

## Management of Membranous Nephropathy: When and What for Treatment

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J Am Soc Nephrol 16: 1188–1194, 2005. doi: 10.1681/ASN.2005010028

**I**diopathic membranous nephropathy (IMGN) remains the most common form of the nephrotic syndrome in adults. Its incidence rate has remained constant over the past three decades in contrast to the increasing numbers in the other common progressive variants of primary glomerulonephritis, such as IgA nephropathy and focal segmental glomerulosclerosis (1–4).

This review discusses newer aspects of evaluating prognosis as well as when and what to use in terms of immunosuppressive treatment of this disorder. All of these factors are critical to evaluate to arrive at the proper balance between the prospects of renal failure *versus* the risks of immunotherapy.

Many individual factors that are relevant to prognosis are already recognized, but crucial to the question of therapy is the ability to predict outcome in a patient as early and as accurately as possible and ideally based on modifiable factors. Only after this assessment is made can we logically determine the risk *versus* benefit of treatment.

We have made the assumption for the purpose of this review that secondary causes of MGN have been ruled out. This is particularly relevant for this disease because up to one third of cases can have an identifiable cause, and the management of these cases is directed toward removing or correcting the underlying cause (5). This can be complicated further because the factors that influence prognosis in IMGN can also increase the likelihood of its being secondary to a specific cause. Examples of this include the age of the individual and the geographic location of the patient. Both of these factors may influence the prognosis in the idiopathic variant (*vide infra*) but also increase the possibility of secondary cause. The risk of an underlying malignancy, as the causative agent for instance, above the age of 60 is at least threefold that of a younger man, and an infectious origin in Asian countries from hepatitis B is much more likely than in the North American patient (6,7). To summarize, although our focus in this article is on primary MGN or

IMGN, it is important to remain alert to the wide range of possible secondary causes.

### Natural History

IMGN is a disorder, by definition, of unknown causative factors whereby the disease process is focused on the kidney alone. Although the percentage of the IMGN population that progresses to end-stage renal failure remains relatively small, the absolute numbers are large, and because it affects people predominantly in their 30s and 40s, it has an enormous long-term impact on their quality of life, productivity, and family circle. In addition, because they have single-organ disease rather than multisystem organ failure, such as occurs in diabetes, they survive longer on dialysis and after renal transplantation. Although they survive longer, they continue to function at a lower level in comparison with the age- and gender-matched normal population and rarely return to the same level of productivity or quality of life as their peers. Even in patients who do not progress, complications that often ensue include life-threatening thromboembolic phenomena and accelerated vascular disease (8). These may be due to an underlying specific defect in coagulation and/or tissue repair and/or the long-term sequelae of their prolonged nephrotic condition.

It is difficult today to define the natural history of this disorder. Once the diagnosis is made today, the management of the edema, BP, and commonly associated hyperlipidemia is mandated and effective in almost all IMGN patients. The impact of the control of these factors alone on the natural history is expected to be positive but is currently unknown. Part of this is due to the unusual characteristic of up to a 30% spontaneous remission in IMGN patients. Although this happens more commonly in the first 2 yr after presentation, it can occur at any time over the course of their illness. In contrast, the other two thirds will generally divide equally into either persistent proteinuria with long-term preservation of renal function or slow progression to renal failure (9–11). This wide variation in outcome is one of the factors that has led meta-analysis and systematic reviews of this disease to reach varying conclusions about the impact of immunosuppressive treatment on patient and renal survival and on proteinuria remission rates (3,12–14).

