Core Concepts in Parenchymal Kidney Disease

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To my daughter Sophia, whose smile and love inspire me every day.

—Fernando C. Fervenza

For my parents, Lung-Nan and Cheng-Hue Lin, for their many years of love and support.

—Julie Lin

To my parents, Saroj Sethi and Indrash Chandra Sethi, for their love and wisdom.

—Sanjeev Sethi

To my brother, Sanjay, with love.

—Ajay K. Singh

Foreword

"Think of that, - a man of my kidney, - think of that, - that am as subject to heat as butter; a man of continual dissolution and thaw:it was a miracle to scape suffocation"
'The Merry Wives of Windsor'

play by William Shakespeare

"Core Concepts in Parenchymal Kidney Disease" is a timely, comprehensive, and informative book, written by an international group of outstanding experts in the field. The book's chapters are enough detailed to be of value to the renal community and to nephrology fellows and trainees in internal medicine and can appeal to a broad medical audience with an interest in how to diagnose and treat the most common glomerulopathies. The book is timely in that classical paradigms in parenchymal renal disease have been recently challenged by real advances and true discoveries that just 10 years ago one could barely imagine. Progress in molecular biology and the formidable chance offered by deciphering the genome have impacted nephrology to a major extent.

In last 10 years numerous abnormalities in genes involved in renal structure and function have been identified, but the molecular basis for the most common renal parenchymal disease is either unknown or incomplete, with a few notable exceptions. All the recent studies have generated more questions than offered answers but have so far contributed to clarify at least some of the mechanisms initiating and driving disease progression of complex disease (that up to now we have only been able to recognise as diverse by different clinical and pathologic features) and find novel and effective treatment in others. Thanks to these advances we start to appreciate what we can expect for the future.

Will focal and segmental glomerulosclerosis (FSGS) for example remain a "diverse group of clinical disorders" as Barua and Pollak are suggesting in their chapter? They point to dysfunction of the podocyte as central to the pathogenesis of the disease. My prediction is that in the future FSGS will be redefined and split into many disease entities that genomic studies are now helping to recognise.

Membranous nephropathy (MN) today is not any longer the disease we were used to think about in terms of pathophysiology and treatment. After more than 50 years of experimental studies—devoted to finding podocyte antigens as target of circulating antibodies for in situ formation of immunocomplexes—at least two relevant antigens have been identified in humans that account for over 70 % of cases of human MN. More than that, genome-wide association studies have contributed to clarify the association between HLA-DQ and PLA2RI loci and the disease in Caucasian patients. An antibody that targets B cell has revolutionised the treatment of this disease and we can easily foresee that in the future novel biological tools will help not simply to treat patient but to unravel the pathophysiology of immunocomplex formation and subsequent injury. The authors of the chapter on MN give an account of these new developments in the treatment of the diseases, which point (their words) to "a direct effect on the pathophysiology of the disease process". They underline that the future is a more specific targeting therapy for MN.

Membranoproliferative glomerulonephritis (MPGN) cannot be considered a single disease today: immunocomplex-mediated MPGN and complement-mediated MPGN due to dysregulation

of alternative pathway of complement are at least distinct disease entity that will likely require different treatment not to mention a number of additional MPGN-associated conditions. These changes of perspective in the classical way of looking at these groups of diseases are well documented in the pages devoted to MPGN and the attempt to underline pitfalls in the current classification and propose a new one building on three decades of past studies and research is of special value. Of great interest, the book devotes a chapter to IgG4-related disease, a newly recognised condition of systemic inflammation and lymphoplasmacytic infiltrates that are rich in IgG4-positive plasma cells and are found virtually in every organ, including the biliary tract, salivary glands, lungs, thyroids, pericardium, and skin. Kidney involvement mainly includes manifestations of tubulo-interstitial nephritis, as it is accurately described in the pages devoted to this disease. Our knowledge about this disease is evolving while other renal phenotypes are emerging that include glomerular changes and lesions of membranous nephropathy that impose significant therapeutic challenges to clinicians. Chapters dealing anti-GBM disease and systemic lupus are less novel but still provide a scholarly overview of pathophysiology, clinical manifestation, and treatment of these diseases that can appeal nephrologists and internists with an interest in renal medicine.

The chapter dealing with thrombotic microangiopathies deserves a special mention. Ten years ago our understanding of the pathophysiology of this group of diseases was very limited. A tremendous research effort has allowed us to reach an extreme grade of sophistication in identifying genetic and acquired initiators and modifiers of atypical HUS, type I MPGNI, Dense deposit diseases (DDD), and C3 nephropathy (C3GN); in developing technology for the diagnosis; and in selecting biomarkers of response to therapy. Finally, we have now better choice to treat these conditions and to prevent post-transplant disease recurrence. All of these can be found at least in part in the book.

The chapter on HUS and TTP also alludes to the similarities rather than to differences in these disease entities in particular as for the pathophysiology of microvascular thrombosis and the role of complement. It is nice to see that this concept, which was very much debated until recently, is now appreciated to the point to find room in book chapter. In a not distant future we will be able to personalise our approach to treatment of monogenic diseases by a limitless potential to modify damaged tissues and organs by genetic engineering and cell transplantation. HUS and TTP, as it emerges from the chapter in the book, will be most amenable to this.

One of the merits of "Core Concepts in Glomerular and Tubulointerstitial Diseases" is to include topics usually not covered by conventional publications. The chapter "Tropical infections diseases of the kidney" offers a comprehensive review of conditions such as tuberculosis, leptospirosis, and malaria and CMV, BK, and other viral infections and some viral hemorrhagic fever. Those living in rich countries tend to forget about such devastating diseases. In several instances, infection may remain silent for years while irreversible kidney destruction takes place.

The chapter on Collagen IV Nephropathies is probably the best chapter in the book. New concepts in genetics and pathophysiology of these diseases are highlighted in a comprehensive, scholarly, and sophisticated way and effectively integrate the even enlarging knowledge on phenotype–genotype correlation and pathophysiology of basement membrane lesions with less recent and very novel related conditions, such as the basement membrane nephropathy and Hanac Syndrome. As it is the chapter dealing with primary disease with systemic features worth reading are the sections on C1q nephropathy, idiopathic nodular glomerulosclerosis, and fibrillary and immunotactoid diseases. The section on diagnosis and treatment in the chapter on amyloidosis and related disorders is of great interest and of particular value to clinicians.

In summary, "Core Concepts in Parenchymal Kidney Disease" is going to become an essential reference book to be found in every renal department library. It will help training fellows in focusing their learning path, but also the experienced nephrologist will not fail to find it an important ally with its refreshing and up-to-date information.

Bergamo, Italy Giuseppe Remuzzi M.D., F.R.C.P.

Preface

We are pleased to offer the 1st edition of *Core Concepts in Parenchymal Kidney Disease*.

