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# Management of Membranous Nephropathy in Asia

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**Key Words**
Membranous nephropathy · Management · Prognosis · Traditional Chinese medicine

**Abstract**
***Background:*** Membranous nephropathy (MN) is the most common cause of nephrotic syndrome (NS) in adults, accounting for about 20.0% of all NS cases. With an increasing prevalence, especially in the elderly, it has received great attention in Asia. ***Summary:*** Recently, the prevalence of idiopathic MN (IMN) has significantly increased among the elderly people in Asia and other places in the world. Although the exact mechanism of IMN remains unveiled, the identification of new antigens such as PLA2R and THSD7A has greatly enhanced our understanding of its pathogenesis. However, consensus has not yet been reached for the treatment of IMN in Asia. For example, there are many choices of immunosuppressive agents, including corticosteroid monotherapy, corticosteroids combined with cytotoxic agents [such as alkylating agents, calcineurin inhibitors or mycophenolate mofetil (MMF)] or traditional Chinese medicine (triptolide, Shenqi and other Chinese herbal soups). Patients with IMN in Asia often have a favorable prognosis, and progression to end-stage renal disease is relatively uncommon compared to other populations. ***Key Messages:*** The prevalence of MN has significantly increased in the last years. The treatment strategies for IMN have not reached consensus in Asia. Traditional Chinese medicine is generally preferred by the Chinese, and compelling results have been reported recently. ***Facts from East and West:*** (1) The prevalence of IMN is increasing worldwide, particularly in elderly patients, and has been reported in 20.0–36.8% of adult-onset NS cases. The presence of anti-PLA2R antibodies in serum or PLA2R on renal biopsy is the most predictive feature for the diagnosis of IMN and is used in both the East and West; however, appropriate screening to rule out secondary causes should still be performed. (2) Several observational (nonrandomized) Asian studies indicate a good response to corticosteroids alone in IMN patients, although no randomized controlled trials have been done in Asian membranous patients at high risk of progression. Corticosteroid monotherapy has failed in randomized controlled trial studies in Western countries and is therefore not recommended. (3) Cyclophosphamide is the most commonly prescribed alkylating agent in Europe and China. Also, chlorambucil is still used in some Western coun-

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tries, particularly in Europe. In North America, calcineurin inhibitors are the more common first-line treatment. (4) Cyclosporine is predominantly used as monotherapy in North America, although KDIGO (Kidney Disease: Improving Global Outcomes) and Japanese guidelines still recommend a combination with low-dose corticosteroids. Clinical studies both in Asia and Europe showed no or little effects of monotherapy with MMF compared to standard therapies. (5) There are encouraging data from nonrandomized Western studies for the use of rituximab and a few small studies using adrenocorticotropic hormone. Clinical trials are ongoing in North America to confirm these observations. These drugs are rarely used in Asia. (6) A Chinese study reported that 36% of IMN patients suffered from venous thromboembolism versus 7.3% in a North American study. Prophylactic anticoagulation therapy is usually added to IMN patients with a low risk of bleeding in both Eastern and Western countries. (7) The Chinese traditional medicine herb triptolide, which might have podocyte-protective properties, is used in China to treat IMN. An open-label, multicenter, randomized controlled trial showed that Shenqi, a mixture of 13 herbs, was superior to corticosteroids plus cyclophosphamide therapy to restore epidermal growth factor receptor in IMN patients, although proteinuria improvement was equal in the two groups. Importantly, Shenqi treatment induced no severe adverse events while standard therapy did.



## Introduction

Membranous nephropathy (MN) is one of the leading causes of nephrotic syndrome (NS), accounting for about 20.0% of NS in adults [1]. According to one study from Japan, 36.8% of 1,203 patients with primary NS had MN. In addition, 22.1% (180/813) of these patients had MN secondary to systemic diseases [2]. One study from mainland China reported that the proportion of MN in primary glomerular disease (PGN) was 9.89% [3]. A single-center study performed by Pan et al. [4] found that the prevalence of MN has kept increasing during the past decades from 6.48% in 1997–1999 to 22.79% in 2009–2011. However, MN is less common in Bangladesh and Saudi Arabia, accounting for 7.37 and 9.90% of PGN patients, respectively [5, 6]. In addition, idiopathic MN (IMN) accounted for 12.3 and 12.0% of all renal biopsies in Korea and Oman, respectively [7, 8]. Like in Asia, the prevalence of IMN in PGN in Europe varied from 11.2 to 29.4% [9–11]. MN is the most frequent PGN in Chinese elderly patients (≥60 years old). Pan et al. [4] found that the proportion of elderly patients has increased significantly from 3.18% in 1997–1999 to 15.21% in 2009–2011 ($p < 0.001$). The average age of patients with new-onset IMN was 52.91 ± 15.30 years in 2005–2014, while it was 48.29 ± 13.81 years in 1995–2004 in our department [in press]. The reasons for this may be related to the increasing number of elderly patients undergoing a renal biopsy and the growing age of the biopsy patients. Similarly, the mean age of the Japanese IMN patients was 62.2 years (range 2–88) at the time of renal biopsy [2].

