

# Chapter 2: General principles in the management of glomerular disease

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There are a number of general principles in the management of glomerular injury which apply to most or all of the histologic variants of GN covered by this guideline. In this chapter, we discuss these general principles to minimize repetition in the guideline. Where there are specific applications or exceptions to these general statements, an expansion and rationale for these variations and/or recommendations are made in each chapter.

## **Kidney Biopsy**

Kidney biopsy is mandatory for diagnosis. It defines the morphologic patterns of GN that will be reviewed in this guideline. The single exception to this rule is SSNS in children. This entity has an operational clinical definition that is sufficiently robust to direct initial treatment, with the kidney biopsy reserved for identifying pathology only when the clinical response is atypical.

**Adequacy of kidney biopsy.** There are two components in terms of assessing adequacy of the tissue sample. The first relates to the size of biopsy necessary to diagnose or exclude a specific histopathologic pattern with a reasonable level of confidence, and the second concerns the amount of tissue needed for an adequate assessment of the amount of acute or chronic damage present.

In some cases a diagnosis may be possible from examination of a single glomerulus (e.g., membranous nephropathy), but generally a substantially larger specimen is required to ensure that the material reviewed by the nephropathologist adequately represents the glomerular, tubular, interstitial, and vascular compartments of the kidney. In addition, sufficient tissue is needed to perform not only an examination by light microscopy, but also immunohistochemical staining to detect immune reactants (including immunoglobulins and complement components), and electron microscopy to define precisely the location, extent and, potentially, the specific characteristics of the immune deposits. We recognize that electron microscopy is not routinely available in many parts of the world, but the additional information defined by this technique may modify and even change the histologic diagnosis, and may influence therapeutic decisions; hence, it is recommended whenever possible.

In some diseases, for example FSGS and necrotizing glomerulonephritis associated with antineutrophil cytoplasmic antibodies (ANCA), lesions are only seen in some segments of some glomeruli. In these cases, it is important

that the biopsy is examined by light microscopy at several levels if lesions are not to be missed. If a lesion that affects only 5% of glomeruli is to be detected or excluded with 95% confidence, then over 20 glomeruli are needed in the biopsy.<sup>1</sup> Although many biopsies will have fewer glomeruli, it is important to realize that this limits diagnostic accuracy, especially when the diagnostic lesions are focal and/or segmental.

An important component of kidney biopsy examination is the assessment of “activity”, that is lesions which are acute and potentially responsive to specific therapy, and “chronicity”, where they are not reversible or treatable. As glomeruli become scarred there is consequent atrophy of the rest of the nephron with interstitial fibrosis, and it is usually the case in GN that the degree of chronic irreversible damage is most easily assessed from the amount of tubular atrophy. The accuracy of this assessment is increased with larger biopsies. The assessment of chronic damage from the biopsy must always be interpreted together with the clinical data to avoid misinterpretation if the biopsy is taken from a focal cortical scar. The amount of information that can be derived from kidney pathology varies substantially in the different GN types; when of particular relevance, this is addressed specifically within the appropriate chapters.

**Repeat kidney biopsy.** Repeat kidney biopsy during therapy or following a relapse may be informative. There is no systematic evidence to support recommendations for when or how often a repeat biopsy is necessary, but given the invasive nature of the procedure and the low but unavoidable risks involved, it should be used sparingly. In general, a decision about the value of a repeat biopsy should be driven by whether a change in therapy is being considered. More specifically, a repeat biopsy should be considered:

- when an unexpected deterioration in kidney function occurs (not compatible with the natural history) that suggests there may be a change or addition to the primary diagnosis (e.g., crescentic GN developing in known membranous nephropathy or interstitial nephritis secondary to the drugs being used in the disease management);
- when changes in clinical or laboratory parameters suggest a change of injury pattern within the same diagnosis (e.g., conversion of membranous to diffuse proliferative LN);
- when the relative contributions to the clinical picture of disease activity and chronicity are unknown, creating therapeutic uncertainty in regards to intensifying, maintaining, or reducing therapy;

- to assist in defining a “point of no return” and to help define therapeutic futility (i.e., such extensive and irreversible kidney scarring that no response to available therapies can be expected).

