45, 89, 91, 92, 93, 94, 95,
 101, 112, 123, 132, 149, 168, 170, 171, 173, 175,
 176, 177, 180, 182, 202, 203, 235, 241, 242, 244
 fragments, 4, 133
 France, 82, 139, 251
 free radicals, 27, 39, 50, 54
 fresh frozen plasma, 233, 241, 242
 functional changes, 32, 191
 funding, 78
 funds, 68
 fungi, 171
 fusion, 40, 175

G

gadolinium, 211
 gangrene, 245
 gastric lavage, 162
 gastrointestinal bleeding, 163
 gastrointestinal tract, 162, 225
 gel, 128
 gene expression, 9, 12, 40, 44, 46, 54
 general surgery, 145, 152
 generalized seizures, 172
 genes, 169, 173, 260
 genetic defect, 240
 Germany, 212, 235
 glomerulonephritis, 4, 11, 12, 37, 39, 40, 41, 49, 176,
 177, 267, 268, 269, 270
 glomerulus, 4, 48, 159, 161
 glucagon, 163, 232
 glucocorticoid(s), 203, 237, 240, 244, 245, 246, 269
 gluconeogenesis, 249
 glucose, 69, 70, 99, 143, 148, 155, 198, 224, 249,
 250, 257, 272
 glutamic acid, 207, 208
 glutathione, 39, 40, 43, 44, 53
 glycine, 44
 glycogen, 50
 God, 59
 governments, 81
 graft maturation, 89
 granulomas, 175, 236
 Greece, 159, 189, 221

growth, 3, 5, 8, 34, 71, 122, 124, 125, 148, 167, 174, 182, 230, 236, 260
 growth arrest, 5
 growth factor, 3, 5, 8, 148, 167, 174, 182, 230, 236, 260
 growth hormone, 260
 guidance, 80, 101, 103, 132
 guidelines, 60, 70, 71, 97, 108, 109, 110, 130, 137, 210, 211, 252

H

half-life, 130, 134, 169
 hantavirus, 174, 177
 haptoglobin, 247
 hazards, 122
 HBV, 177
 healing, 3, 174
 health, vii, 9, 17, 37, 39, 55, 56, 57, 64, 73, 77, 79, 84, 87, 89, 97, 128, 130, 144, 146, 152, 167, 181
 health care, 77, 79, 144
 health care costs, 144
 health care system, 77
 health status, 167
 heart block, 223
 heart disease, 23, 30, 122
 heart failure, 20, 33, 75, 122, 149, 162, 163, 189, 203, 230, 237, 249, 264, 265
 heart transplantation, 167
 heat loss, 249
 heat stroke, 171, 172
 hematomas, 179
 hematuria, 203, 246
 heme, 149, 170, 171, 179, 184, 202, 203
 heme oxygenase, 184
 hemiplegia, 122
 hemodialysis, 29, 30, 31, 32, 48, 69, 71, 76, 81, 82, 83, 84, 85, 86, 87, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 117, 118, 121, 123, 124, 125, 138, 141, 198, 224, 234, 247, 251, 252, 253, 254, 257, 262, 273, 274
 hemodynamic instability, 234, 252
 hemoglobin, 30, 177, 179, 203, 227
 hemolytic uremic syndrome, 178, 187, 265, 266, 267
 hemoptysis, 241
 hemorrhage, 41, 177, 227, 241, 242, 245, 246
 hemostasis, 248
 hepatic failure, 144, 164, 232, 234
 hepatitis, 68, 83, 177, 232, 269
 hepatocellular carcinoma, 218
 hepatorenal syndrome, 162, 164, 181, 234, 260, 261, 262
 heroin, 171, 172

heterogeneity, 5, 13, 14, 148, 156, 196, 199
 high risk patients, 145, 205
 higher education, 59
 Hispanic population, 63
 histamine, 174
 histological examination, 133, 134
 histology, 270
 histone, 9
 history, 71, 79, 94, 105, 122
 homeostasis, 24, 38, 40, 44, 49, 159
 homes, 77, 78
 Hong Kong, 75, 84, 141
 hormone, 25, 230
 hospital death, 155
 hospitalization, 18, 28, 74, 109, 190, 227, 238, 264
 host, 40, 235
 house, 111
 human, 3, 5, 6, 7, 10, 12, 14, 33, 35, 50, 53, 69, 79, 114, 139, 145, 171, 174, 177, 178, 187, 215, 216, 230, 244, 259, 260, 263, 265, 266, 275, 276
 human health, 50
 human immunodeficiency virus (HIV), 114, 169, 171, 174, 175, 177, 178, 186, 188, 266
 Hume, David, 255
 hybrid, 251, 252
 hydrocarbons, 177
 hydrogen, 35, 38, 40, 43, 50, 52, 54
 hydrogen peroxide, 35, 38, 40, 43, 50, 52, 54
 hydroxyapatite, 22, 169
 hydroxyl, 38, 39, 40, 43, 47, 145
 hygiene, 85
 hyperactivity, 26, 27
 hypercalcemia, 124, 169, 223, 225
 hyperemia, 235
 hyperfiltration, 24, 185
 hyperglycaemia, 250
 hyperkalemia, 167, 185, 202, 203, 221, 223, 224, 225, 226, 231, 235, 239, 251, 253, 256, 257
 hyperlipidemia, 149
 hypernatremia, 171, 227, 229
 hyperparathyroidism, 18, 20, 25, 32, 123, 126
 hyperphosphatemia, 239, 249
 hyperplasia, 92, 107, 176
 hyperpyrexia, 172
 hypersensitivity, 174, 175
 hypertension, 2, 18, 19, 20, 22, 23, 24, 27, 28, 29, 30, 31, 32, 33, 34, 39, 56, 61, 62, 71, 143, 145, 146, 150, 151, 162, 163, 190, 191, 203
 hyperthermia, 172, 185
 hyperthyroidism, 171
 hypertrophy, 19, 20, 21, 23, 24, 27, 34, 39, 49, 81, 82, 87, 92, 260
 hyperuricemia, 171, 218, 239