Since the original descriptions of parenchymal kidney disease by Richard Bright in 1927, much has changed about our knowledge of glomerular and tubulointerstitial disease. Newer information on the diagnosis and classification of glomerulonephritis has emerged, and there has been much recent progress in pathogenesis. Our book encapsulates some of these advances and provides an updated review. We hope that this book, either in its paper or electronic forms, is a valuable resource to our target audience—practicing nephrologists and nephrology trainees.

We would like to acknowledge the hard work and commitment of our administrative colleagues and Barbara Lopez-Lucio at Springer, who have been magnificent in their support. We hope that you find the book useful and enriching.

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General Approach to the Diagnosis and Management of Glomerular Diseases

1

David Philibert and Daniel C. Cattran

The diversity in clinical presentation, diagnosis, natural history, and treatment of glomerular diseases is a significant challenge for the practicing physician. Part of the diversity is related to the focal and segmental nature of many of these disorders, and this variation should perhaps be expected, given the approximately 800,000 glomeruli per kidney in normal individuals [1]. This chapter will review the important generic issues that relate to all patients with these disorders. This will include an approach to the main clinical syndromes, with an emphasis on the assessment of the risk factors for progression of the underlying glomerular disease. In addition, we will review the challenges of interpreting older studies, given our current knowledge about these diseases as well as the major principles guiding current treatment with a focus on immunotherapy risks, benefits, and limitations. Our objective is to give an overview to the "in common" problems related to management of this patient population.

Clinical Presentation

Patients affected with glomerular diseases present in a variety of ways. It is the clinician's role to recognize these various syndromes and proceed in an organized manner that will lead the physician to the correct diagnosis, a rational assessment of the patient's risk of progression, and a tailored approach to the patient's management that balances the risk and benefits of treatment.

Hematuria

Hematuria is a cardinal manifestation of almost all renal diseases. This applies regardless of whether it is macroscopic or microscopic in form and whether it is glomerular or non-glomerular in origin. The first challenge in the evaluation of hematuria is establishing whether it is pathological or is within normal limits. Indeed, we do not know with certainty the numerical upper limit of red cells in normal urine, but we do know that they are present in large numbers. In addition, the sensitivity of the dipstick testing is high and close to the normal range [2]. This dictates that if the dipstick shows only trace hematuria, repeat testing must be done before considering it of pathological significance; however, when present on repeat testing even in small amounts, the physician is obliged to investigate further including ruling out benign or unrelated conditions such as its occurrence postexercise or due to contamination related to the menstrual cycle.

Once the presence of hematuria is determined to be abnormal, the next important step is to rule out non-glomerular etiologies. There are a wide variety of potential causes including bleeding disorders, stones, infections, and even genitourinary cancer. It is not the purpose of this chapter to review them all, but the treating physician must be aware of their existence and explore these and other causations if indicated on clinical grounds. These clinical indicators for further investigation vary widely from the working environment of the patient to their age at presentation. The likelihood, for instance, of finding a urological cancer before the age of 40 is very low [3], but this risk rises with increasing age, smoking history, and certain environmental exposures such as hair dyes [4] and various industrial chemical carcinogens. The general screening after a complete history and physical examination (including urinalysis and microscopic examination of the urinary sediment) for non-glomerular causes should include a coagulation screen and a renal ultrasound. If the patient is older (>40), cystoscopy should be considered if an explanation of the hematuria is not found on these initial assessments.

There are specific clues that point towards glomerular hematuria. Attention must be paid to the family history, since the presence of isolated hematuria in other family members is commonly found in patients with thin basement membrane disease and in patients with Alport's syndrome.

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The urine sediment may reveal the presence of granular or red cell casts or >5 % acanthocytes (erythrocytes with blebs protruding from the cell body) [5]. The presence of dysmorphic erythrocytes may be more difficult to interpret, although studies suggest that if they constitute more than 80 % of the erythrocytes in the urine, glomerular disease is likely present [6]. Any of these findings strongly suggests a glomerular cause of the hematuria. These findings in the urine sediment will be specific (healthy people will not show them), but not sensitive (patients with glomerular disease will not always show them).

The following should be considered once benign causes for the hematuria and non-glomerular causes have been ruled out. If the hematuria is microscopic and isolated, i.e., there is no proteinuria, and normal blood pressure and no other features on history or urine sediment examination point towards glomerular disease, further investigation including a kidney biopsy is rarely indicated. Exceptions to this rule may include investigation required for insurance or employment purposes to rule out Alport's syndrome in women of childbearing age or to further assess the kidney's suitability for live donor transplantation. If there is microscopic hematuria and only low-grade proteinuria (<0.5 g/day), then close follow-up is recommended, with further investigation including renal biopsy held in reserve if any other signs indicative of worsening glomerular disease subsequently develop.

Further investigation, including a kidney biopsy, should be considered if the differential diagnoses that remain have a significantly different prognosis and/or the therapeutic options available are likely to alter the patient's management and/or outcome. If other signs and symptoms suggestive of more significant disease, such as proteinuria >1 g/day, systemic disease features, abnormal GFR, hypertension, or red cell casts, are found in the urine, further investigation is warranted straightaway.

Asymptomatic Proteinuria

Proteinuria is another frequent manifestation of renal glomerular disease and similar to hematuria has a broad differential diagnosis. The kidney normally excretes a maximum of 150 mg/day of protein, with most of the healthy population ranging between 40 and 80 mg/day. When the albuminuria is between 30 and 300 mg/day, it is considered pathological and designated microalbuminuria and when >300 mg/day, overt albuminuria (or clinical proteinuria), even though most patients remain asymptomatic up to the 3 g/day level. The urinary loss of albumin, a protein with low molecular weight (69 kDa), generally occurs earlier than the larger weight proteins such as IgG (150 kDa) or IgM (950 kDa), and it is therefore not surprising that albumin excretion of more than 30 mg/day in diabetic patients is one of the first signs indicative of nephropathy. Even without diabetes, microalbuminuria has been associated with increased cardiovascular risk [7, 8], with several lines of evidence suggesting that these low levels of albuminuria reflect glomerular capillary (and perhaps systemic) endothelial dysfunction.

Proteinuria (presumably mostly albumin) is not always of pathological significance, and transient low-level proteinuria can be seen during fever and after vigorous exercise. In the United Kingdom Prospective Diabetes Study (UKPDS), albuminuria >50 mg/dL was present in 4 % of apparently healthy individuals [9]. Similarly, in the Third National Health and Nutrition Examination Survey in the US (NHANES III) population, the authors found the prevalence of microalbuminuria (defined as albumin/creatinine ratio 30–299 mg/g regardless of sex) in the general population without comorbid conditions was 5.1 % [10]. When even these levels of albuminuria or proteinuria are persistent and therefore considered pathological, they should be properly quantitated. There are two different approaches to this assessment. The first is the albumin/creatinine ratio (or the protein/creatinine ratio if albumin/creatinine ≥500 mg/g) on a morning sample. This is the method of choice advocated by the NKF/KDOQI because of its convenience and low risk of error [11]. This ratio is most useful when using traditional units of measurement (because the ratio closely approximates the total protein excreted in 24 h) but is somewhat more complicated when SI units are the standard (where mmoles are used for the creatinine estimate compared to the traditional grams), although the precision of the measurement remains the same. Microalbuminuria is said to be present if the albumin/creatinine ratio is 17–255 mg/g in women and 25–355 mg/g in men. This approach is valuable and is recommended, although the second and more traditional method using 24-h urine collection has some unique values. It is not influenced by the time of day, and it allows the clinician to gather other useful information such as the measured creatinine clearance and sodium excretion. The risk of under- or over-collection is real but can be assessed by examining the urine creatinine in the completed collection and comparing it to the expected value based on the muscle mass of the patient. This method is particularly helpful in clinical trials where repeated samples collected over time in each patient are compared. A compromise is a ratio where the collection period for the aliquot is significantly longer, e.g., 6–8 h.