### Assessment of Kidney Function

Key outcome measures for the management of GN include assessment of kidney function, particularly measurement of proteinuria and glomerular filtration rate (GFR).

**Proteinuria.** Whether urine albumin or urine protein excretion is the preferred measurement to assess glomerular injury continues to be debated. However, 24-hour protein excretion remains the reference (“gold standard”) method for quantification of proteinuria in patients with GN. It averages the variation of proteinuria due to the circadian rhythm, physical activity, and posture. Almost all of the published clinical trials used in the development of this guideline utilized 24-hour measurement of proteinuria to assess responses. Although this method is subject to error due to over- or under-collection, the simultaneous measurement of urine creatinine helps to standardize the collection in terms of completeness, thereby improving its reliability.

Protein-creatinine ratio (PCR) or albumin-creatinine ratio on a random (“spot”) urine sample, or a first morning urine sample, is a practical alternative to 24-hour urine collection.<sup>2</sup> It is increasingly used in clinical practice because the sample is easy to obtain, is not influenced by variation in water intake or by urinary flow rate. There may still be gender and racial variations that are not accounted for, given these factors may modify creatinine generation. There is a correlation between the protein-creatinine ratio in a random urine sample and 24-hour protein excretion. Although the reliability of PCR for the monitoring of proteinuria during treatment is still not proven, it has practical clinical utility, especially in children. In some recent studies, urine samples have been collected over a longer period (e.g., 4 hours) to address the limitations of “spot” urine samples that can be influenced by activity and circadian rhythm, but without the problems associated with a 24-hour urine collections.<sup>3</sup> The correlation of PCR with proteinuria from a 24-hour urine collection does improve steadily as the collection period is lengthened. However, there is currently insufficient evidence to preferentially recommend 24-hour, shorter-timed, or spot urine collections for proteinuria in the management of GN.

The conventional definition of nephrotic syndrome in the published literature is proteinuria  $>3.5$  g per 24 hours (in children,  $>40$  mg/m<sup>2</sup>/hr or PCR  $>2000$  mg/g [ $>200$  mg/mmol] or  $>300$  mg/dl or 3+ on urine dipstick) plus hypoalbuminemia and edema. Nephrotic-range proteinuria is nearly always arbitrarily defined as proteinuria  $>3.5$  g per 24 hours [uPCR  $>2000$  mg/g [ $>200$  mg/mmol] in children) in the absence of clinically overt nephrotic syndrome. Asymptomatic proteinuria, by definition without clinical symptoms, has variable levels of proteinuria in the range of 0.3–1.5 g per 24 hours (or equivalent). Treatment trials even

within the same pattern of GN have used a variety of entry criteria based on severity of proteinuria. This is only one of the issues that make direct comparison of trial outcomes difficult. Nevertheless, quantifying proteinuria (and perhaps even assessing its qualitative nature) is an important measure in the assessment of the patient with GN. This is relevant in almost all the primary and secondary glomerular diseases in this guideline. It is also important and necessary to define, within each of the specific GN types in the subsequent chapters, what levels and changes in proteinuria have been used to categorize both the risk of progression and the definition of response. These parameters are not uniform and vary widely across the spectrum of GN. There is insufficient evidence currently to recommend basing treatment decisions on more detailed qualitative analysis of proteinuria, such as measurement of fractional urinary excretion of immunoglobulin G (IgG),  $\beta$ -2 microglobulin, retinol-binding protein, or  $\alpha$ -1 macroglobulin.