Published online ahead of print. Publication date available at [www.jasn.org](http://www.jasn.org)

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## Predicting Factors

### Age and Gender

Despite these issues related to the natural history of the disease, our ability to predict those who are most likely to progress has improved. Both age and gender have been known to influence outcome for the past two decades in that female gender is protective (or men are at greater risk for failure) and increasing age is associated with a higher risk for renal failure (3,13,14). More recent data have confirmed that young men do progress more rapidly than young women, but there is a significant age interaction. Both older men and women have lower creatinine clearances at presentation, but their disease progression, as measured by the rate of decline in creatinine clearance, is almost identical and it seems that it is because of this lower starting point of their GFR that renal failure is reached sooner in the older patient than in their younger counterparts regardless of their gender (15). This lower starting creatinine clearance with age is correlated with histologic features such as glomerulosclerosis, vascular disease, and interstitial fibrosis and with the clinical features of hypertension but not with the severity of the proteinuria. This may suggest that these factors reflect the underlying condition of the individual at the time they acquire the disease rather than its severity. These preexisting factors then more likely reflect the presenting GFR value, and proteinuria and rate of progression from this point reflect disease activity and severity.

### Proteinuria

The specific quality and quantity of the proteinuria may help to predict both those who are most likely to progress and those who are most likely to respond to therapy (16). The ratio of IgG to  $\alpha$ -1-microglobulin excretion has been measured and found to be helpful not only in determining the severity of the overall renal injury but also in predicting those who are most likely to respond to immunosuppressive treatment (17). These are interesting findings but are based on retrospective data in small numbers and have yet to be validated. The establishment of cutoff values for these ratios is of concern because they may reflect activity only at certain times during the course of the disease and under certain conditions, which may vary widely over time and be independent of the activity of the primary disease.

### Pathology

Certain elements of pathology have been associated with a poor prognosis in IMGN since its original description. These include the degree of interstitial fibrosis, sclerosis, and vascular disease (18). More recently and perhaps more specific in regards to both predicting outcome and immunosuppressive responsiveness has been the suggestion that outcome parallels the amount of focal segmental glomerulosclerosis. Also new are data suggesting that the configuration of the immune composite on electron microscopy may be of help in indicating those who are most likely to respond to treatment. Patients with homogeneous electron dense deposits, *i.e.*, synchrony of the deposits at a single stage, do better than patients with heterogeneous (multistage) deposits on electron microscopy (19,20).

Neither of these indicators has been verified in prospective studies.

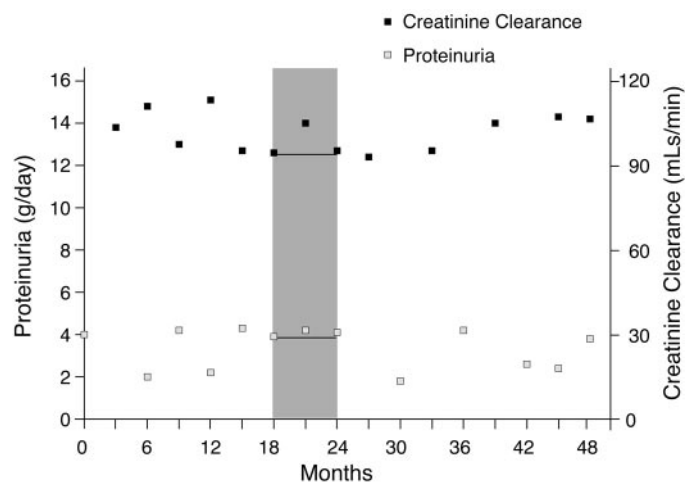
### Renal Function

Impaired renal function at presentation is associated with a lower renal survival (15,18,21). However, because renal function at presentation is widely variable and may be independent of disease severity (*vide supra*), it may not be the only or the best way to assess disease activity. As a measurement of rate of progression, slope of creatinine clearance over time may be a better estimate of disease severity (15).

A major problem with these predictors is that they generally focus on details that are known at the time of presentation and/or biopsy and are qualitative with poor specificity and are not modifiable. We have previously published a predictive algorithm that significantly improved both specificity and positive predictive values with little loss of sensitivity. This improvement was seen when we added a 6-mo observation period to the standard laboratory parameters of creatinine clearance and quantitative proteinuria. In addition, this formula can be used at any point in the trajectory of the illness.