hypokalemia, 168, 171, 172, 192, 227
hypomagnesemia, 167, 168, 192
hyponatremia, 171, 238
hypoparathyroidism, 123, 126
hypotension, 144, 166, 180, 190, 198, 201, 216, 229, 252
hypotensive, 146, 201
hypothalamus, 26, 33, 172
hypothermia, 148
hypothesis, 8, 15, 21, 22, 26, 33, 93, 122, 123, 181, 273
hypothyroidism, 171, 172, 185
hypovolemia, 37, 41, 159, 162, 165, 190, 194, 198, 202
hypoxemia, 225
hypoxia, 7, 14, 15, 144, 167
hypoxia-inducible factor, 14

ICAM, 166, 173, 176
ideal, 79
identification, 98, 129, 141, 145, 187
idiopathic, 174, 237, 240, 244, 268
idiosyncratic, 175
immigration, 167
immune disorders, 172
immune response, 174, 176, 252
immune system, 37, 41
immunocompromised, 207
immunofixation, 128, 139, 140
immunoglobulin(s), 127, 128, 130, 134, 136, 137, 138, 139
immunomodulator, 37
immunomodulatory, 255
immunoreactivity, 32, 42
immunosuppression, 167, 244, 267
improvements, 26, 73, 255
impulses, 33
in vitro, 5, 7, 14, 33, 107, 132, 138, 207, 208
in vivo, 5, 6, 7, 14, 34, 132, 138, 207, 208
independence, 80, 86
independent variable, 59
individuals, 18, 20, 21, 23, 24, 27, 55, 59, 76, 78, 94, 95, 190, 193, 194, 195, 196, 197, 199, 201, 205, 229, 236, 237, 238, 240, 244
induction, 4, 8, 49, 140, 153, 200, 244, 245, 248, 269, 270
industry, 81
ineffectiveness, 63
infancy, 70
infants, 162
infarction, 41, 223, 256

infection, 91, 94, 101, 103, 104, 113, 114, 115, 163, 175, 177, 188, 235, 237, 244, 245, 267, 272, 274
inflammation, 1, 3, 4, 5, 8, 10, 11, 15, 27, 34, 42, 46, 52, 123, 125, 132, 166, 167, 169, 172, 173, 175, 180, 184, 187, 215, 242
inflammatory bowel disease, 175, 186
inflammatory cells, 41, 43, 46, 47, 151, 176
inflammatory mediators, 144, 173, 241, 248, 255
influenza, 185
information technology, 181
infrastructure, 78
inhibition, 12, 108, 149, 169, 173, 177, 183, 229, 236, 260, 263
inhibitor, 15, 39, 47, 141, 149, 178, 182, 185, 187, 200, 215, 263, 267
initiation, 3, 128, 129, 132, 151, 165, 191, 192, 200, 203, 221, 228, 237, 240, 245, 247, 250, 253, 254, 272
insertion, 102, 168, 176
insomnia, 69
insulin, 144, 148, 153, 155, 190, 224, 231, 239, 248, 249, 257, 260, 271
insulin resistance, 248, 249
integration, 56
integrins, 3, 166, 173, 176, 182
integrity, 38, 44, 45, 48, 49, 159, 215, 250
intensive care unit, 153, 155, 181, 183, 206, 207, 233, 251, 258, 272, 273, 274
interface, 64
interference, 59, 90
interferon, 178
interstitial nephritis, 174, 186, 188, 263, 264
interstitium, 3, 10, 48, 159, 161, 173, 174, 175, 176
intervention, 61, 76, 90, 91, 99, 103, 107, 131, 155, 156, 184, 206, 209, 211, 231
intestine, 124
intima, 92
intoxication, 173, 179
intra-aortic balloon pump, 144, 149
intracellular calcium, 150, 170
intravenous immunoglobulins, 183
intravenously, 223, 224, 228, 244, 245
iodinated contrast, 194, 209, 211
iodine, 169, 170, 194, 196
ions, 150, 182
iron, 43, 150, 208, 219
ischaemic heart disease, 23
ischemia, 37, 38, 40, 41, 42, 45, 46, 47, 49, 50, 51, 52, 53, 146, 159, 165, 166, 172, 173, 174, 177, 186, 205, 219, 230, 235, 239, 245, 260, 263, 276
ischemia-reperfusion injury, 53, 165, 174, 186, 219, 263, 276
Islam, 59

isolation, 3, 79, 128
 issues, 57, 58, 60, 63, 64, 86, 127, 250, 257
 Italy, 70

J

Japan, 39, 117
 jaundice, 198
 Jordan, 186

K

kidney failure, 71, 235, 236, 239, 255
 kidney transplantation, 55, 57, 63, 65, 83, 232
 kinetic model, 254
 Kinsey, 157