**Estimation of GFR.** Most of the available evidence for treatment of GN has been based on estimations of excretory kidney function using serum creatinine (SCr) or creatinine clearance (CrCl) requiring a 24-hour urine collection. Very few studies have reported gold standard measurements of GFR using inulin or radioisotope clearance techniques. Other techniques used in past studies include adjustment of SCr for age, weight, and sex using the Cockcroft-Gault formula and reciprocal or log transformation of SCr. Serum cystatin C, as an alternative to SCr has not been validated in subjects with GN. All these methods have limitations, but are informative when sequential measurements are made in each subject.

Recently, estimation of GFR using the Modification of Diet in Renal Disease (MDRD) 4 variable equation has gained increasing acceptance, although it has not been validated specifically in those with GN. Another estimating equation, CKD Epi has recently been proposed, which may be more accurate than the MDRD equation, especially at values  $>60$  ml/min. Ethnicity may also influence estimated glomerular filtration rate (eGFR). There is no robust evidence to recommend the superiority of any of the available methods for estimating GFR in the management of GN. One particular limitation is that eGFR using creatinine-based formulas should be interpreted with caution in nephrotic syndrome, since tubular creatinine handling is altered in this condition. As a result, CrCl and eGFR may overestimate true GFR in nephrotic syndrome by 50% or more.<sup>4</sup> GFR estimations are also unreliable during episodes of acute kidney injury (AKI).

In children, there are alternative validated formulas for eGFR, notably the Schwartz formula.

### Outcome Measures

**Complete remission, ESRD, mortality.** A definitive assessment of the efficacy of a treatment for GN requires the demonstration that end-stage renal disease (ESRD) has been prevented, and mortality reduced. Very few studies in GN have been of sufficient duration or have analyzed sufficient

numbers of patients to accurately assess these outcomes. This is not surprising, given the slow natural history of many of the histologic variants of GN in this guideline. The other accepted outcome measure for many of these disorders is complete remission, assessed by the complete disappearance of abnormal proteinuria (<300 mg per 24 hours). However, most studies rely on other surrogates as predictors of clinical outcomes. These surrogate outcome measures include changes in proteinuria, e.g., partial remission of proteinuria, change in kidney function, “point of no return”, quality of life, and quality of health.

**Changes in proteinuria.** A quantitative change in proteinuria is presented in most studies. This is often categorized as complete remission, usually defined as proteinuria <0.3 g per 24 hours (uPCR <300 mg/g [ $<30$  mg/mmol]) or partial remission defined as proteinuria >0.3 but <3.5 g per 24 hours or a decrease in proteinuria by at least 50% from the initial value and <3.5 g per 24 hours. However, definitions vary and are not used consistently even within a specific GN pattern. The variations in these definitions will be discussed in each chapter.

**Changes in kidney function.** Changes in kidney function are usually measured by changes in SCr or CrCl. These need to be substantial to indicate true disease progression, e.g., doubling of SCr, or halving of CrCl or eGFR. This is because most patients with GN have gradual changes in function and there are many factors that may modify the SCr value besides progression of kidney disease. These factors include changes in intravascular volume, intercurrent illness, comorbid conditions, and many drugs. In addition, there are specific issues related to the SCr value independent of the disease, such as the method used for its measurement, changes in muscle mass, and alterations in urine flow and level of kidney function that both alter the tubular secretion of creatinine. In more recent studies, changes over time in eGFR have been reported. In the absence of ESRD as a defined adverse outcome, slope of CrCl or slope of eGFR may be an adequate and reliable marker of change in kidney function, provided that sufficient data at sequential time points are available, and that the slope is sufficiently linear.<sup>5</sup>

Changes in GFR are often described qualitatively as “deteriorating” or “rapidly deteriorating” kidney function. Although these terms have no precise definitions, they are in common usage especially in certain histologic categories such as vasculitis and lupus nephritis. These are descriptive terms, and the value of a particular therapy can be properly evaluated only when compared to another group with similar clinical and histologic characterizations and in the setting of a randomized controlled trial (RCT). Where available, these will be presented in each chapter.