In the case illustrated in Figure 1, for example, during the 6-mo observation period between 18 and 24 mo (bar), the minimum persistent proteinuria was 4 g/d, the initial creatinine clearance was a 102 ml/min, and there was no change in renal function during that time frame. The risk for progression "R" can be calculated using these numbers and the known constants as illustrated below ( $K_0, K_1, K_2, K_3$ ).

$$\begin{aligned}
 X &= 1.26 (K_0) \\
 &+ [(0.3)(K_1) \times 4 \text{ (minimum persistent proteinuria)}] \\
 &+ [(-0.3)(K_2) \times 0 \text{ (change in CrCl over the 6 mo)}] \\
 &+ [(-0.05)(K_3) \times 102 \text{ (initial CrCl)}]
 \end{aligned}$$



$$\begin{aligned}
 X &= 1.26 + (0.3 \times 3.5) + (-0.3 \times 0) + (-0.05 \times 102) = -2.79 \\
 e^X &= 0.06 \quad "R" = 0.06 / 1.06 = 6\%
 \end{aligned}$$

Figure 1. Predicting risk of renal disease progression. The algorithm uses a time frame of 6 mo (bar) and the initial and change in creatinine clearance over this period plus the minimum persistent proteinuria value to calculate the "R" (risk) value.

$$X = -2.79$$

$$E^X \text{ (exponential of } x) = 0.06$$

$$\text{"R" (probability of progression)} = E^X/E^X + 1 = 0.06/1.06 = 6\%$$

where  $K_s$  are constant and CrCl is creatinine clearance. We subsequently validated this algorithm on two data sets of IMGN patients from Italy and from Finland (22).

The application of this model (Table 1) highlights the significant reduction in overtreatment by a factor of 2 to 3 (increased specificity) and improved ability to predict those who will progress by a factor of 2 (increased positive predictive value) when the algorithm is used compared with using nephrotic-range proteinuria alone (Table 1).

## Response Measurements

The best accepted responses are improved renal survival and complete remission (CR) of proteinuria. Although both are excellent indicators, the first is limited because of the very long duration of the average renal survival in IMGN patients and how strongly this is influenced by their initial creatinine clearance as illustrated above. A better and more sensitive parameter is rate of deterioration as measured by slope of creatinine clearance over time.

Similarly, spontaneous CR occurs at a higher rate in this disease than in any of the other primary progressive nephropathy, so treatment regimens that begin at the point of presentation must have a CR rate significantly greater than would occur without therapy if this is the only end point selected for the study. All of these points have a significantly impact on the capacity of meta-analysis to determine the benefits of immunotherapy. In addition, potentially confusing the benefits of treatment has been the utilization of partial remission (PR) as a positive outcome. To date, this parameter has not been universally accepted as a reliable surrogate for renal survival and has not had a uniform definition.

We recently determined in a cohort of 350 patients with nephrotic IMGN that 10-yr renal survival was 100% in the CR

group, 90% in the PR group, and 45% in the no remission (NR) group. We also found that the rate of decline was  $-1.5$  ml/min per yr in the CR group,  $-2$  ml/min per yr in the PR group, and  $-10$  ml/min per yr in the no remission group ( $P < 0.001$ , NR>CR, NR), which eliminates the influence of variances in starting creatinine clearance (23).

## Allocation of Patients by Risk for Progression

We can arbitrarily assign patients using our algorithm for predicting outcome to different categories in regards to their risk for progression to chronic renal failure.

### Low Risk

Patients in this group are categorized by a  $<5\%$  risk for progression over 5 yr of observation. They are defined by normal renal function and proteinuria  $\leq 4$  g/d over the 6-mo observation period. Evidence to support this approach comes from our validation studies and from our recent data on the clinical relevance of PR (22,23).

**Treatment.** Treatment should be conservative only, given this excellent prognosis: (1) reduce proteinuria, (2) idealized blood pressure, and (3) use angiotensin-converting enzyme inhibitors  $\pm$  angiotensin receptor antagonists.

### Medium Risk

This group is defined by normal renal function and persistent proteinuria between 4 and 8 g/d over 6 mo of observation despite the institution of maximum conservative treatment.

