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# Chapter 7: Idiopathic membranous nephropathy

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## INTRODUCTION

This chapter makes treatment recommendations for patients with biopsy-proven membranous nephropathy (MN) believed to be of unknown cause (IMN). The treatment of secondary forms of MN will not be covered in this chapter, except for MN associated with hepatitis B and C. The cost implications for global application of this guideline are addressed in Chapter 2.

### *7.1: Evaluation of MN*

**7.1.1: Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven MN. (*Not Graded*)**

## BACKGROUND

The diagnosis of MN is made on kidney biopsy. Diagnostic features include capillary wall thickening, normal cellularity, IgG and C3 along capillary walls on immunofluorescence, and subepithelial deposits on electron microscopy. MN is often seen in association with an underlying disorder (secondary MN).[191–193] Secondary MN is more common in children (75%) than adults (25%) (Table 12). The diagnosis of IMN is made by exclusion of secondary causes, using history, physical exam, and appppropriate laboratory tests (e.g., serology, imaging) and by careful examination of the kidney biopsy by light, immunofluorescence, and electron microscopy. In IMN, deposition of the IgG4 subclass of IgG is dominant, whereas other IgG subclasses dominate in secondary forms of MN.[194,195] Distinguishing secondary MN from IMN is very important, since the therapy in the former must be directed at the underlying cause and some of the treatments for IMN are potentially toxic both to the patient and the kidney.

## RATIONALE

MN is due to a clinically recognizable underlying disorder in a variable percentage of cases, depending on age and geography.[191–193,196,197,199–202] The recognition of the underlying disorder responsible for MN has important implications for prognosis and therapy.

MN is typically a disease of adults (fewer than 3% of cases are found in children). The frequency and etiology of secondary causes varies in different geographic areas[191–193,196,197,199–203] (Table 12). IMN is often a "diagnosis of exclusion". A recent study[200] has shown that about 70–80% of IMN patients exhibit circulating antibodies of IgG4 subtype against a conformation-dependent epitope in the M-type phospholipase A2 receptor. Such autoantibodies appear to be absent or very uncommon in patients with secondary MN. If the absence of autoantibodies to phospholipase A2 receptor in secondary MN is validated and a sensitive and specific assay for autoantibodies becomes available, it could become a valuable marker to positively identify ("rule in") IMN. The IgG4 subclass dominates in the deposits of IMN, while IgG1, IgG2, and/or IgG3 dominate in secondary forms of MN.[194,195]

The most important secondary causes include systemic lupus (in younger women), chronic hepatitis B infection (especially in East Asia[196]), drugs (such as nonsteroidal anti-inflammatory agents, gold and mercury compounds) and malignancy (especially in patients presenting over the age of 65 years). Specific evaluations should exclude secondary causes of MN before specific immunosuppressive therapy is considered. Detailed morphological studies show mesangial deposits by electron microscopy and prominent IgG1, 2, or 3 subclass deposits by immunofluorescence in secondary MN. These features can be helpful in suspecting a secondary form of MN (see also Table 13 for a detailed listing of causes of MN).

## RESEARCH RECOMMENDATIONS

- Studies are needed to validate the utility of antibody against M-type phospholipase A2 receptor in terms of its accuracy in separating primary from secondary MN.
- Studies are needed to determine the most cost-effective panel of investigations for screening an underlying (covert) malignancy in the older patient with MN.

### *7.2: Selection of adult patients with IMN to be considered for treatment with immunosuppressive agents (see 7.8 for recommendations for children with IMN)*

**7.2.1: We recommend that initial therapy be started only in patients with nephrotic syndrome *AND* when at least one of the following conditions is met:**

- **urinary protein excretion persistently exceeds 4 g/d *AND* remains at over 50% of the baseline value, *AND* does not show progressive decline, during antihypertensive and antiproteinuric therapy (see Chapter 1) during an observation period of at least 6 months; (*1B*)**
- **the presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome; (*1C*)**

**Table 12 | Reported causes of secondary MN (% in adults)**

| Cause | China Zeng *et al.*[196] (*n*=390) | Japan Abe *et al.*[191] (*n*=137) | France Cahen *et al.*[192] (*n*=82) | Finland Honkanen[197] (*n*=82) | United States Ehrenreich *et al.*[198] (*n*=167) |
|---|---|---|---|---|---|
| IMN | 31.8 | 65.0 | 79.3 | 69.8 | 62.3 |
| Secondary MN | 68.2 | 35.0 | 20.7 | 30.2 | 37.7 |
| Autoimmune diseases | 50.0 | 25.5 | 6.1 | 17.7 | 7.2 |
| Infections | 12.0 | 5.1 | 2.5 | | 2.4 |
| Tumors | 3.1 | 1.5 | 4.9 | 2.1 | 1.8 |
| Drugs or toxins | 3.1 | 2.2 | 6.1 | 10.4 | 4.2 |

IMN, idiopathic membranous nephropathy; MN, membranous nephropathy.
Abe *et al.*, Cahen *et al.*, and Ehrenreich *et al.* also reported diabetes as a secondary cause of MN, accounting for 0.7%, 1.2%, and 16.8% of secondary MN cases, respectively. Reprinted from Zeng CH, Chen HM, Wang RS *et al.* Etiology and clinical characteristics of membranous nephropathy in Chinese patients. *Am J Kidney Dis* 2008; 52: 691–698 with permission from National Kidney Foundation;[196] accessed http://www.ajkd.org/article/S0272-6386(08)01058-5/fulltext.

- **SCr has risen by 30% or more within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min per 1.73 m$^2$ *AND* this change is not explained by superimposed complications. (*2C*)**

**7.2.2: Do not use immunosuppressive therapy in patients with a SCr persistently >3.5 mg/dl (>309 μmol/l) (or an eGFR <30 ml/min per 1.73 m$^2$) *AND* reduction of kidney size on ultrasound (e.g., <8 cm in length) *OR* those with concomitant severe or potentially life-threatening infections. (*Not Graded*)**

## BACKGROUND

The commonest presentation of IMN is nephrotic syndrome with preserved kidney function. About 50% of patients with persistent high-grade proteinuria eventually progress to ESRD, often after many years of observation. Complete remission of nephrotic syndrome predicts excellent long-term kidney and patient survival. A partial remission also significantly reduces the risk of progression to ESRD (see Table 14 for definitions of complete and partial remission used in this chapter). The primary aims of treatment, therefore, are to induce a lasting reduction in proteinuria. All currently used treatment modalities have significant toxicity; therefore, selecting patients at high risk of progression is important so that exposure to treatment-related adverse events is minimized. The degree and persistence of proteinuria during a period of observation helps in selecting patients for this therapy. There is no agreed definition of the "point of no return" in the evolution of IMN after which the risks of immunosuppressive drugs become unacceptable and futile. However, the presence of severe tubular interstitial fibrosis, tubular atrophy, and glomerular obsolescence on biopsy, accompanied by persistent elevation of SCr >3.5 mg/dl (>309 μmol/l) (or eGFR <30 ml/min per 1.73 m$^2$), and reduction in kidney size on ultrasound may be such indicators.