**“Point of no return”.** This concept has no precise definition, but describes a situation in the natural history of a chronic glomerular disease where loss of kidney function is accompanied by such extensive and irreversible kidney injury that any therapeutic strategy being tested cannot reasonably be expected to alter the natural history of progressive

deterioration in kidney function (therapeutic futility). The presumption is that such patients should be excluded from clinical trials, since they are expected to be “nonresponders” and therefore may dilute any treatment effect, and adversely affect the power of the study. Furthermore these subjects with reduced kidney function may be at higher risk of adverse effects of the therapies being tested. In the absence of precise definitions of the “point of no return” it is not possible to know, in most of the published trials, whether the inclusion or exclusion of such patients may have masked any therapeutic benefit.

**Quality of life and quality of health.** Patients’ own perceptions of their quality of life and quality of health, and their preferences are extremely important elements of the assessment of therapy, but are often an underappreciated and/or unmeasured parameter in the evaluation of many of the clinical trials reviewed in this guideline. This is particularly relevant when considering the risk-benefit analysis of interventions, which may include the short- and long-term risks of immunosuppressive treatments but often does not account for the patient’s perspective in relationship to real or perceived impact on their quality of life. These unassessed elements have the potential to significantly obfuscate outcomes (e.g., concerns about body image in young females treated with corticosteroids could impact adherence to therapy). The recent introduction of patient-related outcomes (PROMS) that allows a more rapid assessment has the potential to provide a more uniform quality-of-life determination that is standard across all chronic diseases.

The lack of such data is a substantial evidence gap in the evaluation of studies relating to the management of GN.

### **Impact of Age, Sex, Ethnicity, and Genetic Background**

Published RCTs of treatment for GN remain few, and many are small, short in duration of follow-up, and of variable quality. This has resulted in uncertainty about generalizability, i.e., whether the demonstrated benefits (or lack of efficacy) of any treatments will still emerge if patients are then treated who come from different ethnic groups, and/or are of different age or sex, compared to those included in the published studies. The specific limitations of studies in this regard are discussed in later chapters but the following are examples of this issue: whether it is reasonable to extrapolate treatment recommendations from children to adults with MCD, and vice versa; whether the effectiveness of regimens for LN proven in Caucasians can be extended to those of other ethnicities; and whether the safety observed with a course of immunosuppression in the young applies equally to the elderly.

Furthermore few available RCTs are statistically powered to examine less-common adverse effects of therapy. It is not yet clear if new insights into these and other issues will emerge from a better understanding of the pharmacogenetic variations that can substantially alter the pharmacokinetics and/or pharmacodynamics of immunosuppressive and other agents. Although early evidence is suggestive that such

genetic traits may alter clinical outcome,<sup>6</sup> the cost of such pharmacogenetic testing also needs consideration and, as yet, there is little robust evidence that these factors should modify the treatment of GN.

### Management of Complications of Glomerular Disease

A number of complications of glomerular disease are a consequence of the clinical presentation rather than the specific histopathologic pattern. Active management of such complications—although not subject to evidence review in this guideline—should always be considered and may have a significant positive impact on the natural history of the disease. These include measures to treat blood pressure, reduce proteinuria, control edema, and address other metabolic and thrombophilic consequences of nephrotic syndrome, which can result in significant morbidity and even mortality. If successful, these relatively nontoxic therapies may prevent—or at least modulate—the need for immunosuppressive drugs with their potential adverse effects. Such supportive therapy is usually not necessary in steroid-sensitive MCD with rapid remission, or in patients with GN and only microscopic hematuria, preserved GFR, and neither proteinuria nor hypertension. The latter is a common scenario, for instance, in IgA nephropathy.

**Hypertension.** As in all chronic kidney disease (CKD), the aim of blood pressure control is both to protect against the cardiovascular risks of hypertension and to delay progressive loss of GFR. Lifestyle modification (salt restriction, weight normalization, regular exercise, and smoking cessation) should be an integral part of the therapy for blood pressure control.