In young people (especially young males) with isolated dipstick proteinuria, normal GFR, and normal urine sediment, benign orthostatic proteinuria should be ruled out. The results from two separate 12-h collections, one in daytime

when the patient is predominantly in the upright position and the other while the patient is in the recumbent position, most conveniently performed during the overnight period are compared. The total proteinuria is almost always <1 g/day in this condition, and the diagnosis is made when the 12-h recumbent value is virtually zero and the abnormal proteinuria confined to the upright position time period.

After proteinuria quantification, its quality may need to be evaluated by electrophoresis; this is especially important in older patients where additional signs and symptoms might suggest a systemic condition such as multiple myeloma or amyloidosis.

Evaluation of the patient with significant proteinuria should include measurement of serum albumin and a lipid profile. Blood pressure assessment and GFR measurement should also be determined. Screening for secondary causes should be considered in most cases, including tests for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), complement profile (C3 and C4 levels), and renal anatomy evaluation by ultrasound. If any of these are abnormal and/or if there are systemic symptoms such as unexplained fever or weight loss, a kidney biopsy is usually performed. If the proteinuria is isolated and in the subnephrotic range, and there are no additional systemic features, then the need to perform a kidney biopsy is more controversial. Primary FSGS or membranous nephropathy can sometimes present with isolated low-grade proteinuria, but immunosuppression is not currently indicated at these levels (<3.0 g/day) of proteinuria particularly if the GFR and blood pressure are normal. On the other hand, even though rare, some systemic diseases, such as amyloidosis, can present as isolated proteinuria, so the decision in regard to a biopsy is often dependent on the nephrologist judgment. A conservative approach of watching and waiting is a viable option, provided regular assessment of GFR, blood pressure, and proteinuria is maintained, with the renal biopsy performed only if the clinical setting changes and becomes more suggestive of worsening glomerular or systemic disease.

The Nephrotic Syndrome

If the proteinuria worsens, other features of the nephrotic syndrome may develop such as hypoalbuminemia and peripheral edema. Lipid metabolism is also altered, leading to hyperlipidemia [12]. Patients with this syndrome are more prone to have thromboembolic events [13, 14], especially when it is associated with certain histological subtypes such as membranous nephropathy or focal segmental glomerulosclerosis [15]. In a large review of 898 patients with biopsy-proven membranous nephropathy, for instance, the prevalence of clinically apparent venous thromboembolism was 7.2 %, with hypoalbuminemia (<2.8 g/dL) being the most important risk factor [16]. The reasons for this increased risk have not been fully elucidated, but hypovolemia plus disturbances in the complex balance of thrombogenic/antithrombogenic proteins undoubtedly plays a role [17]. Increased susceptibility to infections can also be seen in nephrotic patients, particularly in children. Physical factors such as fluid collections secondary to the lowered oncotic pressure in the pleural, peritoneal, or other spaces have been implicated in these infections, but additional factors including depressed lymphocyte function, low serum immunoglobulins (especially IgG), and decreased complement levels secondary to urinary losses of these components likely contribute to this risk. Finally, urinary loss of binding proteins and hormones [18], like vitamin D, thyroid-binding globulin, and erythropoietin, occurs in patients with the nephrotic syndrome, although their clinical relevance is often small or difficult to estimate.

The causes of the nephrotic syndrome are numerous. A kidney biopsy should generally be performed in order to determine diagnosis, estimate prognosis, and guide treatment. Antinuclear antibodies (ANA), anti-dsDNA antibodies, levels of complement (both C3 and C4), hepatitis B and C serology, serum protein electrophoresis, and cryoglobulins are reasonable screening tests to rule out secondary causes. A VDRL or equivalent may be needed to exclude syphilis, although this is rare today as causation in developed countries. Anti-GBM antibodies are not usually needed, unless there is associated renal failure or clinical features suggestive of pulmonary involvement. Antineutrophil cytoplasmic antibody (ANCA) tests should be ordered if there are significant systemic features suggestive of an underlying vasculitis such as unexplained fever; malaise; weight loss; upper airway lesions of the ear, nose, or throat; or pulmonary involvement. Although renal-limited ANCA vasculitis with pure nephrotic syndrome is possible, it is uncommon.

A workup for an underlying malignancy should be considered particularly in patients older than 60 and with membranous nephropathy [19]. Examination of the prostate and measurement of prostate-specific antigen (PSA) in males and mammography in female, as well as, in both sexes, a chest X-ray (consider chest CT in high-risk patients) and GI evaluation including an abdominal ultrasound or CT, will cover most primary origins for tumor-associated disease.

Renal Vein Thrombosis

Patients presenting with the nephrotic syndrome particularly with high-grade proteinuria and hypoalbuminemia (<2.8 g/dL) have a higher risk of renal vein thrombosis (RVT) [20]. Previous studies using renal venography noted RVT in 22 % of 151 patients that presented with the nephrotic syndrome regardless of the cause [14]. A more recent review showed

that prevalence of RVT was highest in patients with membranous nephropathy (37 %) [13]. RVT can present with acute loin pain, hematuria, kidney enlargement, rapid increase in lower limb edema, and with unexpected deterioration in renal function. In some cases, the presentation can be quite asymptomatic except for a slow decline in renal function. Its diagnosis therefore requires a high index of suspicion, although routine and repeated screening of every patient with nephrotic range proteinuria is not currently recommended. Pulmonary embolism can accompany RVT and was found in 20 % of the chronic RVT patients who underwent a ventilation/perfusion lung scan in one series [14]. This complication should be considered when RVT is diagnosed even in the absence of acute pulmonary signs and symptoms.