## RATIONALE

- There is low- to moderate-quality evidence to support a recommendation that patients with time-averaged proteinuria <4.0 g/d or those who achieve a complete or partial remission have an excellent long-term prognosis.
- Observational studies of the natural history of IMN have shown that male gender, persistent heavy proteinuria, and elevated SCr at diagnosis predict the risk of later progressive decline in kidney function, although these factors may not all be independent risks.
- About 30–35% of patients with IMN eventually undergo spontaneous remission of nephrotic syndrome; therefore, it is reasonable to delay specific therapy for at least 6 months utilizing supportive therapy, including RAS blockade (see Chapter 1 for details) unless the patient has unexplained rapid deterioration in kidney function or there are complications related to uncontrolled nephrotic syndrome. However, the frequency of spontaneous remissions is lower with higher grades of proteinuria at presentation.
- It may be difficult to define precisely the time of onset of a partial remission, since some patients experience a slow reduction in proteinuria, even in the absence of specific treatment, to non-nephrotic levels over several years.
- There is support for the use of predictive models for determining risk of progression in IMN (i.e., persistent proteinuria >4 g/d and/or decline in kidney function over a 6-month period of observation).
- There is low-quality evidence to support a recommendation that the period of observation may be extended in patients who exhibit a consistent progressive decline in proteinuria during observation, have stable kidney function, and no complications related to the nephrotic state.

About 80% of adults with IMN have nephrotic syndrome at presentation[206] and the remainder have subnephrotic proteinuria (see definitions in Chapter 1). The disease course may be punctuated with spontaneous remissions and relapses.[197,207–214] In about 20% of patients, there is spontaneous complete remission of the nephrotic syndrome, and another 15–20% undergo partial remission. Remission may be delayed for as long as 18–24 months. In a recent

**Table 13 | Reported causes of secondary MN**

| Autoimmune | Infections |
|---|---|
| Autoimmune diseases | Hepatitis B |
| Systemic lupus erythematosus | Hepatitis C |
| Rheumatoid arthritis | Human immunodeficiency virus |
| Mixed connective tissue disease | Malaria |
| Dermatomyositis | Schistosomiasis |
| Ankylosing spondylitis | Filariasis |
| Systemic sclerosis | Syphilis |
| Myasthenia gravis | Enterococcal endocarditis |
| Bullous pemphigoid | Hydatid disease |
| Autoimmune thyroid disease | Leprosy |
| Sjögren's syndrome | |
| Temporal arteritis | |
| Crohn's disease | |
| Graft-versus-host disease | |

| Malignancies | |
|---|---|
| *Carcinomas* | *Noncarcinomas* |
| Lung | Hodgkin's lymphoma |
| Esophageal | Non-Hodgkin's lymphoma |
| Colon | Leukemia (chronic lymphocytic leukemia) |
| Breast | |
| Stomach | Mesothelioma |
| Renal | Melanoma |
| Ovary | Wilm's tumor |
| Prostate | Hepatic adenoma |
| Oropharynx | Angiolymphatic hyperplasia |
| | Schwannoma |
| | Neuroblastoma |
| | Adrenal ganglioneuroma |

| Drugs/Toxins | Miscellaneous |
|---|---|
| Gold | Diabetes mellitus (association or cause?) |
| Penicillamine | Sarcoidosis |
| Bucillamine | Sickle cell disease |
| Mercury compounds | Polycystic kidney disease |
| Captopril | α1-antitrypsin deficiency |
| Probenicid | Weber-Christian disease |
| Trimethadione | Primary biliary cirrhosis |
| Nonsteroidal anti-inflammatory drugs | Systemic mastocytosis |
| Cyclooxygenase-2 inhibitors | Guillain-Barre syndrome |
| Clopidogrel | Urticarial vasculitis |
| Lithium | Hemolytic-uremic syndrome |
| Formaldehyde | Dermatitis herpetiformis |
| Hydrocarbons | Myelodysplasia |

**Table 14 | Definitions of complete and partial remission in IMN**

***Complete Remission***: Urinary protein excretion $<0.3$ g/d (uPCR $<300$ mg/g or $<30$ mg/mmol), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration, and a normal SCr.

***Partial Remission***: Urinary protein excretion $<3.5$ g/d (uPCR $<3500$ mg/g or $<350$ mg/mmol) ***and*** a 50% or greater reduction from peak values; confirmed by two values at least 1 week apart, accompanied by an improvement or normalization of the serum albumin concentration and stable SCr.

MN, membranous nephropathy; uPCR, urine protein:creatinine ratio.
See also Chapter 1.
Based on previously published information, Jha *et al*. and Passerini *et al*.[204,205]

study, the mean time to remission was $14.7 \pm 11.4$ months following presentation.[215] About 15–30% suffer one or more relapses, leaving about 50% of the patients with persistent nephrotic syndrome. Data from natural history studies and placebo arms of intervention studies show that about 30–40% of the patients with persistent nephrotic syndrome progress to ESRD over 10 years.[208,216] Those with a persistent nephrotic syndrome are also exposed to the related complications, including infections, thromboembolic events, and accelerated atherosclerotic cardiovascular disease.

The likelihood of spontaneous remission and progression is dependent upon the age, gender, degree of proteinuria, and kidney function at presentation.[216,217] The risk of progression is highest in those with proteinuria $>8$ g/d, persistent for 6 months. A validated algorithm allowed creation of a model based on time-averaged proteinuria over 6 months, CrCl at diagnosis, and the slope of CrCl over 6 months that correctly identified patients at risk of progression with 85–90% accuracy.[218] Based on this model, patients at low risk for progression present with a normal CrCl, proteinuria consistently $<4$ g/d, and have stable kidney function over a 6-month observation period. Patients at medium risk for progression ($\sim$50–55% probability of developing progressive CKD over 10 years) have normal kidney function that remains unchanged during 6 months of observation, but continue to have proteinuria between 4 and 8 g/d. Those classified as high risk for progression (65–80% probability of progression to advanced CKD within 10 years from diagnosis) have persistent proteinuria $>8$ g/d, independent of the degree of kidney dysfunction.[219,220] Treatment-induced remissions are associated with an improved prognosis.[221,222] The 10-year survival free of kidney failure is about 100% in complete remission, 90% in partial remission, and 50% with no remission. Patients with complete or partial remission have a similar rate of decline in CrCl: $-1.5$ ml/min/y for complete remission, and $-2$ ml/min/y for partial remission. Although spontaneous remissions are *less common* in those with higher baseline proteinuria, they are not unknown; a recent report[215] showed spontaneous remission in 26% among those with baseline proteinuria 8–12 g/d and 22% among those with proteinuria $>12$ g/d. Treatment with RAS blockade, and a 50% decline of proteinuria from baseline during the first year of follow-up, were significant independent predictors for remission. Most reported natural history studies were performed in an era before drugs that act on the RAS became available. The long-term value of RAS blockade in management of IMN has been assessed largely by observational studies and has been observed only in those patients with proteinuria ($<10$ g/d) at baseline. A recent small RCT ($n=27$) compared an ACE-I (lisinopril, up to 10 mg/d) to an ARB (losartan, up to 100 mg/d) in patients with IMN and variable-range proteinuria (2.5–7 g/d). Both agents were of comparable efficacy, reducing proteinuria on average by 2.5 g/d by 12 months. The absence of a placebo control and the failure to include patents with higher-grade

proteinuria (>8–10 g/d) weaken the impact of the study.[223] There is only low-quality evidence to support the value of other predictors, such as hypertension, histologic evidence of interstitial fibrosis and tubular atrophy, persistently elevated urinary C5b-9, and excretion of increased quantities of low- or high-molecular-weight proteins (β2-microglobulin and IgG) in urine.[224,225] Staging of MN by histologic criteria has limited utility for prediction of outcomes or response to therapy in IMN.