L

labeling, 14
 lack of control, 93
 lactate dehydrogenase, 204
 lactate level, 200
 lactic acid, 203, 249
 language barrier, 79
 languages, 62
 laxatives, 180
 lead, vii, 4, 5, 8, 64, 67, 124, 129, 136, 150, 160,
 162, 163, 165, 166, 169, 180, 185, 229, 235, 240,
 246, 248
 lean body mass, 248
 left ventricle, 118, 119, 120, 122
 legality, 59
 legs, 83
 lesions, 30, 35, 41, 42, 46, 47, 122, 166
 leucocyte(s), 3, 5, 6, 8, 15, 236
 leukemia, 137, 204, 218
 leukotrienes, 38, 164
 liberation, 171
 ligand, 132
 light, 18, 68, 127, 128, 129, 130, 132, 133, 134, 135,
 136, 137, 138, 139, 140, 141, 142, 180, 188, 225,
 238
 lipid peroxidation, 34, 38, 42, 44, 48, 50, 53
 lipid peroxides, 45
 lipids, 40, 248, 250
 lipolysis, 249
 lipoproteins, 35, 45, 50
 liquids, 47
 lithium, 165, 172, 173
 lithotripsy, 177

liver, 4, 10, 40, 44, 47, 51, 53, 134, 143, 150, 162,
 163, 164, 167, 168, 181, 190, 191, 192, 193, 198,
 200, 215, 232, 234, 235, 254, 262, 275
 liver cirrhosis, 143, 150, 162, 163, 193, 275
 liver disease, 164, 167, 168, 181, 190, 232, 254, 262
 liver failure, 191, 192
 liver transplant, 198, 200, 215, 232, 234, 235
 liver transplantation, 198, 200, 215, 232, 234, 235
 local community, 63
 loci, 22
 longitudinal study, 21, 92, 113
 low platelet count, 240
 low-density lipoprotein (LDL), 27, 28, 54, 249
 lumen, 5, 48, 69, 92, 102, 112, 132, 180, 250
 lung cancer, 218
 lung function, 51
 Luo, 152
 lupus, 118, 191, 241, 244, 268
 lymph, 4, 163, 179
 lymph node, 4, 179
 lymphocytes, 4, 166, 174, 176
 lymphoma, 177, 204, 218, 244, 269
 lysis, 143, 150, 157, 168, 171, 179, 180, 188, 189,
 204, 218, 223
 lysosome, 192

M

macronutrients, 249
 macrophage inflammatory protein, 42
 macrophages, 3, 10, 14, 40, 46, 176
 magnesium, 123, 168
 magnitude, 238
 Maillard reaction, 35
 majority, vii, 17, 25, 28, 59, 63, 75, 78, 79, 97, 99,
 129, 134, 136, 199
 malaria, 170, 171, 178
 malignancy, 169, 178
 malignant cells, 150
 malignant hypertension, 178
 malignant hyperthermia, 171
 malnutrition, 69, 248, 271
 management, vii, 9, 32, 41, 69, 76, 77, 90, 127, 128,
 139, 145, 147, 148, 150, 155, 157, 172, 178, 180,
 188, 206, 211, 218, 221, 222, 225, 227, 228, 230,
 232, 239, 247, 248, 254, 256, 257, 260, 262, 263,
 265, 267, 271, 275
 manganese, 35
 manipulation, 92
 mannitol, 149, 152, 165, 169, 189, 193, 199, 203,
 214, 229, 258
 mapping, 13, 82, 95, 107, 108
 marrow, 6, 10, 14, 167, 276

- mass, 24, 29, 30, 37, 39, 41, 63, 73, 83, 121, 123, 124, 126
mass media, 63
mast cells, 4, 11
materials, 63
matrix, 3, 4, 5, 6, 7, 8, 11, 15, 30, 43, 44, 91, 106, 166, 169
matrix metalloproteinase (MMPs), 8, 15, 91, 106
matter, 67, 125
MCP-1, 5, 8, 10, 167, 169, 176
mean arterial pressure, 143, 146, 147, 154, 161, 163, 164, 230, 235, 252
measurement(s), 94, 98, 99, 100, 107, 110, 111, 127, 128, 130, 131, 134, 136, 137
meat, 177
media, 62, 92, 145, 146, 153, 184, 209, 210, 211
median, 23, 57, 77, 80, 90, 103, 129, 130, 200, 202, 234, 242, 244
Medicaid, 78
medical, 40, 41, 51, 53, 56, 59, 61, 62, 63, 65, 69, 71, 75, 79, 81, 125, 138, 145, 150, 155, 221, 223, 238, 251, 253, 254
medical history, 223
medical reason, 61
medical science, 81
Medicare, 109
medication, 26, 151, 255
medicine, 70, 155, 187, 256
medulla, 26, 165, 167
medulla oblongata, 26
melatonin, 192
mellitus, 29, 94, 170, 184, 190, 194, 209
membrane permeability, 205, 275
membranes, 28, 38, 48, 69, 168, 207, 226, 252
membranoproliferative glomerulonephritis, 268
memory, 12, 79
mental health, 57
mercury, 165, 173, 185
mesangial cells, 8, 54
mesenchymal stem cells, 151
meta-analysis, 22, 25, 31, 100, 148, 152, 153, 155, 156, 195, 196, 197, 198, 207, 210, 211, 212, 229, 252, 264, 269, 273
metabolic, 185, 226, 239, 249, 275
metabolic acidosis, 145, 150, 168, 221
metabolic changes, 230, 250
metabolism, 2, 33, 37, 41, 44, 46, 87, 124, 126, 141, 256, 271
metabolites, 40, 44, 52, 141, 150, 173, 235
metabolized, 167, 168, 169
metalloproteinase, 187
metals, 165
metformin, 251
methadone, 171
methanol, 171
methodology, 99, 135, 255
methylation, 9
methylcellulose, 225, 226
methylprednisolone, 217, 237, 240, 241, 242, 243, 244, 245, 246, 268
MHC, 13
mice, 4, 5, 6, 7, 11, 42, 50, 53, 236, 260, 276
microangiopathic hemolytic anemia, 178, 239
microcirculation, 146, 170
micronutrients, 249
microparticles, 187
microscopy, 42, 175, 203, 245
migration, 5, 92, 176, 236
mineral disorders, vii, 17, 28
minimal change disease, 175
minorities, 64
mission, 186
mitochondria, 40, 44, 169, 205
mitochondrial damage, 169, 236
mitochondrial DNA, 39
mitogen, 132
mitral regurgitation, 118
mitral valve, 21, 118, 119, 123, 125
mixing, 203
modelling, 74, 97, 107, 135
models, 3, 4, 5, 6, 7, 8, 21, 25, 26, 38, 40, 42, 43, 44, 46, 47, 49, 77, 145, 181, 187, 205, 236, 256
molecular biology, 53
molecular structure, 8, 174
molecular weight, 102, 145, 165, 169, 171, 240, 249, 252, 275
molecules, 5, 8, 27, 28, 50, 135, 166, 169, 173, 252, 254, 260, 275
monoclonal antibody, 240
monocyte chemoattractant protein (MCP), 5, 8, 10, 132, 167, 169, 176
monomers, 130
Montenegro, 51
Moon, 11
morbidity, vii, 1, 17, 18, 24, 28, 55, 57, 63, 75, 83, 93, 98, 109, 131, 145, 147, 149, 167, 200, 205, 247
morphology, 13, 40, 47
morphometric, 9, 42, 48
mortality rate, 18, 75, 164, 198, 201, 213, 233, 251
mortality risk, 21, 22, 28, 31, 32, 81, 97, 252
motivation, 79, 81
MRI, 73
mRNA, 236
multi-ethnic, 57