The ideal goal for blood pressure is not firmly established but current recommendations suggest that 130/80 mm Hg should be the treatment goal. There are limited data to support a lower target of 125/75 mm Hg if there is proteinuria >1 g/d.<sup>7</sup> This issue will be covered in a forthcoming KDIGO Guideline for the Management of Blood Pressure in Chronic Kidney Disease. There is no specific evidence in GN on which to base a recommendation about the preferential importance of systolic or diastolic blood pressure, or about timing of blood pressure measurements. There are strong theoretical and experimental reasons for angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin-receptor blockers (ARB) to be first-choice therapy; this is now well-documented in clinical studies.<sup>8</sup> Children with GN should have blood pressure controlled to below the 50th percentile for systolic and diastolic pressure for age and sex using published<sup>9,10</sup> or locally available standards.

The evidence for blood pressure goals and choice of antihypertensive therapy in GN and other CKD has not been systematically evaluated for this guideline; it will be the subject of a forthcoming KDIGO Clinical Practice Guideline.

**Proteinuria.** Reduction in proteinuria is important, as it reflects control of the primary disease, reduction of glomerular hypertension, and also reduction of podocyte damage (a likely major factor in glomerular scarring).

Most studies suggest that the loss of kidney function in the progressive histologic patterns discussed in this guideline can largely be prevented if proteinuria can be reduced to levels below 0.5 g/d. The exceptions are MCD and SSNS where complete remission defines the disease. Proteinuria or factors present in proteinuric urine may also be toxic to the tubulointerstitium. In nephrotic syndrome, a reduction of proteinuria to a non-nephrotic range often results in an elevation to normal of serum proteins (particularly albumin). This elevation, in turn, alleviates many of the patient's symptoms as well as the metabolic complications of the nephrotic syndrome, thus improving quality of life.

The antiproteinuric agents of choice are ACE-I or ARB, which may reduce proteinuria by up to 40–50% in a dose-dependent manner, particularly if the patient complies with dietary salt restriction. There is little evidence to suggest that ACE-I differ from ARBs in this respect. However, the combination of the two may result in additive antiproteinuric activity, although there is conflicting evidence as to the risk-benefit ratio of this strategy, especially if GFR is significantly reduced. Since ACE-I and ARBs lower GFR, a 10–20% increase in SCr is often observed. Unless SCr continues to rise, this moderate increase reflects their effect on kidney hemodynamics and not worsening disease, and should not prompt withdrawal of the medication.

Recommendations on the dosing of these agents and the target levels of proteinuria are outside the scope of this introduction, but are addressed when there is available evidence for specific forms of GN in subsequent chapters.

Adequate dietary protein should be ensured in the proteinuric patient (0.8–1.0 g/kg daily) with a high carbohydrate intake to maximize utilization of that protein.

The evidence for the benefit of reducing proteinuria in CKD in general, and the choice of specific agents, has not been systematically evaluated for this guideline with the exception of the value of partial remission discussed in the relevant chapters. The evidence for renal protective therapy will be the subject of a forthcoming KDIGO Clinical Practice Guideline on Evaluation and Management of Chronic Kidney Disease.

**Hyperlipidemia.** Treatment of hyperlipidemia in patients with glomerular disease should usually follow the guidelines that apply to those at high risk for the development of cardiovascular disease. This is most relevant in the patients where the manifestations of the disease cannot be completely ameliorated, and when other risk factors for cardiovascular disease coexist, most commonly hypertension and proteinuria. Dietary restriction of fats and cholesterol alone has only modest effects on hyperlipidemia in glomerular disease, in particular in nephrotic syndrome. Statins (HMG CoA reductase inhibitors) are well tolerated and effective in correcting the lipid profile, although not proven to reduce cardiovascular events in nephrotic syndrome. It may also be that statin therapy protects from a decline in GFR, although this is not established. Care is needed when statins are used in combinations with other drugs, notably an

increased risk of myalgia/myositis when combined with calcineurin inhibitors.