### *7.3: Initial therapy of IMN*

**7.3.1: We recommend that initial therapy consist of a 6-month course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents (see Table 15). (*1B*)**

**7.3.2: We suggest using cyclophosphamide rather than chlorambucil for initial therapy. (*2B*)**

**7.3.3: We recommend patients be managed conservatively for at least 6 months following the completion of this regimen before being considered a treatment failure if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present (see also Recommendation 7.2.1). (*1C*)**

**7.3.4: Perform a repeat kidney biopsy only if the patient has rapidly deteriorating kidney function (doubling of SCr over 1–2 month of observation), in the absence of massive proteinuria (>15 g/d). (*Not Graded*)**

**7.3.5: Adjust the dose of cyclophosphamide or chlorambucil according to the age of the patient and eGFR. (*Not Graded*)**

**7.3.6: We suggest that continuous daily (noncyclical) use of oral alkylating agents may also be effective, but can be associated with greater risk of toxicity, particularly when administered for >6 months. (*2C*)**

#### BACKGROUND

Three RCTs have shown that monotherapy with oral corticosteroids is not superior to symptomatic therapy alone in IMN. Orally administered akylating agents (cyclophosphamide or chlorambucil), most commonly in conjunction with steroids, are effective in inducing remission and preventing ESRD (Online Suppl Tables 22–25). The toxicity profile suggests that cyclophosphamide might be preferred to chlorambucil.

#### RATIONALE

- There is moderate-quality evidence to recommend a 6-month cyclical regimen of alternating alkylating agents (cyclophosphamide or chlorambucil) plus i.v. pulse and oral corticosteroids (see Table 15 for description of regimen) for initial therapy of IMN meeting the criteria in Recommendation 7.2.1 above. This evidence indicates this treatment is superior to supportive therapy alone in inducing remissions and preventing long-term decline of kidney function, including the need for dialysis, in patients with IMN and persisting nephrotic syndrome. The risks and adverse events associated with the use of cyclophosphamide in IMN are summarized in Table 16.
- Other combined regimens of cyclophosphamide and corticosteroids have also been used. Some omit i.v. methylprednisolone, others use alkylating agent and corticosteroids concurrently, rather than cyclically, for a longer duration.[226–228] However, the long-term efficacy and safety of these regimens are less well-established than the cyclical regimen.[229] The safety and efficacy of i.v. cyclophosphamide-based regimens for treatment of IMN have not been sufficiently evaluated to warrant any recommendations. One small (underpowered) controlled trial in progressive IMN was negative.[230] The evidence is insufficient to make any recommendations regarding the use of i.v. compared to oral cyclophosphamide.
- A complete or partial remission of nephrotic syndrome is associated with an excellent long-term prognosis; therefore, persisting remission of the nephrotic state is an acceptable surrogate end-point to assess overall efficacy of treatment.
- Treated patients may continue to enter complete or partial remission for as long as 12–18 months following completion of the regimen, so it is reasonable to wait this period of time before deciding whether the initial treatment has been unsuccessful (see Recommendations 7.6.1 and 7.6.2), providing that serum albumin levels or kidney function are not deteriorating, and that morbid events have not supervened. During the period of observation, patients should continue to receive ACE-I or ARBs, other antihypertensives, and other supportive therapies as clinically indicated. In comparative studies, cyclophosphamide has a superior safety profile compared to chlorambucil. There is low-quality evidence that cyclophosphamide can lead to more frequent and longer remissions than chlorambucil. Cumulative toxicities of

**Table 15 | Cyclical corticosteroid/alkylating-agent therapy for IMN (the "Ponticelli Regimen")**

| |
|---|
| Month 1: i.v. methylprednisolone (1 g) daily for three doses, then oral methyprednisolone (0.5 mg/kg/d) for 27 days |
| Month 2: Oral chlorambucil (0.15–0.2 mg/kg/d) or oral cyclophosphamide (2.0 mg/kg/d) for 30 days[a] |
| Month 3: Repeat Month 1 |
| Month 4: Repeat Month 2 |
| Month 5: Repeat Month 1 |
| Month 6: Repeat Month 2 |

IMN, idiopathic membranous nephropathy.
[a]Monitor every 2 weeks for 2 months, then every month for 6 months, with serum creatinine, urinary protein excretion, serum albumin, and white blood cell count. If total leukocyte count falls to $<3500/mm^3$, then hold chlorambucil or cyclophosphamide until recovery to $>4000/mm^3$.

**Table 16 | Risks and benefits of the cyclical corticosteroid/alkylating-agent regimen in IMN**

| Risks | Benefits |
|---|---|
| Enhanced risk of opportunistic infection | Prevention of CKD and ESRD |
| Reactivation of viral hepatitis | Avoidance of complications of nephrotic syndrome (thrombosis, accelerated atherogenesis) |
| Alopecia | |
| Gonadal damage (aspermatogenesis, ovulation failure) | Prolongation of life; improved quality of life |
| Hemorrhagic cystitis (cyclophosphamide only) | |
| Neoplasia (myelodysplastic syndrome, acute myelogenous leukemia | |
| Transitional cell carcinoma of the bladder, ureter or pelvis | |
| Toxic hepatitis | |

CKD, chronic kidney disease; ESRD, end-stage renal disease; MN, membranous nephropathy.

alkylating agents can be significant and require careful monitoring by the treating physician. A recent study of the use of cyclophosphamide- or chlorambucil-based regimens in IMN has raised concerns regarding safety, given a reported adverse-event rate that exceeded 80%.[231] This is in contrast to the older long-term RCT of cyclical alkylating agents and steroids, where the regimens were well-tolerated with an acceptably low frequency of serious adverse events.[229,232,233] Risks of this regimen are now known to be increased if alkylating agents are used in patients with reduced renal function, older age, and/or concomitant comorbidities as evidenced in this recent report.

- Since the decline in GFR in IMN is often very gradual, especially in the absence of massive proteinuria, any acceleration of the rate of decline indicates the possibility of a superimposed disease process (such as crescentic glomerulonephritis or acute interstitial nephritis, which is often drug-related) that might dictate a change in treatment approach. A repeat kidney biopsy is necessary to identify these conditions.
- Relapses of nephrotic syndrome occur in about 25% of patients treated with the "Ponticelli" regimen. A similar fraction of patients with spontaneous remissions also will relapse (see treatment of relapses in IMN in Section 7.7).

An open-label RCT utilizing a 6-month course of chlorambucil and steroids in alternating monthly cycles was initiated in the 1980s (see Table 15 for the description of the regimen).[229,232,233] After 10 years of follow-up, 92% of the treated ($n = 42$) and 60% of the control ($n = 39$) patients were alive with normal kidney function ($P = 0.0038$). There was remission in 61% (40% complete remission) and 33% (5% complete remission) in the two groups. In another RCT,[234] this same regimen was compared to one where steroids alone were used for the entire 6-month period (chlorambucil was substituted with oral prednisolone 0.5 mg/kg/d). A significantly higher proportion of patients in the chlorambucil arm were in remission in the first 3 years. The difference was lost at 4 years, probably because of a small number of at-risk cases. The duration of remission was also longer in those treated with chlorambucil. Another RCT[235] compared the same combination of chlorambucil and steroids to one in which chlorambucil had been replaced with oral cyclophosphamide (2.5 mg/kg/d). Remission of nephrotic syndrome was noted with equal frequency in the two arms (82% vs. 93%; $P = 0.116$) (Online Suppl Tables 22–25). However, severe adverse effects leading to discontinuation of therapy occurred more frequently in the chlorambucil group compared to the cyclophosphamide group (12% vs. 4%). Other small trials and several meta-analyses and systematic reviews have indicated that the alkylating agents are associated with a higher remission rate, although the long-term benefits on kidney function could not be demonstrated.[204,236–240]

A more recent open-label study[204] gave similar results to the initial trials of Ponticelli. Quality of life, as measured by a visual analog scale, was significantly better in the treatment group throughout the follow-up period. The complication rate was not different in the two groups.