**Specific Treatment.** The monthly cycling of corticosteroids and cytotoxic drugs on alternate months over 6 mo has significantly improved renal survival in this type of patient with IMGN. Ten-year renal survival improved from 60% in the control population to 92% in the treatment group (24). The initial cytotoxic drug was chlorambucil, but a subsequent study that replaced it with cyclophosphamide showed similar results

Table 1. Results of model fitting and validation

	Toronto	Finland	Italy
Chronic renal insufficiency	47/184 (26%)	13/78 (17%)	25/101 (25%)
sensitivity			
proteinuria $>3.5$ g/d	93%	100%	84%
model	89%	77%	60%
specificity			
proteinuria $>3.5$ g/d	38%	30%	17%
model	86%	89%	92%
positive predictive value			
proteinuria $>3.5$ g/d	34%	24%	25%
model	67%	59%	64%
negative predictive value			
proteinuria $>3.5$ g/d	94%	100%	76%
model	94%	95%	82%
accuracy			
model	52%	43%	34%
model	85%	87%	79%

and fewer patients had adverse effects (25). Cyclophosphamide therapy was given at a dose of 2.5 mg/kg per d in months 2, 4, and 6, and corticosteroid therapy was initiated as methylprednisolone pulses of 1 g/d for 3 d at the beginning of months 1, 3, and 5 followed by oral prednisone 0.5 mg/kg on the remaining days of each of these months.

More recently, oral cyclophosphamide 1.5 to 2 mg/kg per d for 12 mo plus steroids (methylprednisolone pulses  $3 \times 1$  g intravenously at the beginning of months 1, 3, and 5 plus oral prednisone 0.5 mg/kg per 48 h for 6 mo) has proved to be effective in patients with this degree of proteinuria plus mild to moderate renal insufficiency. A substantial improvement in both PR and CR rate and renal function stabilization for up to 7 yr was observed compared with a historical control group. However, relapse rate was substantial (32%), and serious treatment-related complications occurred in 66% of patients mainly related to bone marrow depression and infection (26).

Cyclosporine has also been shown to be effective in the patient with medium risk for progression. In a randomized, controlled trial over 6 mo of treatment, approximately 70% of patients achieved either a CR or a PR compared with 23% in the placebo group (27). Cyclosporine was given daily at a dose of 3 to 4 mg/kg in two divided doses for 6 mo.

A relapse rate between 30 and 40% within 2 yr of discontinuing medications was seen with both of these treatment modalities. This should be considered a relapse rather than failure of therapy, however, because reintroduction of the primary treatment or its alternative, *i.e.*, cyclosporine instead of the cytotoxic/corticosteroid routine or *vice versa*, commonly resulted in the another remission. More prolonged therapy or lower dose cyclosporine perhaps should be considered for long-term maintenance of patients who achieve only a PR, especially when the patient is at high risk for relapse or previously had significant adverse effects on full-dose therapy. Three randomized, con-

trolled trials have shown that corticosteroids alone are not effective in this group of patients in terms of either significantly reducing proteinuria long term (28,29) or preserving of renal function (29,30).

### High Risk

This group is defined by deteriorating renal function and/or by persistent high-grade proteinuria  $\geq 8$  g/d during the 6 mo of observation. This represents a small proportion of patients with IMGN (10 to 15%).

A rapid change in either of these parameters, especially in a previously stable patient, should raise the possibility of a new complication such as renal vein thrombosis, interstitial nephritis from diuretics or other medications, or even a change in pathology with the development of crescent formation.

**Specific Treatment.** Cyclosporine has been shown to be effective in a small randomized, controlled trials in patients with IMGN and documented progression. Phase 1 of the study was maximum conservative therapy for all of the patients, with entry into phase 2 only when there was an absolute decrease in creatinine clearance of  $\geq 10$  ml/min during the year of observation. The patients who did progress were randomly allocated to 1 yr of cyclosporine or placebo. The creatinine clearance averaged 75 ml/min and proteinuria was 7 g/d at entry to phase 1, but in those who were eligible for phase 2, the mean creatinine clearance had fallen to between 45 and 50 ml/min and proteinuria averaged between 11.5 and 13 g/d. The rate of deterioration in kidney function as measured by slope of creatinine clearance in the nine patients who were randomized to cyclosporine was reduced from  $-2.4$  to  $-0.7$  ml/min per mo compared with the placebo patients, whose change was insignificant,  $-2.2$  to  $-2.1$  ml/min per mo during the treatment year ( $P = 0.02$ ) (31). There has not been a randomized, controlled trial of cytotoxic plus corticosteroids in this high-risk patient