multiple myeloma, 127, 128, 129, 130, 131, 132,
133, 134, 135, 136, 137, 138, 139, 140, 141, 142
multiple sclerosis, 179
multivariate analysis, 21, 24, 27, 56, 61, 94
muscles, 172, 185, 239
muscular dystrophy, 171
Muslims, 58, 59, 60
mutation(s), 167, 172, 177, 267
mycobacterial infection, 175
myocardial infarction, 21, 23, 122, 124, 144, 211,
212
myocarditis, 162
myocardium, 20, 21, 23, 41, 120, 123, 124
myofibroblasts, 3, 5, 6, 13, 14, 92, 176
myoglobin, 149, 165, 170, 171, 179, 202, 203
myopathy, 251
myositis, 203

N

nasogastric tube, 247
National Health and Nutrition Examination Survey
(NHANES), 62
National Health Service (NHS), 55, 57, 77, 80, 82,
85
National Institutes of Health, 152
natural disaster(s), 172
nebulizer, 224, 226
necrosis, 82, 126, 166, 177, 183, 205, 223, 231, 262
nephrectomy, 26, 37, 41, 42, 52, 62, 190, 206
nephritis, 52, 118, 186, 241, 244, 264, 268
nephrolithiasis, 41
nephrologist, 96
nephrology, 8, 78, 79, 89, 108, 256
nephron, 24, 38, 39, 48, 49, 132, 159, 187, 230
nephrosis, 169, 183
nephrotic syndrome, 162
nephrotoxic drugs, 143, 151, 164, 167, 192, 235
nerve, 26, 27, 33, 34
nervous system, 227
Netherlands, 52, 68
neurogenic bladder, 179
neuroimaging, 121
neuroleptic malignant syndrome, 171
neuropathy, 251
neutropenia, 192
neutrophils, 43, 46, 243, 245
New England, 85
New Zealand, 74, 76, 84
Nile, 171
nitrates, 225
nitric oxide, 38, 43, 45, 51, 53, 91, 149, 230, 232,
236

nitrogen, 169, 183, 249, 250, 271
norepinephrine, 26, 27, 33, 149, 150, 154, 162, 230,
259
North America, 59, 83, 95
NSAIDs, 162, 165, 170, 174, 175, 190, 191, 193,
198, 226, 236, 237, 247
nuclei, 26, 48
nucleic acid, 150, 173
nurses, 77
nursing, 80, 253
nutrient(s), 248, 249, 250, 272
nutrition, 249, 250, 271, 272

O

obstacles, 58, 64, 89
obstruction, 11, 12, 38, 41, 48, 102, 149, 159, 160,
161, 166, 171, 177, 178, 179, 180, 188, 202, 231
obstructive uropathy, 11, 12, 260
occlusion, 93, 101, 113, 147
Oceania, 59
oedema, 98, 251
oligosaccharide, 182
open heart surgery, 214, 215
operations, 167, 190, 215
opioids, 225
opportunities, 107
optimization, 147, 155, 213, 231, 253
organ(s), 4, 17, 18, 19, 39, 43, 44, 45, 46, 47, 55, 56,
58, 59, 60, 61, 62, 63, 64, 65, 123, 133, 134, 139,
146, 151, 157, 161, 163, 164, 181, 183, 215, 221,
227, 245, 252, 272, 273
organelles, 168
organism, 42, 104
osmolality, 189, 196, 197, 211, 229
osmotic pressure, 47
ossification, 121
osteoarthritis, 191
osteoporosis, 169, 242
ototoxicity, 147, 192, 228
outpatient(s), 195, 196, 209
overlap, 14
overproduction, 42, 129
oxalosis, 249
oxidation, 38, 39, 40, 49, 150, 180, 249
oxidative damage, 43
oxidative stress, 17, 18, 19, 23, 27, 28, 34, 35, 37,
38, 39, 40, 41, 42, 43, 44, 46, 48, 50, 51, 163,
169, 182, 186, 236, 263
oxygen, 21, 23, 37, 38, 39, 41, 43, 44, 45, 46, 47, 49,
52, 146, 147, 154, 155, 186, 198, 225, 229, 230,
248
oxygen consumption, 229

ozone, 37, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50,
51, 52, 53, 54
ozonides, 40