**Nephrotic edema.** The mainstay of treatment is diuretics accompanied by moderate dietary sodium restriction (1.5–2 g [60–80 mmol] sodium per 24 hours). Nephrotic patients are often diuretic-resistant even if GFR is normal: oral loop diuretics with once- or twice-daily administration are usually preferred, given the ease of administration and longer therapeutic effect compared to i.v. therapy. However, in severe nephrotic syndrome, gastrointestinal absorption of the diuretic may be uncertain because of intestinal-wall edema, and i.v. diuretic, by bolus injection or infusion, may be necessary to provoke an effective diuresis. Alternatively, combining a loop diuretic with a thiazide diuretic or with metolazone is often an effective oral regimen that may overcome “diuretic resistance”. i.v. albumin infusions may be combined with diuretics to treat diuretic resistance, but are of unproven benefit. Occasionally, mechanical ultrafiltration is required for resistant edema.

Significant hypovolemia is not often a clinical problem, provided that fluid removal is controlled and gradual, but the pediatric and the elderly populations are at more risk of this complication. In the elderly, associated conditions such as diabetes mellitus and hypertension may increase the likelihood of hypovolemic shock and acute ischemic kidney injury.

**Hypercoagulability.** The risk of thrombotic events becomes progressively more likely as serum albumin values fall below 2.5 g/dl (25 g/l). Immobility as a consequence of edema, obesity, malignancy, intercurrent illness, or admission to hospital for surgery can further aggravate the risk. Prophylactic low-dose anticoagulation (e.g., heparin 5000 units subcutaneously twice daily) is common practice at times of high risk. Full-dose anticoagulation with low-molecular-weight heparin or warfarin is mandatory if an arterial or venous thrombosis, or pulmonary embolism, is documented. It should also be considered if serum albumin drops below 2.0–2.5 g/dl (20–25 g/l) with one or more of the following: proteinuria >10 g/d; body mass index (BMI) >35 kg/m<sup>2</sup>; family history of thromboembolism with documented genetic predisposition; New York Heart Association class III or IV congestive heart failure; recent abdominal or orthopedic surgery; or prolonged immobilization. Contraindications to prophylactic anticoagulation are: an uncooperative patient; a bleeding disorder; prior gastrointestinal bleeding; a central nervous lesion prone to hemorrhage (brain tumor, aneurysms); or a genetic abnormality influencing warfarin metabolism or efficacy.

During treatment with heparin, a significantly higher than average dose may be required because part of the action of heparin depends on antithrombin III, which may be lost in the urine in the nephrotic patient. Warfarin is the long-term treatment of choice but should be monitored with special care because of potential alterations in the protein binding of the drug with fluctuations in serum albumin in the nephrotic patient. A target international normalized ratio (INR) of 2–3

is usually recommended, although not supported by specific evidence.

**Risk of infection.** A high order of clinical vigilance for bacterial infection is vital in nephrotic patients. This is particularly important in nephrotic children with ascites, in whom the fluid should be examined microscopically and cultured for spontaneous bacterial peritonitis. Bacteremia can occur even if clinical signs are localized to the abdomen. Erythrocyte sedimentation rate is unhelpful, but an elevated C-reactive protein may be informative. Parenteral antibiotics should be started once cultures are taken and the regimen should include benzylpenicillin (to treat pneumococcal infection). If repeated infections occur, serum immunoglobulins should be measured. If serum IgG is less than 600 mg/dl (6 g/l), there is limited evidence that infection risk is reduced by monthly administration of i.v. immunoglobulin 10–15 g to keep serum IgG >600 mg/dl (>6 g/l).<sup>11</sup>

Those with GN and nephrotic syndrome are at increased risk of invasive pneumococcal infection and should receive pneumococcal vaccination with the heptavalent conjugate vaccine (7vPCV) and the 23-valent polysaccharide vaccine (23vPPV) as well as the annual influenza vaccination. The response does not seem to be impaired by concurrent corticosteroid therapy. Vaccination with live vaccines (measles, mumps, rubella, varicella, rotavirus, yellow fever) is contraindicated while on immunosuppressive or cytotoxic agents, and should be deferred until prednisone dose is <20 mg/d and/or immunosuppressive agents have been stopped for at least 1–3 months. Exposure to varicella can be life-threatening, especially in children. Treatment should be given with zoster immune globulin if exposure does occur and antiviral therapy with acyclovir or valaciclovir begun at the first sign of chicken pox lesions<sup>12</sup> (See Chapter 3, SSNS, for additional details on management in children).