One small open-label RCT ($N = 29$) examined the efficacy of cyclophosphamide for 12 months plus moderate-dose steroids in IMN patients considered to be at high risk of progression (based on urinary IgG and urine β2 microglobulin levels) that previously indicated these patients would have an increase in SCr levels by $>25\%$, and reach a SCr $>1.5$ mg/dl ($>133$ μmol/l) or have an increase of $>50\%$ from baseline. The study compared an early-start group (urinary abnormalities at baseline) vs. the group started only after SCr had risen by $>25$–$50\%$. They found a more rapid remission in proteinuria in early-start patients, but no differences between the two groups in overall remission rates, SCr levels, average proteinuria, relapse rates, or adverse events after 6 years.[241] This study agrees with earlier observational studies from the same authors, and supports an initial conservative treatment approach in IMN patients. However, toxicity with this specific approach has been reported to be substantially increased by both prolonging its duration and by selecting patients with impaired kidney function (SCr $>1.5$ mg/dl [$>133$ μmol/l]). The overall evidence for this approach is moderate.[241–243] The adverse effects of alkylating-cytotoxic agents are substantial, and include gonadal toxicity, bladder carcinoma, bone marrow hypoplasia, leukemogenesis, and serious opportunistic infections (Table 16). The balance of risk and benefit may be altered by patient-dependent factors, such as age and comorbidities. Table 17 lists some of the contraindications to

**Table 17 | Contraindications to the use of the cyclical corticosteroid/alkylating-agent regimen in IMN**

| |
|---|
| Untreated infection (HIV, hepatitis B and C, tuberculosis, fungal infection, etc.) |
| Neoplasia (lung, skin [except squamous cell]), breast, colon, etc. |
| Urinary retention |
| Inability to comply with monitoring |
| Pre-existing leukopenia ($<4000$ leukocytes/mm$^3$) |
| SCr $>3.5$ mg/dl ($>309$ μmol/l) |

HIV, human immunodeficiency virus; MN, membranous nephropathy; SCr, serum creatinine.

the use of the cyclical alkylating-agent/steroid regimen. Cyclophosphamide has a more favorable side-effect profile compared to chlorambucil. The available evidence does not suggest a beneficial effect of i.v. cyclophosphamide on the course of IMN, and its use is not recommended. Based on limited pharmacokinetic data, the dose of alkylating agents should be reduced when GFR declines, in order to avoid bone-marrow toxicity. Azathioprine does not favorably influence the course of IMN, either alone or with corticosteroids.[244–246]

Evidence from studies of immunosuppressed patients with diseases other than IMN indicates that patients on corticosteroids should receive prophylaxis for *Pneumocystis jiroveci* with trimethoprim-sulfamethoxazole. Those at risk for osteoporosis (e.g., elderly or postmenopausal females) should also receive bisphosphonates, unless these are contraindicated, such as an eGFR $<30$ ml/min per 1.73 m$^2$ (see also Chapter 1).

Deterioration of kidney function in IMN is usually slow, and development of advanced CKD most often takes several years of persistent high-level proteinuria. A rapid deterioration of kidney function in the absence of massive proteinuria (e.g., $>15$ g/d) usually indicates the superimposition of another pathologic process, such as acute bilateral renal-vein thrombosis, a superimposed crescentic GN, or acute interstitial nephritis. A repeat kidney biopsy is the most appropriate tool to identify any pathology changes that may require a change in treatment. In patients with severe proteinuria ($>10$–$15$ g/d), however, an acute decline in kidney function ($<50\%$ reduction in GFR) can be seen, possibly as a result of hemodynamic changes. This usually reverses with remission of the nephrotic state, and hence does not require a change in the therapeutic approach.

Prospective controlled studies of the use of immunosuppressive agents for treatment of patients with IMN and impaired renal function (e.g., eGFR 30–60 ml/min per 1.73 m$^2$) are very limited. The current evidence is insufficient to make any specific recommendation in this group of patients. The hematological toxicity of alkylating agents can be heightened in subjects with impaired renal function, and the nephrotoxicity of CNI in those with already impaired renal function remains a concern. These agents should be used with caution in patients with IMN and chronically reduced renal function.

#### RESEARCH RECOMMENDATIONS

- Clinical, pathological, and biological markers are needed to identify patients who will benefit most from therapy, and also to avoid unnecessary drug exposure risk to the rest. There is a lack of evidence to guide ideal dosing to minimize drug toxicity, especially the gonadal and bladder toxicity of cyclophosphamide.
- RCTs are needed to compare alkylating agents or CNIs to MMF, rituximab, or adrenocorticotropic hormone (ACTH) as initial therapy of IMN with nephrotic syndrome (with or without impaired renal function at diagnosis).
- Studies are needed to determine the value of renal pathology and urinary biomarkers in predicting prognosis and/or treatment responsiveness.
- Serial anti-PLA2R antibodies and urinary biomarkers (such as urinary IgG, β2-microglobulin) should be measured in natural history studies, and in all future treatment trials for IMN, in order to assess their value in determining spontaneous remission, response to treatment, and prognosis.

### *7.4: Alternative regimens for the initial therapy of IMN: CNI therapy*

**7.4.1: We recommend that cyclosporine or tacrolimus be used for a period of at least 6 months in patients who meet the criteria for initial therapy (as described in Recommendation 7.2.1), but who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen. (See Table 18 for specific recommendations for dosage during therapy.) (*1C*)**

**7.4.2: We suggest that CNIs be discontinued in patients who do not achieve complete or partial remission after 6 months of treatment. (*2C*)**

**7.4.3: We suggest that the dosage of CNI be reduced at intervals of 4–8 weeks to a level of about 50% of the starting dosage, provided that remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 months. (*2C*)**

**7.4.4: We suggest that CNI blood levels be monitored regularly during the initial treatment period, and whenever there is an unexplained rise in SCr ($>20\%$) during therapy. (*Not Graded*) (See Table 18 for specific CNI-based regimen dosage recommendations.)**

#### RATIONALE

There is low- to moderate-quality evidence to support a recommendation for CNI therapy (cyclosporine or

**Table 18 | CNI-based regimens for IMN**

*Cyclosporine*: 3.5–5.0 mg/kg/d given orally in two equally divided doses 12 hours apart, with prednisone 0.15 mg/kg/d, for 6 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity (Sandimmune®, Neoral®, and generic cyclosporin considered equivalent).

*Tacrolimus*: 0.05–0.075 mg/kg/d given orally in two divided doses 12 hours apart, without prednisone, for 6–12 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity.