Rapidly Progressive Glomerulonephritis

The most dramatic presentation of glomerular disease is the somewhat misnamed rapidly progressive glomerulonephritis (RPGN). This is a clinical scenario, not a type of glomerulonephritis, characterized by rapid deterioration in renal function over weeks or months, associated with glomerular hematuria and proteinuria (usually not in the nephrotic range) and often, but not always, systemic symptoms and hypertension. When this scenario occurs, immediate investigation is warranted since more renal parenchyma is likely to be preserved the earlier appropriate treatment is begun. The progression of the renal disease can be dramatic, leading in some cases to end-stage renal disease in a matter of days (e.g., anti-GBM disease). The classic histological correlation is the presence of crescents on renal pathology. Crescentic glomerulonephritis can be divided into four variants according to the immunofluorescence (IF) findings:

- Type I: Anti-GBM disease, characterized on IF by linear deposits of IgG along the glomerular basement membrane.
- Type II: A heterogeneous group of diseases characterized by prominent granular deposits usually along the capillary loops but occasionally confined to the mesangium associated most commonly with lupus nephritis, cryoglobulinemia or an underlying primary glomerulonephritis such as IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, or post-infectious proliferative glomerulonephritis.
- Type III: Pauci-immune glomerulonephritis, a condition where the glomerular deposits by immunofluorescence are rare or absent. The ANCA-associated variants are found within this class.
- Type IV: They have features of both types 1 and 3, being double-antibody diseases.

Today the ANCA-associated glomerular diseases dominate the clinical scenario of RPGN. They are responsible for more than 80 % of the cases in patients that present over the age of 60. Systemic signs and symptoms are often associated with these diseases and should be diligently sought since these can be the important clues to this underlying condition.

When a patient presents with a clinical picture compatible with RPGN, determining the specific renal pathology should be considered an emergency. In addition to a renal biopsy, serologic testing, including anti-GBM, ANCA, and ANA (and anti-dsDNA), complement, and cryoglobulins should be assessed on presentation to help in determining the most likely cause of the scenario. Treatment is often started on clinical suspicion of the diagnosis (see individual chapters for treatment of particular diseases), often before the histology or serologic screening test results are available, because with active crescent formation, irreversible kidney tissue damage can occur within days.

Some patients with a known glomerular disease, such as diffuse proliferative lupus nephritis, IgA nephropathy, or Henoch-Schönlein purpura, can develop crescents at any time in the course of their disease and present with an acute deterioration in their previously stable chronic renal disease. It is important to establish the correct cause of this deterioration since it will often alter management. For instance, an episode of acute kidney injury in a patient with IgA nephropathy may be associated with an intercurrent illness and only findings of acute tubular necrosis on biopsy or, at the other extreme, the development of crescentic glomerulonephritis.

There can be a clinical scenario of RPGN secondary to diffuse proliferative glomerulonephritis. They can present clinically as an acute nephritic syndrome (acute renal failure, elevated blood pressure, glomerular hematuria) but with pathology showing only a pattern of endocapillary proliferation and no crescent formation [21]. This variant of RPGN illustrates another reason for rapid histological diagnosis, since recovery with only symptomatic management is a common outcome with this histology (e.g., complete recovery following a streptococcal-related glomerulonephritis).

The definition of rapidly progressive glomerulonephritis implies that a rapid deterioration in renal function has been documented. In clinical practice, patients will not always have previous creatinine measurement to compare with their presenting value. If a clinical setting is compatible with RPGN, i.e., if there is no other obvious cause of renal failure (e.g., prerenal, obstruction, infection, etc.), a renal biopsy should not be delayed but should be done in concert with seeking this other information.

Factors That Bear on Progression of Glomerular Diseases

Progression of both diabetic and nondiabetic glomerular disease is influenced by both comorbid conditions and factors directly related to the disease process. A full discussion

on cardiovascular management of the patient with chronic kidney disease is beyond the scope of this chapter. Instead, we will review the specific impact of proteinuria, arterial hypertension, and hyperlipidemia, which are factors considered to influence the rate of kidney disease progression.

Proteinuria

Proteinuria is one of the cardinal manifestations of glomerular injury. In many of the glomerular diseases, its severity is closely linked to prognosis. It has been used as a surrogate endpoint of renal survival in many studies because of this relationship. Moreover, in recent years, studies have suggested that proteinuria not only reflects the degree of glomerular damage but also may have a direct nephrotoxic effect at the post-glomerular level [22, 23]. There is strong experimental data that indicates proteinuria per se can cause tubular epithelial cell dysfunction and interstitial inflammation and fibrosis. Many mechanisms have been implicated in this process including upregulation of the transcription factors that are felt to mediate inflammatory, vasoactive, and fibrogenic genes, as well as those that are involved in activation of the complement cascade. In addition, studies have indicated that tubular cell activation by protein-bound circulating molecules can result in an apoptotic response to the presence of protein in the tubule. The net effect is tubular and interstitial toxicity. The extent of the toxicity is probably dependent on both the duration of exposure and the specific composition of the proteinuria: albumin, for example, is likely to be less toxic than oxidized lipoproteins. These activation pathways have largely been derived from in vitro experimental models, but many clinical studies have indicated a close association between the quantity of proteinuria and progression of the underlying renal disease. In the REIN study, which included a variety of renal diseases (but excluded diabetics), the reduction in proteinuria was inversely correlated with the rate of decrease in GFR. This correlation was seen despite almost identical BP control [24]. Similar findings have been found in diabetic nephropathy. In the RENAAL study [25, 26], for example, the severity of albuminuria was almost linearly related to renal outcome. Formal proof of causation between proteinuria and clinical progression has not been established, but these studies and others strongly support the experimental evidence of the direct nephrotoxicity of proteinuria.

It is clear, however, that all proteinuria is not the same. Its nephrotoxic potential should be considered both in terms of quantity and quality. Small increases in proteinuria even in the sub-nephrotic range in patients with diabetes mellitus or IgA nephropathy [27] are associated with a worse renal survival. However, this is not true in every glomerular disease; for instance, in membranous nephropathy, the long-term outcome of proteinuria in the 1–2 g/day range remains excellent. The nature of the proteinuria currently evaluated by a variety of techniques including immunoelectrophoresis and, in the future, by more sophisticated analyses of the urinary proteome is likely to provide us with much more detail about the variations in tubular/interstitial damage caused by individual protein moieties. We are already aware of other significant variations in the quality of the proteinuria. One example is in myeloma nephropathy, where there are clear differences in renal damage observed when lambda versus kappa light chains are produced. We also know that little tubular interstitial damage occurs in minimal change disease despite heavy proteinuria. It is likely that in part this is related to the composition (quality) of the proteinuria, i.e., almost entirely albumin, and also to the limited duration of exposure of the tubules to protein, given the usual rapid reversal of this condition with treatment.

Hypertension

Arterial hypertension also directly damages the kidney. It is a strong independent risk factor for end-stage renal disease, even without underlying glomerular disease [28]. The presence of hypertension, however, in association with glomerular disease remains an important and independent risk factor for progression. This was recently confirmed in a study of 298 patients with IgA nephropathy [29]. The authors found that the level of blood pressure and proteinuria over time (but not at presentation) were the only independent factors related to progression. Certainly, it has been demonstrated repeatedly that controlling the blood pressure in patients with diabetic nephropathy, predominantly a glomerular process, significantly slows progression rate [30]. Similar results have also been found in studies of patients with nondiabetic nephropathy, such as the MDRD trial, where BP reduction was associated with both a decrease in proteinuria and disease progression rate [31, 32].