### IMGN TREATMENT ALGORITHM

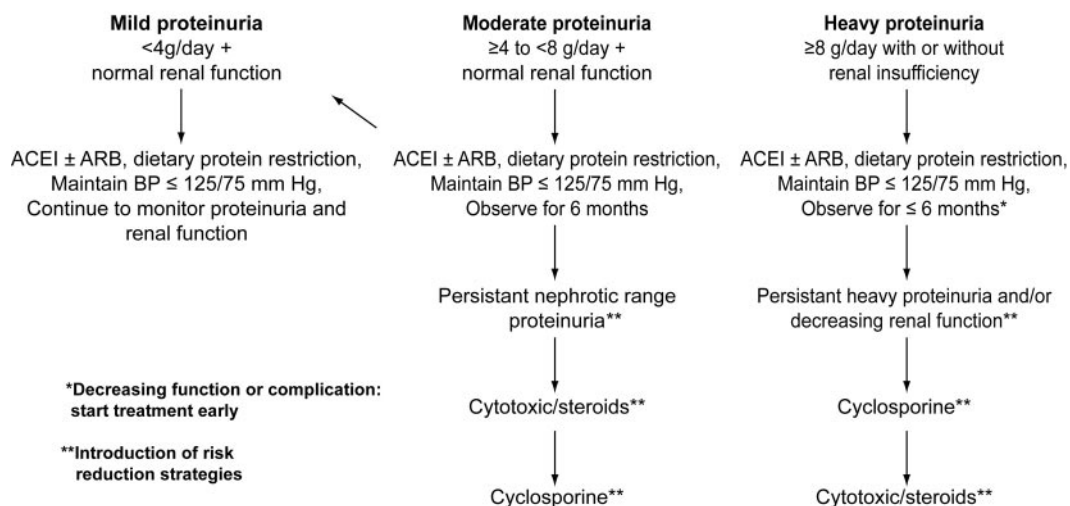


Figure 2. A treatment algorithm that combines the predictive factors and best evidence for conservative and then immunosuppressive treatment.



group. The best study using these medications was a study by Torres *et al.* (32) that compared conservative therapy in a historical control group with prednisone plus chlorambucil in patients who had IMGN and had shown progression. Treatment was prednisone 1 mg/kg tapered to 0.5 mg over 6 mo plus chlorambucil 0.15 mg/kg for 14 wk. In a group of 39 patients who were followed for up to 8 yr, renal survival was 90% in the treated group compared with only 20% in their historic control group. A summary of this risk assessment combined with treatment options is outlined in Figure 2.

### Treatment of Relapses

Re-treatment in 15 patients who had relapsed, with the routine of 1 yr of cyclophosphamide plus 6 mo of prednisone (as listed under the medium-risk category of patients), and would fit in this high-risk for progression category, *i.e.*, mild to moderate renal insufficiency plus high-grade proteinuria, has been reported to reduce proteinuria and stabilize renal function. This was not a randomized study, however, and the relapse rate was high (25%) and adverse effects were substantial and often necessitated a dose reduction or discontinuation of therapy (26,33).