IMN, idiopathic membranous nephropathy.
Note: Monitoring of blood levels during therapy is discussed in the text.

tacrolimus) as an alternative to cyclical corticosteroid/alkylating-agent therapy in IMN (Online Suppl Tables 28–31). There is low-quality evidence to suggest that a minimum of 6 months therapy with CNI should be employed, which should be continued for at least 6–12 months if there is a beneficial effect on proteinuria, based on the high relapse rates if therapy is discontinued early. The suggested dosage regimens for CNIs in IMN are given in Table 18.

### Cyclosporine

Early uncontrolled studies suggested an initial benefit, but a high relapse rate, with cyclosporine in IMN.[247,248] In a single-blind, randomized controlled study, 51 patients with steroid-resistant MN were treated with low-dose prednisone plus cyclosporine and compared to placebo plus prednisone.[249] Complete and partial remissions in proteinuria were seen in 69% of the patients, but the relapse rate when cyclosporine was discontinued was high, approximately 45% of the end of 1 year. Observational data from the German Cyclosporine in NS Study Group suggests that prolonging cyclosporine treatment for 1 year results in higher (34%) complete remission at 1 year, and more sustained rate of remissions.[144] Current recommendations, for patients who respond to cyclosporine, are to continue treatment for at least 1 year.[182] Prolonged low-dose cyclosporine ($\sim$1.5 mg/kg/d) could be considered for long-term maintenance of patients who achieve a complete or partial remission, especially in patients at high risk for relapse.[250] Regular monitoring of cyclosporine blood concentration as well as kidney function is often recommended, according to data accumulated from experiences in kidney transplantation. There is no evidence in patients with IMN to indicate optimal cyclosporine blood levels. Cyclosporine levels usually regarded as nontoxic are 125–175 ng/ml [104–146 nmol/l] (C0, trough level) or 400–600 ng/ml [333–500 nmol/l] (C2, 2-hour post-dose level).[182] Online Suppl Tables 28–31 summarize studies using cyclosporine.[208,247,251–253]

There has been only one small RCT using cyclosporine in patients with high-grade proteinuria and progressive kidney failure.[251] At the time of initiation of treatment, mean CrCl was 55 ml/min, and mean proteinuria 11 g/d. After 12 months of treatment with cyclosporine, there was a significant reduction in proteinuria, and the rate of loss of kidney function decreased from $-2.4$ to $-0.7$ ml/min/mo, whereas, in those receiving placebo, there was no change: $-2.2$ to $-2.1$ ml/min/mo ($P < 0.02$). This improvement was sustained in $\sim$50% of the patients for up to 2 years after cyclosporine was stopped.[208,247,251–253]

### Tacrolimus

In an RCT using tacrolimus monotherapy in IMN, patients with normal kidney function ($n = 25$) and mean proteinuria ($\sim$8 g per 24 hours) received tacrolimus (0.05 mg/kg/d) over 12 months with a 6-month taper, and were compared to conservatively treated controls ($n = 23$).[254] After 18 months, the probability of remission was 94% in the tacrolimus group but only 35%, in the control group. Six patients in the control group and only one in the tacrolimus group reached the secondary end-point of a 50% increase in SCr.[254] Almost half of the patients relapsed after tacrolimus was withdrawn, similar to patients treated with cyclosporine. There is only low-quality evidence to support prolonged use of low-dose tacrolimus to maintain remission; the safety of this approach is uncertain.[226,227,229,230,233–235,238,240,242,243,255–258]

### Comparison Studies of CNIs vs. Alkylating Agents

An RCT in IMN patients of Asian ancestry has compared tacrolimus ($n = 39$) for 6–9 months to oral cyclophosphamide ($n = 34$) for 4 months (both groups received prednisone tapered off over 8 months).[259] The results indicated no difference between treatments in terms of partial or complete remission of proteinuria (79% vs. 69%), or adverse events at 12 months of follow-up. Relapses occurred in approximately 15% of both groups. These data support the use of tacrolimus, short-term (with or without concomitant steroids) as an alternative to an oral alkylating-agent regimen.[254] However, the long-term efficacy of a tacrolimus-based regimen for IMN remains uncertain.[259]

### Use of CNIs in Patients with Reduced Renal Function

The nephrotoxicity of CNIs can be enhanced in the presence of pre-existing renal functional impairment. Cyclophosphamide-based regimens may be preferred in this situation, but dose reduction of the alkylating agent is advisable. There is weak evidence for preferring CNI or alkylating agent–based regimens in this group of patients. An RCT examining this controversial area is in progress (ISRCTN99959692). The use of other agents, including rituximab, MMF, and/or ACTH in this group of subjects is worthy of further study, but the evidence is currently insufficient to make any specific recommendations. The evidence concerning the value of quantification of the degree of interstitial fibrosis and/or tubular atrophy in renal biopsy as a guide for the choice of treatment regimens for IMN is presently insufficient to make any recommendations.

**RESEARCH RECOMMENDATIONS**

- RCTs are needed in IMN to assess the efficacy, safety, and risks of long-term CNI therapy.
- Studies are needed to determine the value of monitoring blood levels of CNIs during therapy of IMN.

### *7.5: Regimens not recommended or suggested for initial therapy of IMN*

**7.5.1: We recommend that corticosteroid monotherapy not be used for initial therapy of IMN. (*1B*)**

**7.5.2: We suggest that monotherapy with MMF not be used for initial therapy of IMN. (*2C*)**

**BACKGROUND**

A number of treatments, other than combined therapy of corticosteroid/alkylating agents or CNIs, have been tried as initial therapy in IMN (meeting the criteria outline in Recommendation 7.2.1). However, none of these have been shown in appropriately sized RCTs to be consistently effective and safe, and therefore are not recommended as "first-line" initial therapy in IMN.

**RATIONALE**

**Corticosteroid Monotherapy**

There is moderate-quality evidence to recommend not using corticosteroid monotherapy for inducing remissions or delaying the onset of progressive CKD in IMN. An early study reported that a 2- to 3-month course of high-dose, alternate-day prednisone resulted in a significant reduction compared to placebo in progression to kidney failure, although there was no sustained effect on proteinuria.[260] A subsequent RCT in patients with IMN, using an identical corticosteroid regimen vs. placebo, showed no improvement during drug exposure, or over a 3-year follow-up in either proteinuria or kidney function (SCr). An additional RCT comparing a 6-month course of prednisone given on alternate days ($n = 81$) to no specific treatment ($n = 77$) showed no significant benefit of corticosteroid treatment alone, in either induction of remission or preservation of kidney function, even after the data were adjusted to include only patients with proteinuria at entry $> 3.5$ g per 24 hours.[261] Nevertheless, retrospective studies conducted in subjects of Asian (Japanese) ancestry have suggested possible benefits for steroid monotherapy.[262] These analyses could be confounded by unmeasured variables and failure to subject patients to an observation period prior to initiation of therapy. The negative RCTs mentioned included too few Asian subjects for subanalysis.

**MMF** (Online Suppl Tables 32–34)

MMF as initial therapy in IMN has not been shown in RCTs to be consistently effective for inducing remissions or delaying the onset of progressive CKD. Thirty-two patients with IMN and impairment of kidney function (SCr $> 1.5$ mg/dl [$> 133$ μmol/l]) were treated with oral MMF 1 g twice daily for 12 months, in combination with corticosteroids, and compared to 32 patients—historical controls treated for the same duration with oral cyclophosphamide in combination with corticosteroids (cyclophosphamide; 1.5 mg/kg/d).[263] Cumulative incidences of remission of proteinuria at 12 months were 66% with MMF vs. 72% with cyclophosphamide ($P = 0.3$). Adverse effects occurred at a similar rate in the two groups, but relapses were very much more common with MMF, and relapses were noted even while on treatment.[263]

There have been two small RCTs that have compared MMF plus steroids to the Ponticelli regimen of an alkylating agent (cyclophosphamide or chlorambucil) plus steroids.