P

PAA, 192
paclitaxel, 218
palpation, 98
pancreas, 45
pancreas transplant, 45
pancreatitis, 162, 174
paracentesis, 150, 262
parallel, 20, 153, 163
parathyroid, 25, 33
parathyroid hormone, 25, 33
parathyroidectomy, 126
parenchyma, 1, 5, 8, 159, 161, 178
participants, 77, 94, 198
pathogenesis, 4, 5, 10, 14, 15, 22, 32, 136, 139, 168,
170, 173, 180, 181, 182, 187, 260, 265
pathogens, 104
pathology, 4, 7, 18, 40, 62, 131, 132, 186
pathophysiological, vii, 17, 18, 28, 123, 230, 235
pathophysiology, 10, 17, 18, 19, 32, 49, 159, 161,
172, 182, 184, 185, 188, 227, 260
pathways, vii, 79, 129, 132
pelvis, 159, 161, 178, 231
peptide(s), 12, 29, 33, 143, 148, 199, 201, 215, 216,
230, 259
perfusion, 7, 20, 21, 23, 24, 146, 154, 161, 193, 202,
204, 221, 228, 235, 236, 238, 251, 259, 272
pericardial effusion, 203
pericarditis, 162, 251
pericytes, 7, 14
peripheral blood, 140, 268
peripheral vascular disease, 94, 97, 144, 167, 190
peritoneal cavity, 190
peritoneum, 70
peritonitis, 51, 69, 70, 162
permeability, 40, 69, 70, 168, 172, 173, 236
permeable membrane, 238, 275
peroxidation, 44, 48, 173
peroxide, 43
peroxynitrite, 43, 47, 53, 54
personal benefit, 79
pharmacokinetics, 135, 183, 207
pharmacological treatment, 199
phenothiazines, 171, 172
phenotype(s), 4, 6, 10, 132
Philadelphia, 52
phobia, 79

phosphate, 2, 21, 22, 25, 30, 31, 33, 57, 73, 81, 124,
126, 150, 168, 171, 179, 180, 188, 204, 249
phospholipids, 45, 168, 169, 173
phosphorous, 9
phosphorus, 73, 81, 85, 123
physical characteristics, 99
physical health, 57, 73
physicians, 81, 228
physiological, 22
physiology, 32, 49, 150, 229, 259
physiopathology, 38, 49
pilot study, 112, 135, 151, 216, 261, 271, 274
placebo, 33, 96, 113, 197, 199, 200, 201, 202, 214,
215, 216, 217, 228, 229, 236, 239, 257, 258, 259,
260
plaque, 20
plasma cells, 128
plasmapheresis, 142, 240, 241, 242, 244, 245, 248,
255, 268
plasminogen, 8, 103, 177, 187
platelet aggregation, 176
platelet count, 240
platelets, 40, 46, 178, 187
platinum, 183, 193, 208
plausibility, 96
PMMA, 188
pneumonia, 118, 241, 246, 268
pneumothorax, 162
polarity, 47, 166
policy, 95, 108
polymerase, 169, 203
polymers, 70
polymethylmethacrylate, 188
polymorphism, 9
polymyositis, 171, 185
polyuria, 162, 168, 169, 179, 228, 231
pools, 60
population, vii, 1, 2, 3, 5, 6, 9, 17, 18, 19, 20, 22, 23,
24, 27, 28, 29, 31, 39, 55, 56, 57, 58, 59, 60, 62,
63, 64, 70, 73, 77, 79, 98, 101, 103, 109, 122,
132, 136, 197, 198, 199, 200, 244, 247, 251
population group, 57
portability, 80
portal hypertension, 163, 164, 234, 260
positive correlation, 27
post-hoc analysis, 157
postoperative outcome, 155, 156
post-streptococcal glomerulonephritis, 176
post-transplant, 56, 61, 63, 202
postural hypotension, 227
potassium, 168, 171, 179, 180, 202, 222, 223, 224,
225, 226, 229, 239, 242, 254, 256, 257
potassium sparing diuretics, 223

precipitation, 132, 150, 180, 269
 prediction models, 145
 prednisone, 203, 237, 240, 241, 242, 243, 244, 245, 246
 pregnancy, 178
 preparation, vii, 40, 48, 180
 preservation, 38, 45, 46, 47, 48, 49, 103, 169, 216
 prevention, vii, 42, 63, 112, 114, 143, 145, 146, 148, 149, 151, 153, 155, 156, 161, 188, 189, 190, 192, 194, 195, 197, 198, 199, 200, 201, 202, 204, 205, 206, 210, 211, 212, 213, 218, 221, 228, 229, 231, 239, 258, 259
 priming, 4
 principles, 98
 probability, 57
 professionals, 79
 progenitor cells, 167
 prognosis, 11, 19, 21, 22, 23, 26, 27, 56, 134, 138, 150, 163, 168, 176, 181, 239, 242, 244, 246
 progressive kidney disease, vii, 1, 97
 pro-inflammatory, 38, 49, 164, 166, 167, 170, 173, 248
 proliferation, 8, 39, 128, 205, 208, 243, 251
 promoter, 7
 propagation, 23
 prophylactic, 41, 102, 111, 189, 214, 215, 229
 prophylaxis, 114, 156, 199, 206, 210, 216, 218, 246, 268
 prostaglandins, 5, 161, 165, 170, 179
 prostate cancer, 260
 protease inhibitors, 180
 proteasome, 141
 protection, 38, 41, 42, 43, 44, 45, 47, 50, 51, 52, 146, 148, 153, 207, 208, 213, 214, 215
 protective role, 43
 protein kinases, 132
 protein misfolding, 133
 protein synthesis, 51, 177, 248
 proteinase, 176
 proteins, 12, 22, 25, 27, 28, 30, 35, 43, 44, 128, 129, 132, 136, 137, 138, 139, 164, 170, 178, 180, 248
 proteinuria, 2, 5, 9, 12, 40, 42, 49, 56, 127, 129, 131, 133, 134, 175, 180, 242, 243, 246
 proteoglycans, 187
 proteolytic enzyme, 173
 proton pump inhibitors, 174
 prototype, 175
 proximal convoluted tubules, 38, 49
 proximal tubules, 45, 127, 128, 129, 132, 188, 192, 258
 pseudogout, 124
 psychiatry, 79, 173
 psychology, 68