Renin-Angiotensin System Inhibition

Renin-angiotensin system (RAS) inhibition is now a central part of the treatment of both diabetic nephropathy and nondiabetic proteinuric nephropathy. Both angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) protect the kidney by their antihypertensive effect and by inducing efferent arteriole dilation, which in turn leads to a fall in intraglomerular pressure and a reduction of proteinuria. These agents are well known to decrease proteinuria and slow progression to end-stage renal disease (ESRD) in diabetic nephropathy [26, 33, 34]. A benefit of RAS inhibition also seems present in nondiabetic proteinuric disease and has been mostly studied with ACE

inhibitors, where various meta-analyses have suggested a reduction in the rate of progression to ESRD and doubling of serum creatinine [35, 36], although it is not clear if this effect is independent of blood pressure control. Patients without significant proteinuria (<500 mg/day) do not seem to benefit from the same protection, although duration of the follow-up may be the limiting factor in these studies [36]. ARB may well have a similar effect, but the data are more limited [37]. Despite suggestion that patients with early (stage 1–3) chronic kidney disease may not benefit as much from RAS blockade [38], ACEI and ARB remain effective and well-tolerated antihypertensive agents, hence their widespread use in clinical practice. However, combination therapy with agents must be done with great care and is not generally recommended, even though it may lead to greater proteinuria reduction. This is based on the large ONTARGET trial that showed a worsening of renal endpoints with a combination of ramipril and telmisartan compared to single-agent therapy [39].

Lipids

In many animal models of renal damage, hyperlipidemia has been shown to accelerate renal dysfunction [40, 41]. It has also been associated with accelerated progression of kidney disease in some studies in humans [42]. However, the beneficial effect of statins to directly slow progression of glomerular-based kidney disease has not been proven in humans. Although many studies and meta-analyses [43] support this contention, this effect is not consistently observed. More recently, the SHARP trial [44] showed no significant difference in the progression to end-stage renal disease in a population of CKD patients, although many in the cohort did not suffer specifically from a glomerular disease and were already at an advanced stage of renal failure prior to study entry. Despite this, in the broader context of cardiovascular disease prevention, the efficacy of statins has been well established, and since many patients with glomerular disease have both hyperlipidemia and accelerated vascular disease, the use of such agents is now a critically important element in their management.

Interpretation of Studies in Glomerular Diseases

Evidence-based medicine is a well-established paradigm in clinical medicine, but it has limitations. When dealing with diseases with a low incidence and often-slow progression rate over many years, it is difficult and expensive to carry out the appropriate randomized controlled trials that would provide grade A evidence for different treatment modalities. On review of the current literature, the lack of such trials is evident. Currently, much of the evidence on which we rely for support of our treatment comes from less high-quality trials and retrospective or observational studies.

Many other issues are relevant to the interpretation of studies in glomerular diseases. Studies based on renal pathology illustrate one particular type of limitation. A kidney biopsy, by definition, is a cross-sectional assessment, and although usually sufficient to make a diagnosis, a clear estimate of the prognosis, especially in the setting of a slowly progressive glomerular disease, is unlikely. Pathology does allow us to establish the amount of damage that has occurred as reflected by the severity of tubular and interstitial injury, but the rate of disease progression and the determination of the acuity of ongoing injury are often difficult to quantitate using our current techniques.

Another confounding issue in the interpretation of evidence relates to the temporal sequence in the development of therapeutic strategies. A classic example is the use of corticosteroids in IgA nephropathy. In the best RCT studying this approach [45], a 6-month course of steroids was shown to reduce proteinuria and to protect against subsequent deterioration in renal function. However, only a fraction of the patients received angiotensin-converting enzyme inhibition, whose efficacy was being tested in IgA nephropathy during the same time frame of the corticosteroid study. The use of agents to blockade the renin-angiotensin system is now considered first-line treatment and is currently recommended to be given prior to the introduction of immunosuppressive agents. This makes the assessment of the additive value of corticosteroid treatment in IgA nephropathy more problematic, given that trial did not have a uniform baseline renin-angiotensin system blockade in place.

In addition, many factors previously unknown or unrecognized that impact on the prognosis of the disease complicate the interpretation of earlier studies. Part of this problem is because although the histological label of the disorder has remained unchanged, the number of causative agents that will produce the identical lesions has grown dramatically. In recent years, for instance, the discovery of genetic mutations in some of these glomerular diseases (such as IgAN and FSGS) has confirmed new factors that impact on both susceptibility and progression rates of these classical patterns of injury. Additionally, new external factors have been identified as causative agents through the development of new technology. This has allowed us to recognize, for instance, a new virus designated hepatitis C, which was subsequently found responsible for many of the previously designated idiopathic cases of membranoproliferative glomerulonephritis. This finding has cast considerable doubt on previous therapeutic studies in this disease completed prior to this association being recognized. Other examples include the recent discovery of antibodies directed against phospholipase

A2 receptor as the main culprit in the so-called primary (idiopathic) membranous nephropathy [46]. Another development has been the changing incidence and age at presentation of many of the major progressive GN variants. The prevalence of membranoproliferative glomerulonephritis, for instance, has steadily decreased over the past 20 years in the developed world [47], whereas the frequency of FSGS on biopsy has tripled over the same time frame.

The use of surrogate endpoints in the study of most glomerular diseases is almost unavoidable, given the most commonly observed temporal pattern is slow progression over years. The most important criterion for the validity of a surrogate endpoint is its ability to predict the effect of an intervention on the most definitive endpoint, renal survival [48]. The most frequently used surrogate endpoints in nephrology are changes in GFR, serum creatinine, or proteinuria. Although the majority of nephrologists believe these surrogate markers meet this fundamental criterion, a number of challenges persist in regard to their assessment. The measurement of GFR, often considered as the best surrogate endpoint, is most useful in studying patients who have a rapid rate of deterioration in renal function. This is because early in the course of most renal disease, functional changes compensate for organic damage and true estimate of change in GFR may only be seen after this compensation is exhausted. In addition, GFR is influenced by acute hemodynamic changes, such as volume contraction that can be induced by diuretic therapy, high-grade proteinuria especially when associated with lowered oncotic pressure, or with certain drug treatments such as the calcineurin inhibitors. In some studies, GFR is estimated by measurement of creatinine clearance. In these cases, the assumption is that creatinine generation and nonrenal excretion remain constant throughout the study. This is not always the case. Protein restriction, for example, can have an impact on creatinine generation and secretion, as illustrated in the MDRD study [49]. An alternate approach often used in studies consists of comparing slopes of GFR decline between groups. This approach is complicated by the imprecision in slopes associated with patients with shorter follow-up. Although this can be partially accounted for by giving more weight to patients with longer follow-up, this could introduce a different bias since subjects with shorter follow-up may have the most clinically significant endpoints like death or end-stage kidney failure.

Another common approach uses the "time-to-event" endpoints, such as time to doubling of serum creatinine. In comparison with slope-based analysis, time to event is more sensitive for fast progressors and, because by definition it requires a large change in GFR, is a closer approximation of the definitive endpoint of ESRD. However, in patients with early stage CKD or with slow progression, the low event rate makes time-to-event endpoint analysis almost unachievable or requires a very large sample size. Moreover, the possibility of competing events, such as cardiovascular disease, may lead to informative censoring. Including death as part of the composite can account for this problem, but then it must be recognized that the data may actually be confounded since all causes of death are not necessarily related to renal disease progression.