In one study of 20 low risk-of-progression adults that were all drug-naïve with nephrotic syndrome due to IMN, the efficacy of a regimen of MMF plus corticosteroids was compared to a modified Ponticelli regimen (with chlorambucil).[264] There was no significant difference in the proportion of patients achieving remission: 64% with MMF, 67% with the modified Ponticelli regimen. The frequency of relapses and incidence of infections were similar in both groups. There was more leucopenia with the modified Ponticelli regimen, compared to MMF. In the other small RCT[264A] 21 drug naïve IMN patients, MMF plus steroids was compared to the Ponticelli regimen. The complete or partial response rate was 64% (7/11) in the MMF versus 80% (8/10) with the alkylating/steroid regimen. In a short follow-up period no patience relapsed in the MMF group and only one in the Ponticelli regimen (NS).

By contrast, in a pilot RCT in a low risk-of-progression adults that were all drug naïve with nephrotic syndrome due to IMN, the efficacy of a MMF based monotherapy regimen (no concomittantt steroids) was compared to conservative therapy alone. This study randomized 36 patients with IMN and nephrotic syndrome to conservative therapy (RAS blockade, statins, low-salt and low-protein diet, and diuretics) plus MMF (2 g/d, without concomitant steroids) ($n = 19$) or conservative therapy alone ($n = 17$) for 12 months.[265] The probability of a complete or partial remission did not differ between the two groups after 12 months.

Thus, while a regimen of MMF plus steroids might have comparable efficacy to the standard regimen of cyclical alkylating agents and steroids, the present evidence is conflicting, of low quality, and only short-term. The high frequency of relapses with MMF substantially reduces enthusiasm regarding this approach to therapy of IMN.[263] Monotherapy with MMF appears to be ineffective.[265]

**Rituximab**

As yet, there are no RCTs using rituximab for initial therapy of IMN, although large observational studies have provided encouraging data. A pilot study used four weekly doses of rituximab (375 mg/m$^2$) in eight nephrotic patients with IMN and followed them for 1 year.[266,267] Proteinuria significantly decreased at 12 months, and kidney function remained stable

in all patients. Adverse effects were reported as mild. An observational study from the same investigators suggested that rituximab is likely to be most effective in patients with minimal degrees of tubulointerstitial injury.[268]

A prospective observational study in 15 patients with IMN and proteinuria >4 g per 24 hours—despite ACE-I/ARB use for >3 months and systolic blood pressure <130 mm Hg—has been reported.[269] At 6 months, patients who remained with proteinuria >3 g per 24 hours, and in whom total CD19+ B-cell count was >15 cells/μl, received a second identical course of rituximab. Baseline proteinuria of 13.0 ± 5.7 g per 24 hours (range 8.4–23.5) decreased to 9.1 ± 7.4 g, 9.3 ± 7.9 g, 7.2 ± 6.2 g, and 6.0 ± 7.0 g per 24 hours (range 0.2–20) at 3, 6, 9, and 12 months, respectively (mean ± SD). The mean decline in proteinuria from baseline to 12 months was 6.2 ± 5.1 g/d and was statistically significant ($P = 0.002$). Rituximab was well-tolerated, and was effective in reducing proteinuria in some patients with IMN. The complete and partial remission rate was almost 60%, higher than would have been expected based on known spontaneous remission rates.

Another observational study used circulating B-cell counts to guide dosing, significantly reducing total dose of rituximab.[270] At 1 year, the proportion of patients who achieved disease remission was identical to that of 24 historical patients who were given a standard rituximab protocol of four weekly doses of 375 mg/m$^2$.

More recently, another prospective observational study in 20 patients with IMN and baseline persistent proteinuria >5.0 g/d received rituximab (375 mg/m$^2$ weekly for four doses), with retreatment at 6 months regardless of proteinuria response.[271] Baseline proteinuria of 11.9 g/d decreased to 4.2 g/d and 2.0 g/d at 12 and 24 months, respectively, while CrCl increased from 72.4 to 88.4 ml/min per 1.73 m$^2$ at 24 months. Among 18 patients who completed 24 months of follow-up, four achieved complete remission, 12 achieved partial remission (complete plus partial remission of 80%). One patient relapsed during follow-up. More than 50% of the patients in this pilot trial had not responded to prior therapy. No short-term toxicity of rituximab was observed. This study also reinforced the observation, made with alkylating agent/corticosteroid therapy that proteinuria declines gradually, and many months may be required for proteinuria to reach its nadir.

An RCT is needed to confirm these encouraging results, but the findings indicate a high probability that rituximab has beneficial actions on the disease process. The long-term relapse rate is unknown but in the short term, it appears to be low.[271] Due to the lack of RCTs, no specific recommendations can be made regarding the use of rituximab for initial therapy of IMN.

**ACTH** (Online Suppl Tables 26–27)

One observational study and one small RCT provide preliminary, low-quality evidence for the use of long-acting ACTH as initial therapy in IMN.

Depot synthetic ACTH (Synacthen®) administered for 1 year in an observational study decreased proteinuria in patients with IMN.[272,273] More recently, a small open-label pilot RCT compared i.v. methylprednisolone and oral corticosteroids plus a cytotoxic agent ($n = 16$) vs. synthetic ACTH ($n = 16$) as initial therapy in IMN, and found them to be of similar efficacy, at least over short-term follow-up.[274] Side-effects associated with the use of synthetic ACTH included dizziness, glucose intolerance, diarrhea, and the development of bronze-colored skin, which resolved after the end of therapy. Larger, more-powerful RCTs are required before synthetic ACTH can be recommended for initial therapy of IMN. Preliminary reports of uncontrolled studies showing a similar effect of native, intact (porcine) ACTH in a gel formulation have very recently appeared, but no RCTs have yet been conducted with this formulation of ACTH. Until broader and more powerful RCTs are performed, no recommendations can be made for the use of ACTH (synthetic or intact) for initial therapy of IMN.

**RESEARCH RECOMMENDATIONS**

- Larger RCTs with longer follow-up are needed to test MMF and corticosteroids vs. established regimens as initial therapy.
- An RCT is needed to compare rituximab to cyclical corticosteroid/alkylating-agent therapy or CNIs for initial treatment of IMN with nephrotic syndrome.
- An RCT is needed to compare synthetic or native (intact, porcine) ACTH in gel form with cyclical corticosteroid/alkylating-agent therapy or CNIs for initial treatment of IMN with nephrotic syndrome.

### *7.6: Treatment of IMN resistant to recommended initial therapy*

**7.6.1: We suggest that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI. (*2C*)**

**7.6.2: We suggest that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent/steroid-based therapy. (*2C*)**

**BACKGROUND**

The results of trials using an initial cyclical treatment alternating steroids and an alkylating agent or an initial CNI have shown excellent kidney survival and a high rate of remission, even in the long term.[204,233–235,249,254,275] However, 9–28% of patients are treatment-resistant (fail to achieve a remission) to steroids and alkylating-agent therapy, and approximately 25% of patients are treatment-resistant to CNI therapy. Patients who fail to achieve a complete or partial remission of nephrotic syndrome should be considered for additional therapy if no contraindication to such treatment exists. The response to alternative therapeutic strategies in treatment-resistant disease cannot presently be predicted with any degree of accuracy. Failure to respond to one

regimen does not reliably predict a failure to respond to another regimen.