PTFE, 69, 90, 111
 public health, 2, 55, 56
 public sector, 81
 pulmonary edema, 203, 221, 225, 227, 238, 254
 pulmonary embolism, 162
 pulmonary hypertension, 162
 purification, 141
 purpura, 177, 248
 pyelonephritis, 40
 pyrophosphate, 26, 33

Q

QRS complex, 223
 quality assurance, 69
 quality of life, 38, 39, 41, 48, 49, 57, 64, 68, 73, 75, 78, 80, 85, 87, 145
 quantification, 127, 130
 Queensland, 17, 89
 questionnaire, 57

R

race, 64, 94, 182, 254
 racism, 62
 radiation, 39, 40, 178, 179
 radiation therapy, 178, 179
 radical formation, 43, 49, 50
 radicals, 27, 44, 52
 radiotherapy, 150, 218
 randomized controlled clinical trials, 196
 RANTES, 167
 rapidly progressive glomerulonephritis, 176, 242, 268
 rash, 175
 reactions, 28, 175, 235
 reactive oxygen, 3, 5, 27, 37, 38, 49, 50, 52, 144, 163, 164, 166, 170
 reagents, 129
 receptors, 8, 15, 25, 26, 44, 51, 132, 161, 229, 230
 recognition, 23, 96, 143, 144, 151, 206
 recommendations, 70, 146, 221, 252, 268
 recovery, 4, 41, 47, 131, 134, 135, 136, 138, 141, 147, 154, 155, 167, 201, 205, 227, 228, 230, 231, 236, 237, 249, 251, 252, 253, 258, 260, 263, 273, 274
 recruiting, 136
 recurrence, 58, 118, 233
 red blood cells, 227
 reflexes, 34, 251
 reforms, 80
 regeneration, 10, 230, 256, 259, 276

registry(s), 9, 57, 58, 71, 74, 76, 77, 78, 79, 85, 86, 109
 regression, 15, 59, 93, 123, 149
 regression analysis, 59, 93, 149
 rehydration, 132
 reintroduction, 167
 rejection, 58, 173, 202
 relapses, 245
 relaxation, 43, 54, 161
 relief, 232
 religion, 59, 60
 religiosity, 59
 religious beliefs, 62
 remission, 240, 241, 245, 246, 269, 270
 remodelling, 31, 91, 106
 renal cell carcinoma, 206
 renal dysfunction, 27, 124, 153, 155, 163, 164, 184, 193, 209, 211, 212, 213, 214, 215, 216, 229, 239, 240, 245, 248, 259, 265
 renal interstitial compartment, vii, 1
 renal level, 40, 46
 renal osteodystrophy, 126
 renal replacement therapies (RRTs), 234, 251
 renin, 19, 22, 24, 26, 31, 32, 150, 157, 161, 163, 230
 repair, 3, 7, 10, 13, 15, 98, 99, 100, 111, 151, 213, 256, 260, 276
 reparation, 39
 repression, 42
 requirements, 55, 56, 166, 228, 230, 237, 248, 249, 250, 252, 271
 resection, 118, 119
 residues, 8, 39
 resins, 225
 resistance, 20, 38, 40, 46, 71, 93, 104, 164, 179, 188, 205, 232, 238
 resolution, 4, 15, 42, 123, 232
 resource allocation, 80
 resource utilization, 152, 206
 resources, 60, 63, 79
 respiratory failure, 234, 245
 responsiveness, 166, 230, 255
 restoration, 3, 73, 103, 113, 146
 restrictions, 78
 retardation, 13
 retinal ischemia, 126
 retinol, 214
 reverse transcriptase, 169
 rhabdomyolysis, 143, 149, 171, 172, 184, 185, 189, 202, 203, 206, 217, 223, 239, 265
 rhythm, 167, 223
 risk factors, 9, 19, 23, 28, 29, 32, 56, 87, 94, 117, 121, 134, 145, 149, 151, 170, 183, 189, 190, 191, 194, 198, 203, 206, 212, 213, 217, 263

rituximab, 245, 246
 RNA, 203
 rods, 104
 Rouleau, 212
 Royal Society, 83
 rubber, 69

S

safety, 69, 112, 140, 145, 153, 183, 197, 207, 209, 211, 234, 268, 275
 salicylates, 171
 salmonella, 171, 174
 salt substitutes, 225
 SAP, 161
 sarcoidosis, 174, 175
 saturation, 43, 147
 scavengers, 52
 science, 71, 214
 scleroderma, 178, 203, 217, 218, 270, 271
 sclerosis, 39, 203
 scope, 2
 second generation, 169, 196
 secrete, 5, 91, 167
 secretion, 10, 25, 27, 33, 34, 133, 161, 163, 164, 173, 232
 sedatives, 171
 selenium, 192
 self-esteem, 69
 sensitivity, 63, 128, 129, 130, 131, 133, 137, 167, 205
 sensitization, 207
 sepsis, 143, 146, 151, 153, 157, 159, 162, 164, 167, 168, 181, 190, 198, 205, 221, 227, 229, 231, 235, 236, 249, 254, 255, 263, 273, 274
 septic shock, 143, 146, 151, 154, 230, 235, 236, 259, 262, 272, 274, 275
 septum, 67
 serine, 103
 serotonin, 185
 serum albumin, 20
 serum bicarbonate, 203
 services, 56, 59, 78
 sex, 122, 126, 167, 190, 204, 254
 shear, 91, 92, 106
 sheep, 131
 shock, 37, 50, 144, 146, 154, 162, 164, 177, 181, 191, 206, 230, 236, 259, 263, 274
 shortage, 68
 showing, 252
 side effects, 37, 41, 250, 255
 signal transduction, 42, 44
 signalling, 7