Changes in proteinuria have both biological plausibility and a strong correlation with end-stage renal disease in most glomerular disease. This has led to its use as a surrogate endpoint, although it is not per se a required element in the deterioration of renal function. Its utilization as a surrogate endpoint therefore requires rigorous analysis. The well-recognized relation between proteinuria, as both an effect and cause of progression, does not necessarily mean that a treatment that decreases proteinuria will slow progression, since the treatment may affect progression through an entirely independent pathway. In some diseases like diabetes and IgA nephropathy, we have sufficient data to confirm that reduction in proteinuria is associated with reduction in ESRD, whereas this is not the case in all glomerular diseases. Proteinuria may impact on renal parenchymal tissue damage by both its quantity and quality differently, and therefore, its reduction does not necessarily translate into similar benefit (see section "Proteinuria" above). Reducing proteinuria from 3 g/day to <1 g/day, for example, does not have the same prognostic significance in membranous nephropathy that it does in IgA nephropathy.

Principles of Immunotherapy

Specific treatment protocols of immunosuppression in the different histological variants of glomerular disease will be reviewed in the following chapters. We will discuss immunosuppression only from the perspective of assessing risk of such therapy in a patient with progressive glomerular disease. Risk is particularly difficult to assess when the adverse effects of therapy have a different timeline than the benefit, appearing either early in treatment or long after therapy has been discontinued. Benefit of treatment, on the other hand, at least its definitive effect on slowing or preventing ESRD, often falls between these two extremes of time. This difficulty in including the risk of treatment also applies to most predictive algorithms of progression that have been developed. They rarely, if ever, include patient morbidity issues related to treatment. Part of the difficulty in adding this element is the inability to generalize or semi-quantitate the potential adverse effects since they often are very dependent on the specific characteristics of the sample population. The patient's chronologic age, for instance, is easy to determine, but adding risks for any and all comorbid conditions is virtually impossible. Therefore, although all decision about treatment should be based on best available evidence, there must be clinical judgment brought to bear in every case.

There are generic ways of reducing the likelihood of morbidity: specifically lower doses of the treatment, shorter duration of therapy, alternative administration route, or the choice of other agents. In addition, there are specific preventive strategies that can be used to combat potential adverse events that impact on morbidity. Many of these approaches have been applied in glomerular diseases and will be discussed in subsequent chapters. We will only review the fundamental principles about the commonly used immunosuppressive agents in glomerular disease, their risks, and management strategies to minimize these effects.

Glucocorticoids

Corticosteroids, probably the best known and certainly one of the oldest immunosuppressive agents, have been used for many years in the treatment of glomerular diseases. Their biological effects are broad [50], but in large part they act by binding to specific intracellular receptors, leading to conformational change in DNA, and subsequent modulation of gene transcription. This results in the production of anti-inflammatory products and, through inhibition of nuclear factor kappa B (NF-κB), to the inhibition of synthesis of many inflammatory cytokines. The end result is a broad effect not only on immune function of B and T lymphocytes but on functional elements of circulating neutrophils and monocytes.

Multiple studies have confirmed the clinical efficacy of steroids in the glomerular diseases, e.g., minimal change disease. Steroids are also commonly used in conjunction with other immunosuppressive agents in other glomerular diseases such as lupus nephritis and membranous nephropathy.

The side effects of steroids are well known. They are related to both the total dose and the duration of use, but even doses as low as 5 mg/day are thought to carry increased risk of adverse effects [51]. The most important ones include accelerated atherosclerosis, alterations of glucose metabolism, psychiatric issues including psychosis, increased susceptibility to infection, development of cushingoid features, and musculoskeletal complications such as osteoporosis, myopathy, and avascular necrosis. Steroids have one distinct positive feature compared to all other immunosuppressive agents in that they do not increase the risk of cancer. This is a substantial advantage in the glomerular disorders that evolve over years and that often require more than one course of treatment.

There are strategies for minimizing adverse events. These include prophylaxis for osteoporosis and advising physical exercise for prevention of myopathy. In addition, alternate day administration can be used. It is always important that the duration of treatment should be kept to a minimum. Another approach consists of alternating this therapy with another agent such as in membranous nephropathy [52, 53], where the routine is a 6-month course of treatment that consists of corticosteroids alternating monthly with a cytotoxic agent.

Pulse treatment with methylprednisolone is another strategy. Bolus steroids are felt to have a more rapid onset of action, a longer effect, and higher bioavailability than oral corticosteroids [54]. This approach has been used in the treatment of rapidly progressive glomerulonephritis and in the treatment of vasculitis.

Special attention should be paid to bone-sparing strategies. It is now recognized that most of the corticosteroid damage to bones occurs in the first few weeks of utilization [55], and hence prophylaxis with calcium supplements, vitamin D, and bisphosphonates is advised [56] when therapy beyond weeks is considered. Bisphosphonates are quite safe even in the mild to moderate renal failure category that commonly accompanies the glomerular diseases [57, 58]. When GFR is lower than 30 mL/min, they should be used with caution [59] because of the concern that other nonresponsive bone disorders, such as adynamic bone disease, may be present at that level of renal function.

Cyclophosphamide

Cyclophosphamide is an alkylating agent thought to act largely through the alkylation of purine bases producing its cytotoxicity effect. Induction of DNA damage leads to cell death or altered cell function [60]. Both T- and B-cells are affected, making cyclophosphamide a potent immunosuppressive agent commonly used in a variety of the progressive glomerular diseases including crescentic glomerulonephritis, vasculitis, and lupus nephritis.

Cyclophosphamide is toxic. It increases the long-term risk of leukemia, skin and bladder cancers, as well as other malignancies. In a retrospective study of its use over 20 years in a cohort of rheumatoid arthritis patients, relative risk for malignancies was 1.5 [61]. Hematological long-term toxicity includes an increased risk of the development of myelodysplastic syndrome [62]. In a review of 293 patients with Wegener's granulomatosis [63], a cumulative dose of more than 36 g was associated with a significantly higher risk of malignancies, especially acute myeloid leukemia, bladder cancer, and nonmelanoma skin cancer (standardized incidence ratio of 59, 9.5, and 4.7). Many of these malignancies occurred years after initiation of therapy (between 6.9 and 18.5 years for leukemia and bladder), thus emphasizing the importance of long-term follow-up.

Gonadal toxicity and infertility constitute the second most concerning adverse effect of this class of agents. In females,

risk factors are mainly the total cumulative dose, irrespective of the route of administration [64], and the age at which therapy is initiated. Women whose therapy was given before the age of 25 are at lower risk of this complication than those started after the age of 30 [65]. In men, long-term gonadal toxicity can occur at a cumulative dose as low as 100 mg/kg [66].