#### RATIONALE

Unresponsiveness to initial therapy is observed in 10–30% of patients following a complete course of treatment. There is low-quality evidence to suggest that failure to respond to one regimen does not reliably predict failure to respond to another regimen.

If there is no remission following cyclical treatment with an alkylating agent/corticosteroid regimen, an alternative is to use CNIs. Cyclosporine is the best studied, although tacrolimus has also been shown to induce a high initial rate of remission, comparable to the overall response rate observed with combined steroids and alkylating agents, particularly after a prolonged administration and associated with moderate doses of steroids.[249]

Many treatment-resistant patients also have deteriorating kidney function. There has been only one small RCT using cyclosporine in patients with high-grade proteinuria ($>10$ g/d) and progressive kidney failure (initial CrCl approximately 55 ml/min). It showed a significant reduction in the rate of loss of kidney function with cyclosporine.[251] For those patients who receive a CNI for initial therapy and show no response after a period of at least 6 months, we suggest treatment with an alkylating agent–based regimen, using the same regimen as for initial therapy. However, adverse effects of treatment may be more frequent in patients with established or progressing kidney impairment. A randomized trial examining the relative safety and efficacy of conservative, alkylating agent or CNI therapy in this group of subjects with IMN is in progress in the UK (ISRCTN 99959692), the results of which could alter recommendations in this area.

In patients with kidney impairment,[243,251] bone marrow is more susceptible to the toxic effect of alkylating agents, and there may also be heightened susceptibility to infections. Therefore, it is recommended not to exceed daily doses for chlorambucil of 0.1 mg/kg and cyclophosphamide of 1.5 mg/kg in patients with SCr $>2.0$ mg/dl [$>177$ μmol/l][276] and to limit the total duration of therapy to $<6$ months. A higher incidence of side-effects with this regimen is to be expected. The use of CNIs in this group of subjects may also be associated with worsening renal function due to nephrotoxicity.

The roles of MMF, rituximab, or ACTH in patients resistant to both alkylating agent–based and CNI-based regimens remain undefined; there have been no RCTs.[111,205,263,265,272,274,277]

Additional causative factors should be considered when there is deteriorating renal function in IMN. Rapidly progressive renal failure may occur from an acute hypersensitivity interstitial nephritis in IMN patients receiving diuretics, antibiotics, or nonsteroidal anti-inflammatory drugs. A superimposed crescentic GN associated with anti-GBM antibodies or ANCA can also rarely develop in those patients with high-grade proteinuria.[278,279] Kidney biopsy is often necessary to confirm the diagnosis, and complete recovery of kidney function may follow a course of high-dose oral prednisone in those with acute hypersensitivity interstitial nephritis or intensive immunosuppression in those with crescentic disease (see Chapters 13 and 14).

Finally, pulses of i.v. methylprednisolone as monotherapy should not be used for treatment of resistant disease, unless the steady evolution of IMN is interrupted by a rapidly progressive course, and an extracapillary (crescentic) GN superimposed on IMN is shown by kidney biopsy.

#### RESEARCH RECOMMENDATIONS

- RCTs are needed to assess risks and benefits of rituximab, MMF, and ACTH in the treatment of IMN patients resistant to first-line therapy.
- RCTs are needed to assess risks and benefits of the cyclical alkylating agent/corticosteroid regimen or with a CNI regimen in IMN patients with impaired or deteriorating kidney function.

### *7.7: Treatment for relapses of nephrotic syndrome in adults with IMN*

**7.7.1: We suggest that relapses of nephrotic syndrome in IMN be treated by reinstitution of the same therapy that resulted in the initial remission. (*2D*)**

**7.7.2: We suggest that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy (see Recommendation 7.3.1), the regimen be repeated only once for treatment of a relapse. (*2B*)**

#### BACKGROUND

Clinical trials using cyclical treatment of alternating steroids and alkylating agents or CNIs in IMN have shown excellent kidney survival in those subjects with complete or partial remission, even in the long term. However, relapses of nephrotic syndrome occur in 25–30% of patients within 5 years of discontinuation of therapy with alkylating agents, and 40–50% of patients within 1 year of discontinuation of CNIs. For those patients who show a complete or partial remission and then a relapse of nephrotic syndrome, a second course of treatment can be given.[280]

#### RATIONALE

There is very low–quality evidence to suggest that responses to re-treatment of a relapse are similar to those observed after the first treatment.

There is moderate-quality evidence to suggest that there are significant risks of neoplasia induction, opportunistic infections, and gonadal damage when alkylating agents are used for an extended period.

If there is a relapse of nephrotic syndrome in IMN following remission, reintroduction of a corticosteroid/alkylating-agent regimen or CNIs will often, but not uniformly, induce another remission.

Most data on repeated courses of immunosuppressive therapy relate to patients in whom relapses occurred after a partial remission, and with normal kidney function.[281,282] There are no RCTs to guide therapy for patients with IMN who relapse after a first course of therapy and have kidney impairment.[283]

Cancer induction is a major concern when alkylating agents are used for an extended period. Cumulative doses of more than 36 g of cyclophosphamide (equivalent to 100 mg daily for 1 year) were associated with a 9.5-fold increased risk of bladder cancer, in patients with Wegener granulomatosis. Extended courses have also been associated with an increased risk of lymphoproliferative, myelodysplastic, and leukemic disorders.[284] Because of this, repeated courses (more than two) of cyclical alkylating-agent therapy are not advised.

Mild relapses (redevelopment of subnephrotic proteinuria after a complete remission) do not require any specific treatment, and should be managed conservatively. Blood pressure should be kept $<125/75$ mm Hg and an ACE-I or ARB should be used as the first line of treatment (see Chapter 1).

Other agents such as MMF, rituximab, or ACTH might be considered for treatment of relapses in IMN. There is some observational evidence that rituximab may be beneficial in patients relapsing whenever the dose of CNI is reduced (CNI dependency),[285] but the evidence is currently insufficient to make any specific recommendations.

#### RESEARCH RECOMMENDATION

- RCTs are needed to examine the efficacy and safety of MMF, rituximab, or ACTH in relapsing patients with IMN.

### *7.8: Treatment of IMN in children*

**7.8.1: We suggest that treatment of IMN in children follows the recommendations for treatment of IMN in adults. (*2C*) (See Recommendations 7.2.1 and 7.3.1.)**

**7.8.2: We suggest that no more than one course of the cyclical corticosteroid/alkylating-agent regimen be given in children. (*2D*)**

#### BACKGROUND

IMN in children is uncommon, and usually presents as nephrotic syndrome or asymptomatic proteinuria. IMN contributes less than 5% of cases of nephrotic syndrome in children.[286,287] Most cases ($>75\%$) of MN in children are secondary to chronic viral infections (e.g., hepatitis B), autoimmune diseases (SLE, thyroiditis), or drugs.

#### RATIONALE

There is low-quality evidence to suggest children with IMN should be treated with the same regimens as adults, with appropriate dosage modification.