### Use of Corticosteroids and Immunosuppressive Therapy

The chapters that follow will focus on the effectiveness of therapy based on current evidence in the most common histologic variants of GN.

The therapeutic decisions of the physician are predicated on the continuing need to balance the risks and benefits of treatment. Nothing stated in this guideline replaces the physician's assessment in this regard. The physician ideally seeks a treatment regimen that reduces immunosuppressive therapy exposure to the minimum, minimizes immediate morbidity (e.g., achieving remission of nephrotic syndrome), and prevents disease progression. However, physicians must also recognize that more prolonged treatment may be required, given the long-term threat that failure to prevent ESRD will shorten life expectancy and may only delay prolonged immunosuppressive drug exposure that would be required after kidney transplantation.

The focus in the management of chronic patterns of GN has shifted from cure to control, exemplified by recognition of the short- and long-term benefits of a reduction in proteinuria (in addition to the benefits known to accrue with

complete remission). This paradigm has translated into use of more extended (or repeated) treatment regimens with the corollary of more toxic drug exposure.

The specific adverse effects of the recommended immunosuppressive agents and the need for routine prophylactic measures are beyond the scope of this guideline, but are familiar in clinical practice, and have been reviewed.<sup>13</sup> Specific regimens that potentially require prolonged exposure to these immunosuppressive agents are identified in the chapters to follow.

**Adverse effects.** The potential adverse effects of immunosuppressive therapy must always be discussed with the patient and family before treatment is initiated. This part of the management cannot be overemphasized. The risks of treatment with many of the agents are significant and may have a substantial latent period (e.g., cyclophosphamide). A balance must be struck between the potential risks of immunosuppressive treatment for GN, and the seriousness of the patient's condition. It is sometimes difficult to reconcile the immediate risks of immunosuppression, in the otherwise clinically well patient, vs. the potential for progression to ESRD. However, given that advanced CKD—and, particularly, ESRD—is associated with a significant shortening of life expectancy even with dialysis or transplantation, the balancing of risks and benefits over time must be considered. The physician must be aware of this conundrum and where the evidence for treatment is weak (but potentially life-altering) and the risk for harm strong, a full disclosure is mandatory. Individual patient perceptions of the acceptability of any adverse effect may strongly influence the decision (e.g., the possibility of hirsutism with cyclosporin therapy may be perceived as less tolerable in a young female than in an older male). What might be seen as an acceptable trade-off by the physician may not be viewed similarly by the patient, leading to an issue over compliance with therapy.

With more intensive immunosuppressive regimens, prophylaxis may be required to minimize possible adverse effects. Specific recommendations are beyond the scope of this guideline, and are without an evidence base specific to treatment of GN, but better evidenced when immunosuppression is used in kidney transplantation. Common examples are the use of prophylactic antimicrobials to minimize opportunistic infection, and H<sub>2</sub>-receptor antagonists or proton pump inhibitors to prevent peptic ulceration. Two other important and more drug-specific examples are the use of bisphosphonates (except in the presence of kidney failure) to minimize loss of bone density during prolonged treatment with corticosteroids, and the need to offer the opportunity for sperm or ovum storage/preservation—where available—before treatment with the gonadotoxic agents, cyclophosphamide and chlorambucil.