Bone marrow depression is common with this agent and is manifested most commonly by leucopenia. White blood cell count must be monitored frequently, and intravenous doses should be adjusted to target absolute neutrophil count above 1,500 per μL. For patients on oral cyclophosphamide, drug should be stopped if total white cell count falls below 4,000 per μL; medication can be restarted at 75 % of previous dose once total white cell count increases to >5,000 per μL. Increased susceptibility to infections also occurs and is a worrisome consequence of treatment. Prophylaxis against Pneumocystis pneumonia with an agent such as trimethoprim-sulfamethoxazole is recommended. Infections can evolve rapidly and can be fatal in the immunocompromised host, and cyclophosphamide therapy should be discontinued if significant infection develops.

Other effects although less serious to life but important to the patient include alopecia which usually recovers once the medication is stopped, gastrointestinal intolerance limited to the duration of treatment, and hemorrhagic cystitis especially when bolus IV therapy is used. To lower this, mesna (which binds to acrolein, a toxic metabolic of cyclophosphamide) may be prescribed [67]. A suggested protocol is 300 mg/m^2 at the beginning of infusion and then 150 mg/m^2 4 h later.

Total cumulative dose plays a major role in long-term toxicity of cyclophosphamide, and therefore, reduction in total drug exposure is a major prevention strategy. The CYCAZAREM trial [68] determined that it was both safe and effective to substitute azathioprine for cyclophosphamide as maintenance therapy in patients with ANCA-associated vasculitis. This substantially reduced the total exposure to cyclophosphamide and subsequent adverse events. A similar strategy in lupus nephritis of substituting mycophenolate mofetil or azathioprine was associated with lower rates of infection and less amenorrhea compared to ongoing cyclophosphamide therapy [69]. An alternate and equally effective strategy has been the substitution of intravenous bolus treatment for oral cyclophosphamide in the treatment of lupus nephritis and ANCA vasculitis [70, 71].

In summary, cyclophosphamide is a potent immunosuppressive medication that has proven efficacy in a variety of glomerular diseases. Its high toxicity, however, has limited its use, and the physician should carefully consider the alternatives and balance its benefits versus risks whenever it is being considered as a treatment option.

Mycophenolate Mofetil

A more recently developed antiproliferative agent is mycophenolate mofetil (MMF). The drug acts through the inhibition of inosine monophosphate dehydrogenase, an enzyme implicated in the de novo synthesis of purine bases. This leads to both a decrease in T- and B-cell proliferation and a decrease in antibody formation.

There have been a number of clinical treatment studies published since its introduction. The highest-quality glomerular-based disease studies have been in lupus nephritis where it has proven to have equivalent efficacy but less toxicity than cyclophosphamide as both induction and maintenance therapy [72, 73].

Gastrointestinal intolerance, including nausea, diarrhea, and abdominal pain, is very common with this agent, but its frequency and severity are reduced with time [74]. Dose reduction or splitting the daily dose into smaller but more frequent ones can help manage these side effects. Anemia or leucopenia is seen in 10–20 % of patients secondary to bone marrow suppression. Regular assessment of the complete blood count with MMF dose adjusted if necessary is mandatory. Other adverse effects, in common to all immunosuppressive agents, include increased susceptibility to infection and increased risk of malignancy. Most of the latter data comes from transplant studies, where MMF has been used in combination with other potent immunosuppressive drugs and information regarding risk as monotherapy is scarce.

In summary, MMF is less cytotoxic than cyclophosphamide, and in addition, it has many advantages over the other common class of immunosuppressive agents, the calcineurin inhibitors (CNI). This class of agent has, for instance, no effect on blood pressure or renal function and no alteration in the lipid profiles or on glucose metabolism, common side effects with CNI's treatment.

Azathioprine

This drug, one of the oldest immunosuppressive agents, is a purine analogue that has an antiproliferative effect. Although it has been largely replaced by MMF in transplant patients, it is still used in glomerular diseases, most commonly as maintenance therapy replacing cyclophosphamide after induction [68]. Azathioprine is usually well tolerated and has a lower teratogenicity potential than cyclophosphamide in pregnancy. Bone marrow toxicity occurs and is most commonly limited to the leukocyte lineage. It is also significantly less expensive than MMF and showed similar tolerability to this agent and possibly even better efficacy in ANCA vasculitis maintenance therapy [75]. However, in lupus, MMF has recently demonstrated significantly better efficacy than azathioprine for maintenance therapy [76].

Calcineurin Inhibitors

Cyclosporine

Cyclosporine is a potent immunosuppressive drug first used in the field of solid organ transplantation. Upon entry into the cell, it binds to the immunophilins, and this complex inhibits calcineurin. Calcineurin is normally involved in dephosphorylation of nuclear factor of activated T-cells (NFAT). Following the dephosphorylation, it normally enters the nucleus and activates the transcription of various cytokines, including interleukin-2. Inhibition of calcineurin blocks this process, thus inhibiting T-cell activation.

Cyclosporine has proven to be effective, either alone or in combination with steroids, in the treatment of minimal change disease, FSGS, and membranous nephropathy.

Cyclosporine has many adverse effects. The most worrisome and feared side effect is nephrotoxicity that can be severe and has been documented to progress to renal failure when prolonged high doses of the drug have been given. There appear to be two separate mechanisms involved: an acute renal hemodynamic effect that can be managed by decreasing the dose and a second more worrisome one associated with chronic tubulointerstitial nephrotoxicity that may progress without a matching decline in GFR until late in the process. This seems linked to both dose and duration of treatment and is aggravated by the narrow therapeutic window between efficacy and toxicity of this agent. Most feel cyclosporine is safe [77] even long term, provided the daily dose is kept under 3–4 mg/kg with 12-h trough level maintained <150 ng/mL. It has been this concern about nephrotoxicity that has limited the use of cyclosporine to refractory cases or to situation where alternatives are not available or have been less effective. Cyclosporine, as with all immunosuppressive agent, is associated with an increased risk of cancer and infection. Most of the toxicity data we have come from transplant studies where it is most commonly used in combination with other immunosuppressive agents. Toxicity of cyclosporine in patients with glomerular disease, when used as a single agent and in the low-dose regimen outlined above, has substantially less toxicity, although this risk should be constantly monitored. Some additional effects are more cosmetic in nature, like hypertrichosis and gum hypertrophy. However, both can be severe and may lead to nonadherence or the need for alternate treatments. Other side effects include arterial hypertension, induction of hyperkalemia, and hypomagnesemia. These can be managed medically.