- signals, 11
 signs, 98, 104, 175, 238, 239
 silica, 177
 sine wave, 223
 skeletal muscle, 170, 249
 skeleton, 39
 skin, 133, 162, 203
 sleep disorders, 73
 sleep disturbance, 83
 smooth muscle, 5, 13, 22, 23, 25, 27, 30, 39, 54, 91,
 161, 166, 230
 smooth muscle cells, 22, 25, 30
 snakes, 171
 social care, 79
 social network, 60, 65
 social support, 60
 society, 79
 socioeconomic status, 64
 sodium, 19, 24, 25, 32, 102, 150, 153, 194, 195, 196,
 201, 209, 210, 216, 224, 225, 227, 229, 230, 252,
 254, 260
 soleus, 257
 solid tumors, 169
 solubility, 149, 180
 solution, 85, 102, 114, 193, 203, 224, 226, 227, 232
 solvents, 165
 somatic cell, 256
 South Asia, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65
 specialists, 150, 160
 species, 3, 5, 27, 28, 37, 38, 49, 50, 144, 163, 164,
 166, 169, 170, 186
 spectroscopy, 24
 speed of response, 131
 spending, 97
 spiders, 171
 spinal cord, 179
 Sri Lanka, 263
 stability, 251, 252
 stable angina, 219
 staffing, 80
 staphylococci, 104
 starch, 165, 169
 state(s), 6, 24, 26, 31, 42, 68, 98, 105, 124, 180, 198,
 238, 248, 254, 258
 statin, 148, 156, 172, 197, 212
 status asthmaticus, 171
 status epilepticus, 171, 172, 184
 stem cells, 151, 157, 182, 231, 256, 259, 276
 stenosis, 21, 23, 92, 96, 98, 99, 100, 106, 108, 110,
 111, 119, 247
 stent, 262
 steroids, 20, 143, 148, 237, 269
 sterols, 168
 stimulation, 7, 25, 27, 34, 38, 40, 43, 44, 45, 46, 47,
 48, 49, 51, 161, 163, 169, 173, 259
 stimulus, 39, 248
 stratification, 151, 206, 209, 213
 stress, 27, 35, 40, 41, 44, 50, 53, 91, 92, 106, 182,
 186, 246, 258
 strictures, 179
 stroke, 117, 118, 121, 123, 124, 125, 126, 147, 184
 stroke volume, 147
 stroma, 4
 stromal cells, vii, 1, 6, 13
 structural changes, 47
 structure, 7, 30, 38, 39, 43, 45, 47, 102, 121, 166,
 169
 style, 71
 subgroups, 96
 substitution(s), 133, 241, 249, 273
 substrate(s), 8, 43, 123
 success rate, 239
 sucrose, 165, 169
 sulfonamides, 174
 Sun, 9, 156
 supplementation, 153, 198, 239, 249
 suppression, 130
 surface area, 204
 surgical resection, 122, 125
 surgical technique, 90
 surveillance, 4, 89, 98, 99, 100, 101, 110, 111
 survival rate, 61, 68, 240, 244, 246, 274
 survivors, 152
 Sweden, 235
 swelling, 168
 sympathetic nervous system (SNS), 34, 150, 161,
 163, 164
 symptoms, 83, 175, 221, 223, 226, 238, 239, 245,
 251
 syndrome, 13, 37, 41, 68, 143, 149, 150, 157, 161,
 162, 163, 164, 169, 170, 171, 172, 173, 174, 176,
 177, 178, 179, 180, 181, 185, 187, 188, 189, 204,
 216, 218, 229, 232, 238, 248, 252, 260, 265, 266,
 267, 268, 270, 273
 synergistic effect, 123
 synthesis, 14, 25, 27, 33, 34, 44, 53, 102, 128, 155,
 163, 165, 166, 169, 170, 173, 179, 205, 207, 236
 systemic lupus erythematosus, 174, 177, 268
 systemic sclerosis, 203, 217, 270
 systolic blood pressure, 23, 73, 122

T

T cell(s), 4, 11, 12
 tachycardia, 223, 225
 tamoxifen, 178

target, 8, 50, 70, 123, 135, 146, 149, 204, 206, 207
 Task Force, 211
 taxation, 79
 teams, 69
 techniques, 14, 53, 89, 98, 99, 100, 110, 128, 129, 134, 155, 235, 251, 252, 253, 255, 257
 technological advances, 75
 technology, 67, 69, 80, 255
 tendon, 251
 tension, 162
 testing, 129
 therapeutic approaches, 235, 257
 therapeutic targets, 15
 therapeutic use, 261
 thrombocyte, 248
 thrombocytopenia, 178, 240
 thrombocytopenic purpura, 178, 187, 244, 265, 266, 267
 thrombolytic agents, 104
 thrombolytic therapy, 125
 thrombosis, 91, 92, 93, 95, 98, 99, 100, 101, 103, 106, 108, 111, 113, 236, 240
 thrombus, 101, 117, 120, 121, 123
 thymine, 39
 time constraints, 79
 tissue, 1, 3, 4, 5, 6, 7, 8, 13, 25, 27, 33, 34, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 54, 102, 103, 112, 113, 123, 133, 154, 159, 167, 171, 172, 173, 174, 179, 219, 221, 246, 248
 tissue perfusion, 154
 tissue plasminogen activator, 102, 103, 112, 113
 titanium, 70
 TNF-alpha, 187
 toluene, 171
 tonometry, 23
 tourism, 60, 61, 63, 65
 toxic aldehydes, 44
 toxic effect, 42, 50, 159, 165, 167, 170, 171, 172, 180
 toxic substances, 168
 toxicity, 53, 186, 207, 208, 233, 246, 268
 toxicology, 50
 toxin, 177, 207, 251
 trade, 33
 trade-off, 33
 trafficking, 60, 65
 training, 77, 78, 80, 84, 109
 transcatheter, 103, 114
 transcription, 25, 42, 44, 132, 169, 173
 transcription factors, 44, 173
 transformation, 5, 6, 14
 transforming growth factor (TGF), 3, 6, 7, 12, 14, 132