## New Therapies

### Mycophenolate Mofetil

Mycophenolate mofetil (MMF) has been used in the field of solid organ transplantation for >10 yr. It has been shown to reduce acute rejection and more recently to prolong renal allograft survival. It works at least in part via the inhibition of the rate-limiting enzyme for the *de novo* pathway of purine synthesis and has less bone marrow toxicity than other purine antagonists such as azathioprine. The best study to date using MMF in patients with IMGN was a pilot trial by Miller *et al.* (34). All 16 patients in this project were treated for 6 to 16 mo with up to 2 g/d MMF. The patients had previously failed a variety of other immunosuppressive drugs. During the study, six patients had a  $\geq 50\%$  drop in proteinuria, two had a minor reduction in proteinuria, four had no change, three were withdrawn because of significant adverse effects, and one stopped the drug on his own volition after <6 mo of treatment. The nadir in proteinuria was reached within 6 mo in all responders, suggesting that this may be the necessary exposure time before therapy is considered a failure. MMF has a significant superiority compared with the calcineurin inhibitors in that it is not nephrotoxic. Its effect on the bone marrow is also less pronounced compared with other drugs in its class, and infectious complications seem to be reduced. It does have potent and sometimes drug-limiting gastrointestinal side effects. This agent should be studied in greater depth in this population as a single agent, as an adjunct to cyclosporine, or perhaps as a replacement for cyclophosphamide in the cytotoxic/corticosteroid regimen.

### Rituximab

Rituximab is a chimeric monoclonal antibody against the CD20 epitope of B cells. It has been used successfully for several years in the treatment of non-Hodgkin's lymphoma known to be associated with CD20-positive B cell proliferation.

In a small study, eight patients with IMGN and persistent nephrotic-range proteinuria were treated with a month of weekly intravenous injection of this drug. This course of treatment completely depleted the CD20+ cells for up to 12 mo. Five of the eight patients had a slow but progressive decline in proteinuria to subnephrotic levels over the first 6 mo, and the three other patients had a smaller decline in proteinuria. The proteinuria remained low for up to 1 yr after treatment. Adverse effects were rare and included chills and fever in one patient and an anaphylactic reaction in another patient. The theory for the therapy is that an autoreactive clone is depleted by rituximab, thus preventing the formation of the immune complexes. Although a specific antibody of this description has not been found in human disease, there is some support for this hypothesis from experimental studies (35). Further trials with this medication are needed to confirm these early results. The possibility that this is an effective therapy is exciting because it moves us toward a more specific and directed immunotherapy than our current broad-based immunosuppressive regimens.

### Ecuzumab

Ecuzumab is another new agent of some promise. It is a humanized monoclonal antibody that prevents the cleavage of human complement component C5 into its proinflammatory elements. This drug must also be given intravenously. In a recent abstract of a randomized, controlled trial in 200 patients with IMGN, neither of the two dose regimens of ecuzumab showed any significant effect on proteinuria or renal function when compared with placebo (36). It may be that both of the dose regimens were too low because adequate inhibition of complement was seen in only a small percentage of the patients. Adverse effects were rare, but if the safety as well as the benefits are dose dependent, then neither was truly assessed by this trial.

## Current Status

The major points of management are summarized in Table 2. We have made progress in this disorder. There is now a validated predictive algorithm that is capable of semiquantifying the risk for renal disease progression at any point in the disease course. In addition, there are newer tools, such as the protein selectivity index, that may further improve our ability to select patients who are at greatest risk for progression as well as help determine those who are most likely to respond to immunotherapy. Furthermore, we now have evidence that a PR is an

Table 2. Major points

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Conservative treatment first
Use angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or both
Complete and partial remission are appropriate "end points"
Relapse does not equal failure
Cyclosporin or cyclophosphamide/prednisone is effective

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excellent surrogate for renal survival and an appropriate therapeutic target, and we recognize that failure to remain in remission after a course of treatment should not be considered a failure of therapy but is better designated as a relapse and treatment reintroduced when an appropriate risk-benefit ratio exists.

New evidence-based lower targets and more potent and safer drugs for control of BP, hyperlipidemia, and proteinuria have reduced the vascular risk profile for these patients and are also likely to have a direct effect on slowing progression. When these conservative measures fail to reduce the proteinuria to subnephrotic levels, established regimens will be effective in the majority of cases. A treatment algorithm combining prognosis and known therapy is outlined in Figure 2. Newer drugs have already been tested in preliminary studies and are likely to reach the clinical domain soon.

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