Most knowledge of the natural history of IMN in children, treatment options, and long-term outcome is derived from small, uncontrolled observational studies[288] that suggest a relatively high spontaneous remission rate, and a low incidence of ESRD. Children with IMN will not usually require more than conservative therapy, unless they are severely symptomatic, as they seem to have a higher spontaneous remission rate than adults. For children with severe symptomatic disease, the same drug combinations used in adults are suggested, with appropriate dosage adjustments.[289] Most of these protocols use chlorambucil 0.15–0.2 mg/kg/d or cyclophosphamide 2 mg/kg/d for 8–12 weeks, with alternate-day prednisone. The risk for gonadal toxicity with chlorambucil and cyclophosphamide is greater in boys than in girls, and is related to both the duration and total dose of treatment.[290] The cumulative dose of cyclophosphamide should not exceed 200 mg/kg in order to avoid gonadal toxicity.

There are no data on the use of CNIs in children with IMN; the use of CNIs is based only on the evidence from adults RCTs. MMF, rituximab, or ACTH has not been studied in children (see also Table 19).

#### RESEARCH RECOMMENDATION

- The absence of RCTs of treatment of IMN in children makes treatment recommendations and suggestions moot. RCTs are needed to compare the use of alkylating agents and CNIs for initial therapy of IMN children with nephrotic syndrome.

### *7.9: Prophylactic anticoagulants in IMN*

**7.9.1: We suggest that patients with IMN and nephrotic syndrome, with marked reduction in serum albumin ($<2.5$ g/dl [$<25$ g/l]) and additional risks for thrombosis, be considered for prophylactic anticoagulant therapy, using oral warfarin. (*2C*)**

#### BACKGROUND

IMN seems to constitute a special hazard for venous thromboembolism and spontaneous vascular thrombosis (such as deep venous thrombosis or pulmonary artery embolism/thrombosis), even more so than other causes of nephrotic syndrome (see also Chapter 1).[301–303] This may also apply to other types of primary GN associated with severe nephrotic syndrome; the evidence base, however, is lacking. There have been no RCTs of prophylactic anticoagulation in IMN with nephrotic syndrome.[301–303]

#### RATIONALE

There is very low–quality evidence to suggest the use of prophylactic anticoagulation with warfarin in patients with

**Table 19 | Pediatric MN studies**

| Author | N | NS | Steroids | Other immunosuppression | Remission | Persistent disease | CRI | ESRD |
|---|---|---|---|---|---|---|---|---|
| Habib *et al.*[291] | 50 | 72% | 54% | 44% (mechlorethamine and chlorambucil) | 52% | 38% | ? | 10% |
| Olbing *et al.*[292] | 9 | 78% | 89% | 22% cyclophosphamide, 11% azathioprine | 33% | 33% | 33% | 0% |
| Chan and Tsao[293] | 10 | 80% | 100% | None | 50% | 40% | 0% | 10% |
| Trainin *et al.*[294] | 14 | 79% | 79% | 57% "cytotoxics" | 43% | 29% | 7% | 21% |
| Latham *et al.*[295] | 14 | 100% | ⩽93% | ⩽93%: cyclophosphamide | 29% | 50% | 7% | 14% |
| Ramirez *et al.*[296] | 22 | 82% | 50% | 5% azathioprine + cyclophosphamide, 5% chlorambucil | 27% | 45% | 23% | 5% |
| Tsukahara *et al.*[297] | 12 | 25% | 42% | 17% cyclophosphamide | 67% | 33% | 0% | 0% |
| Lee *et al.*[298] | 19 | 58% | 84% | 16% cyclosporine | 68% | 16% | 5% | 11% |
| Chen *et al.*[299] | 13 | 38% | 77% | 38% CNI, 23% azathioprine, or MMF | ? | 61% | 23% | 0% |
| Valentini *et al.*[300] | 12 | 75% | 83% | 58% cyclophosphamide | 75% | 17% | 8% | 0% |

CRI, chronic renal insufficiency; ESRD, end-stage renal disease; MN, membranous nephropathy; MMF, mycophenolate mofetil.
With kind permission from Springer Science+Business Media: Pediatr Nephrol. Membranous nephropathy in children: clinical presentation and therapeutic approach. 2010; 25:1419–1428. Menon S, Valentini RP[288]; accessed http://www.springerlink.com/content/2222k3x102551528/fulltext.pdf.

IMN and severe nephrotic syndrome. However, based on Markov modeling of anticipated benefits and risks derived from observational studies, prophylactic anticoagulation might be considered when the serum albumin concentration is $<2.0$–$2.5$ g/dl ($<20$–$25$ g/l) with one or more of the following: proteinuria $>10$ g/d; BMI $>35$ kg/m$^2$; prior history of thromboembolism; family history of thromboembolism with documented genetic predisposition; NYHA class III or IV congestive heart failure; recent abdominal or orthopedic surgery; prolonged immobilization.[301–303] Treatment with warfarin should always be preceded by a short period of treatment with heparin (fractionated or unfractionated) in sufficient dosage to obtain prolongation of the clotting time. Dosage adjustments for fractionated heparin may be required if kidney function is impaired. Due to insufficient experience with the use of newer oral or parenteral anticoagulants in nephrotic syndrome, no recommendations can be made regarding their use for prophylaxis of thrombosis. The duration of prophylactic anticoagulation needed for optimal benefit compared to risk is not known, but it seems reasonable to continue therapy for as long as the patient remains nephrotic with a serum albumin $<3.0$ g/dl ($<30$ g/l).

## RESEARCH RECOMMENDATION

- An RCT is needed of prophylactic warfarin in patients with nephrotic syndrome with/without additional risk for thromboembolism in IMN patients.

## DISCLAIMER

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## SUPPLEMENTARY MATERIAL

*Supplementary Table 22:* Evidence profile of RCTs examining alkylating agents plus steroid treatment vs. control in patients with membranous nephropathy.
*Supplementary Table 23:* Existing systematic review on alkylating agents vs. control for idiopathic membranous nephropathy in adults with nephrotic syndrome.
*Supplementary Table 24:* Summary table of RCTs examining alkylating agents plus steroid treatment vs. control in patients with membranous nephropathy (categorical outcomes).
*Supplementary Table 25:* Summary table of RCTs examining alkylating agents plus steroid treatment vs. control in patients with membranous nephropathy (continuous outcomes).
*Supplementary Table 26:* Summary table of RCTs examining alkylating agents plus steroid treatment vs. ACTH in patients with membranous nephropathy (categorical outcomes).
*Supplementary Table 27:* Summary table of RCTs examining alkylating agents plus steroid treatment vs. ACTH in patients with membranous nephropathy (continuous outcomes).
*Supplementary Table 28:* Evidence profile of RCTs examining CsA/TAC treatment vs. control for idiopathic membranous nephropathy.
*Supplementary Table 29:* Existing systematic reviews on CsA/TAC treatment vs. placebo for idiopathic membranous nephropathy in adults with nephrotic syndrome.
*Supplementary Table 30:* Summary table of RCT examining CsA/TAC treatment vs. control for idiopathic membranous nephropathy (categorical outcomes).
*Supplementary Table 31:* Summary table of RCT examining CsA/TAC treatment vs. control for idiopathic membranous nephropathy (continuous outcomes).
*Supplementary Table 32:* Evidence profile of RCTs examining MMF treatment vs. control for idiopathic membranous nephropathy in adults with nephrotic syndrome.
*Supplementary Table 33:* Summary table of RCTs examining MMF treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome (categorical outcomes).
*Supplementary Table 34:* Summary table of RCTs examining MMF treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome (continuous outcomes).
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/GN.php