transfusion, 170
 transition metal, 43
 transitional cell carcinoma, 246
 translocation, 250
 transplant, 34, 57, 58, 60, 61, 63, 64, 65, 77, 85, 175, 202, 262, 267
 transplant recipients, 34, 61, 85, 175
 transplantation, 22, 28, 34, 37, 39, 41, 49, 55, 56, 58, 60, 61, 62, 63, 64, 65, 71, 75, 76, 77, 84, 87, 126, 140, 173, 178, 183, 186, 191, 202, 217, 233, 268
 transport, 80, 168, 183, 229, 255, 257, 275
 transport costs, 80
 transportation, 41
 trauma, 162, 172, 177, 179, 184, 228, 248
 tricuspid valve, 124
 triggers, 164, 176
 tuberculosis, 174
 tumor(s), 11, 41, 46, 54, 117, 118, 119, 120, 121, 122, 124, 125, 126, 157, 177, 179, 180, 188, 189, 191, 204, 208, 218, 223, 252, 255, 263
 tumor cells, 180, 204
 tumor growth, 11
 tumor necrosis factor (TNF), 46, 50, 54, 187, 236, 252, 255, 263
 tumours, 157
 turnover, 5
 type 2 diabetes, 29

U

ultrasonography, 107, 164
 ultrasound, 92, 94, 95, 98, 99, 100, 107, 110
 uniform, 137, 160
 united, 1, 31, 39, 55, 62, 63, 64, 65, 83, 84, 85, 103, 109, 127, 132, 140, 143
 United Kingdom (UK), 1, 2, 9, 55, 56, 57, 61, 62, 63, 64, 65, 67, 68, 70, 71, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 127, 130, 132, 143, 258
 United States (USA), 11, 12, 31, 39, 49, 53, 62, 63, 65, 78, 83, 84, 97, 103, 109, 138, 190, 194
 unstable patients, 253
 updating, 211
 urea, 28, 35, 57, 69, 71, 83, 252, 254
 ureters, 159, 161
 urethra, 159, 161, 231
 uric acid, 150, 171, 180, 188, 204, 218, 239
 uric acid levels, 204, 239
 urinalysis, 129
 urinary bladder, 159, 161
 urinary tract, 159, 160, 161, 178, 179
 urine, 127, 128, 129, 132, 133, 134, 136, 137, 139, 146, 149, 150, 155, 160, 161, 167, 168, 169, 180,

189, 193, 202, 203, 204, 205, 224, 227, 228, 229,
230, 231, 233, 245, 246, 254, 259
urine immunofixation, 137
urokinase, 103, 113, 114
uveitis, 174

V

validation, 99, 110, 152
valve, 21, 118, 126, 143, 144
valvular heart disease, 170
vancomycin, 174
variables, 84, 154, 184, 250
variations, 58
vascular ablation, 37, 41
vascular access, 69, 89, 90, 94, 96, 97, 98, 99, 100,
101, 105, 106, 107, 109, 110, 111, 112, 251
vascular endothelial growth factor (VEGF), 7
vascular surgery, 156
vascular wall, 34
vasculature, vii, 1, 7, 21, 27, 39, 133
vasculitides, 269
vasculitis, 15, 40, 246, 269, 270
vasoconstriction, 24, 38, 43, 146, 150, 161, 162, 163,
164, 166, 170, 171, 179, 180, 204, 229, 232, 235
vasodilation, 146, 150, 162, 163, 164, 170
vasodilator, 43, 45, 47, 228
vasopressin, 150, 230, 233, 238, 261, 271
vasopressor, 146, 151, 154, 164
VCAM, 166, 176
vegetation, 118, 123, 124
vein, 90, 92, 93, 96, 102, 103, 106, 107, 112
velocity, 21, 23, 99
venipuncture, 68, 82, 92, 98, 105
venography, 103
ventricle, 118, 119
ventricular tachycardia, 223

venules, 3
vessels, 21, 22, 23, 90, 94, 106, 107, 124, 159, 163,
166, 172
victims, 184
Vietnam, 272
viral infection, 177
virus infection, 269
viscosity, 46
vision, 14, 79
vitamin A, 249
vitamin B1, 249
vitamin C, 192, 249
vitamin D, 2, 30, 123, 242
vitamin E, 192
vitamin K, 249
vitamins, 249, 272
VLA, 176
vomiting, 162
vulnerability, 183

W

Wales, 78, 82
war, 68, 145
waste, 28, 168, 253
water, vii, 17, 19, 24, 28, 29, 43, 150, 168, 173, 179,
189, 203, 225, 226, 235, 238, 249, 254, 260, 275
weakness, 60, 223
weight loss, 164, 238
weight reduction, 31
wheeze, 225
withdrawal, 164, 170, 233, 236
workers, 185, 255
workforce, 80, 82
workload, 238
worldwide, 37, 70, 236, 250
wound healing, 2, 10