Tacrolimus

Tacrolimus is a newer calcineurin inhibitor that has a similar biological effect as cyclosporine. Its use has been largely limited to the field of transplantation, although data on its use in glomerular disease is increasing, notably in membranous nephropathy [78]. Its adverse effect profile is similar to cyclosporine, with the exception that it has less hypertrichosis and does not have the potent "skunky" smell associated with the former. On the other hand, it does appear to have a greater effect on glucose metabolism, and new onset diabetes is higher with its use.

mTOR Inhibitors

This class includes sirolimus and a similar agent, everolimus. mTOR inhibitors are relatively new agents currently restricted to the solid organ transplantation field. They are known to have both an immunosuppressive and antiproliferative effect. They act by inhibition of the mammalian target of rapamycin (mTOR) protein, which is involved in cell-cycle regulation via the signal transmission of cytokines such as IL-2. The clinical studies of these drugs in glomerular disease are very limited. In rats with Adriamycin nephropathy, some data suggest a reduction in renal scarring [79]. An open-label trial of patients with steroid-resistant FSGS has shown a substantial benefit in terms of reducing proteinuria with supporting concurrent physiological studies that indicated it reduced glomerular pore size and improved the ultrafiltration coefficient [80]. In contrast, a safety study of sirolimus in FSGS [81] was prematurely stopped because of serious adverse events in five out of six patients including acute renal failure, increasing proteinuria, and dramatic elevation in triglyceride values. Presently, it is not recommended in the treatment of glomerular diseases.

Rituximab

Rituximab is a chimeric monoclonal antibody directed against the CD20 molecule found on pre-B-cells and mature B-cells. It prevents proliferation of B-cells, which then undergo apoptosis. It was originally designed for the treatment of non-Hodgkin's lymphoma, but because many autoimmune diseases, including some types of glomerulonephritis, have an important humoral component, interest has been high in studying the drug's effects in these conditions. In ANCA vasculitis, two randomized trials have shown it was as effective as cyclophosphamide for the induction phase of treatment [82, 83]. Adverse event rates were similar. In membranous nephropathy, pilot studies have suggested rituximab reduces proteinuria and can induce remission even in patients who have failed alternate immunosuppressive regimens [84, 85]. Other potential uses include refractory lupus nephritis, where the data is more limited, and hepatitis C-related mixed cryoglobulinemia, where studies have suggested it could increase the rate of remission [86, 87]. Main

adverse effects of rituximab are usually mild and related to infusion reactions such as fever and chills. More serious adverse effects have been described but, in general, are more commonly seen in the original indication for the agent, i.e., non-Hodgkin's lymphoma, and are related to the tumor burden rather than to the drug itself.

Plasma Exchange

Plasma exchange has been used in various types of autoimmune diseases for more than 30 years. It has proven efficacy in antiglomerular basement membrane disease [88]. The results in the ANCA-associated vasculitis trial in patients with poor renal function (serum creatinine >500 μ[mu]mol/L), the MEPEX trial [89], suggested that the addition of plasma exchange to standard therapy increased both the percent of patients and the speed of renal recovery compared to IV methylprednisolone. Other suggested indications have included thrombotic microangiopathy and lupus erythematosus [90]. In lupus erythematosus, it may be used in certain patients with life-threatening or therapy-resistant manifestations, but the evidence base is weak, and its major advantage seems to be its safety. Although generally felt to be a benign therapy (but expensive), adverse events are not negligible, and a recent report from the World Apheresis Registry indicated such effects in 11 % of 388 procedures; many of them were related to citrate anticoagulation. No deaths were reported [91]. A specific chapter is devoted in this textbook to the use of plasma exchange in patients with kidney diseases.

Intravenous Immunoglobulins

Initially introduced in the 1950s as replacement therapy for patients with congenital antibody deficiencies, intravenous immunoglobulins (IVIG) are now used in a wide range of immunological/autoimmune conditions. Their mechanism of action, although incompletely understood, seems to depend largely on antigen binding and modification of effector functions [92], including the modulation of T- and B-cell activation. They may control the disease process without inducing severe immunosuppression in contrast to cytotoxic agents [93]. Pilot studies in both lupus nephritis and ANCA-associated glomerulonephritis have been done, but these studies are small and the benefits hard to assess [94, 95]. Its appeal is its safety profile. Adverse effects, although common, are usually mild. Nephrotoxicity is a potential complication affecting up to 6.7 % of patients in one series [96], and this adverse effect may not always be reversible.

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Minimal Change Disease in Adults

2

Jonathan Hogan and Jai Radhakrishnan

Introduction

Minimal change disease (MCD) is defined when nephrotic syndrome occurs without any glomerular lesions on light microscopy (or only minimal mesangial prominence), negative staining on immunofluorescence microscopy (or low-level staining for C3 and IgM), and foot process effacement but no electron dense deposits on electron microscopy (Fig. 2.1) [1].

Most children with the nephrotic syndrome are not biopsied; instead, they are typically treated empirically with steroids. However, most adult patients with the nephrotic syndrome are biopsied. Hence this chapter will deal with biopsy-proven, adult-onset MCD.

Pathophysiology

The pathophysiology of minimal change disease is not well understood. The animal model which most closely resembles MCD is puromycin aminonucleoside nephrosis (PAN) in rats. Administration of puromycin aminonucleoside to rats causes the production of reactive oxygen species which leads to direct DNA damage. This alters the podocyte actin cytoskeleton, resulting in foot process effacement, detachment from the glomerular basement membrane, and proteinuria. This effect is dose-dependent, and the podocyte changes and proteinuria spontaneously reverse if doses are limited [2].

Regulatory T-Cell Dysfunction

Shalhoub was the first to propose that "lipoid nephrosis is produced by a systemic abnormality of T-cell function resulting in the secretion of a circulating chemical mediator toxic to an immunologically innocent glomerular basement membrane." This theory was based on several observations: lack of a humoral antibody response, remission induced by measles and steroids/cyclophosphamide (which modify cell-mediated immunity), and the occurrence in Hodgkin's lymphoma [3].

Many cases of idiopathic nephrotic syndrome remit spontaneously, and significant transient albuminuria may occur during viral and febrile illnesses. This implies that there is different or additional pathogenesis of persistent, non-remitting, and relapsing nephrotic syndrome and MCD. Recent research has focused on the role of regulatory T-cell (Treg) dysfunction in MCD.

Garin et al. [4] examined urine soluble CTLA-4 levels in patients with MCD in relapse and remission, other glomerular disease, and control subjects. CTLA-4 is a protein secreted by Treg cells which binds to CD80 and therefore blocks the costimulatory activation of T cells. Although there was not a significant difference in urine sCTLA-4 levels between these groups, there was a significant decrease in the urinary ratio of sCD80/sCTLA-4 in patients with MCD in remission, pointing to a role of Treg dysfunction and relative CTLA-4 deficiency in suppression the continued activation of CD80 in MCD.

Araya et al. studied T cells in a small group of patients with MCD in relapse, MCD in remission, control patients, and MPGN [5]. They found that Treg suppression of T-effector cells was decreased in MCD patients in relapse versus MCD patients in remission and control patients. This was the first direct evidence of impaired Treg function in MCD. More recently, investigators have reported that nuclear factor-related kappa B, which is involved in chromatin remodeling, is upregulated in CD4+ T cells and B cells in relapsing MCD, suggesting that alterations in transcription factors of immunity may also play an important role [6].

LeBerre et al. used Buffalo/Mna rats, a model for idiopathic nephrotic syndrome with histological focal segmental

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