**Drug monitoring.** Immunosuppressive agents with a narrow therapeutic index include the calcineurin inhibitors, cyclosporin and tacrolimus. There are no RCTs that compare response to treatment in GN and different achieved blood

levels of these agents. Dosing and target blood levels are based on established practice in kidney transplantation. The main goal of blood level monitoring is to avoid toxicity due to high drug levels, while still maintaining efficacy. The latter can often be assessed by proteinuria reduction, which can sometimes be achieved with trough blood levels of calcineurin inhibitors that would be considered subtherapeutic for solid-organ transplantation. The value of monitoring mycophenolic acid levels to guide dosing of mycophenolate has not been studied in GN.

### **Pregnancy in Women with GN**

In women of child-bearing potential, the risks of pregnancy must be considered. A major predictor of pregnancy outcome is the GFR at time of conception. Other issues include the toxicity, especially in the first trimester, of immunosuppressive agents, ACE-I, and ARBs, and also the hazards to fetal and maternal outcome of pregnancy with uncontrolled proteinuric conditions. There is also a risk of relapse of LN both during and after pregnancy.

### **Treatment Costs and Related Issues**

These guidelines have been developed with the goal of providing evidence-based treatment recommendations for GN that can be used by physicians in all parts of the world. Most of the medications recommended are available at low cost in many parts of the world. These include prednisone, azathioprine, and cyclophosphamide tablets. Monitoring (e.g., by regular checks of blood count) is also cheap and widely available.

The cost of some agents (e.g., calcineurin inhibitors and mycophenolate) remains high, but the development and marketing of generic agents and biosimilars is now rapidly reducing costs. However, care must be taken to ensure that variations in bioavailability with these less expensive generic agents do not compromise effectiveness or safety.

Plasmapheresis remains unavailable in some parts of the world, related not only to the high cost and limited availability of replacement fluids (including human albumin and fresh frozen plasma) but also to the equipment and staffing costs.

Some treatments suggested as potential “rescue” therapies in this guideline (e.g., rituximab) remain prohibitively expensive in most parts of the world. This is another indication of the urgent need for developing trials that will provide robust evidence of their efficacy. Uncertainty about the value of such high-cost agents would also be mitigated if there were comprehensive national or international registries collecting comprehensive observational data on their use, but unfortunately none exist.

### **Post-transplantation GN**

Virtually all of the histologic variants discussed in this guideline (with the exception of MCD) may recur after transplantation. Recurrent disease is recognized as the third most common cause of kidney transplant failure. Currently

there are no proven strategies to prevent recurrent GN in kidney transplant recipients. Despite the high rate of recurrent disease, long-term graft survival is still very good and transplantation remains the best treatment option for patients with ESRD secondary to GN. Where there are specific recommendations in particular variants of GN that relate to management before transplantation, they will be discussed in each relevant chapter.

### **RESEARCH RECOMMENDATIONS**

The evidence review underpinning this clinical practice guideline has confirmed the paucity of robust data from RCTs to support the treatment recommendations and suggestions that have been made. This raises the question of why there are so few RCTs of good design and sufficient power in GN, compared to many other areas of nephrology and internal medicine. The slowly progressive natural history of many patterns of GN means that trials designed to provide definitive outcome data (using ESRD or mortality) require long follow-up, significantly increasing their cost as well as effort for both the physician and the patient. Studies often employ “composite end-points” in order to enhance event rates. Furthermore, there are two competing elements in GN trial design. On the one hand, there is the recognition that most GN variants are uncommon; on the other hand, there is a need to acquire an adequate sample size within a reasonable time frame, an essential element for any successful study. This virtually mandates multicenter and multinational trial organization which, in turn, is challenging from both organizational and cost perspectives. These factors have

made trials in GN less attractive both to funding agencies and pharmaceutical companies, compared to more common and higher-profile clinical domains such as cardiovascular disease and cancer.

However there is an urgent need for such studies to be carried out. The costs—both to society, and to patients with GN and their families, if disease progression is not prevented—are often grossly underestimated. As an integral part of this guideline, we make recommendations in each chapter about the most pressing areas of uncertainty where RCTs and other areas of research would significantly inform clinical practice.

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