Based on these data, MN is quite common in Asia, especially in the elderly people, and has become even more common recently. Although large progress has been made, the etiology and pathogenesis of MN are still incompletely understood, and a treatment strategy is needed for future studies, which will be summarized in this review.

## Pathogenesis

MN is an immune complex-mediated glomerular disease that is histologically characterized by uniform thickening of the glomerular basement membrane caused by subepithelial immune complex deposits. Although it is less common compared to the primary form, MN can be caused secondary to systemic diseases, such as autoimmune diseases, virus infections, malignant tumors or drugs/toxic agents [2, 3, 7, 8]. The discovery of the major antigen PLA2R was a great achievement in understanding the mechanism of IMN [12]. Since then, many studies have been performed with a focus on the role of PLA2R and its antibody (Ab). Liu and colleagues [13] suggest that PLA2R is a major target antigen in Chinese IMN and that the detection of anti-PLA2R Ab is a sensitive test for IMN through the measurements of anti-PLA2R Ab in both IMN and secondary MN patients. Our team compared the potential role of anti-PLA2R Ab in IMN patients. We confirmed that anti-PLA2R Ab was specifically detected in the serum of IMN patients. However, there is controversy about the use of PLA2R and anti-PLA2R Ab in the differential diagnosis of IMN or as a biomarker to predict the prognosis of the disease (unpubl. data). More recently, Tomas et al. [14] found another new antigen, THSD7A, in IMN patients. However, the detailed mechanisms remain unclear. Further studies are needed to identify the mechanisms that elicit the expression of the neoantigens on podocytes and to discover whether there are novel antigens which contribute to the production of local immune complex formation [15].

## Treatment

The IMN treatment strategies basically include two aspects. (1) General treatment, i.e. the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blocker (ARB) to reduce proteinuria or of statins to reduce cholesterol, and antiplatelet adhesion or anticoagulant treatment to prevent thrombosis, especially renal vein thrombosis. (2) Specific treatment, which varies in different Asian countries. The principal options are corticosteroid monotherapy or corticosteroids combined with cytotoxic agents, such as alkylating agents, calcineurin inhibitors or mycophenolate mofetil (MMF). In China, traditional Chinese medicine, like triptolide or other Chinese herbal soups, is commonly used to treat IMN as well. Rituximab and adrenocorticotropic hormone (ACTH) have been studied in Western clinical trials but are not yet used in Asia.

*General Treatment*

Most of the IMN patients from Asia present with heavy proteinuria [16]. ACEI or ARB are often used to reduce proteinuria and protect the kidney. It was found that ACEI (lisinopril) could lower the glomerular filtration pressure and restore the dysfunction of the glomerular barrier by increasing the expression of nephrin based on an experimental model of MN [17]. Not many studies conducted in Asia have focused on the efficacy of ACEI or ARB. However, of these studies, a clinical trial with a small sample size (12 patients) from China showed that 50% of the patients treated with ACEI (Captopril 25–50 mg/day) and antiplatelet adhesion agents experienced complete remission (CR), 17% partial remission (PR) and 33% did not respond to treatment, but their renal function was stable during the 3-year follow-up [18]. From our experience, we suggest that IMN patients with normal renal function, proteinuria levels <4 g/day and serum albumin levels >25 g/l should be treated with ACEI or ARB combined with prophylactic antiplatelet therapy [19].

Venous thromboembolism is a severe complication in MN patients. According to a Chinese study, 36% of patients had venous thromboembolism, 33% had renal vein thrombosis and 17% had pulmonary embolism. They all remained asymptomatic [20]. Thus, it is quite important to add anticoagulant agents or antiplatelet adhesion treatment in the daily support care for MN patients with hypoalbuminemia.

*Specific Treatment*

Many Western studies reported that IMN has the tendency of spontaneous remission. Schiepatti et al. [21] studied the natural disease course of IMN by recruiting both nephrotic and non-nephrotic IMN patients. They found that 65% of the patients (24/37) achieved a CR or PR of proteinuria within 5 years. End-stage renal disease (ESRD) presented in 16% of the patients. The authors concluded that most untreated IMN patients maintained their renal function for prolonged periods and were likely to have spontaneous remissions [21]. As IMN might retrieve spontaneously in some of the patients, it is quite important to know when to use the immunosuppressants. KDIGO (Kidney Disease: Improving Global Outcomes) has recently published a guideline illustrating when to start treatment with immunosuppressants in IMN patients. Proteinuria, serum creatinine and severe IMN are the three principal decisive factors [22]. According to the KDIGO guideline, treatment with immunosuppressive agents is suggested (1) when urinary protein excretion persistently exceeds 4 g/day or remains at >50% of the baseline value and does not show a progressive decline with the treatment of antihypertensive and antiproteinuric therapy during an observation period of at least 6 months. (2) In the case of severe, disabling or life-threatening events, or when serum creatinine has risen by ≥30% within 6–12 months from the time of diagnosis but the epidermal growth factor receptor is not <25–30 ml/min/1.73 $m^2$ and this change cannot be explained by superimposed complication symptoms related to NS [22]. Confronted with a variety of immunosuppressive agents, there are different options for doctors to choose, and the protocols vary across different Asian countries.

Corticosteroid Monotherapy

Corticosteroid monotherapy is not recommended by KDIGO for IMN. One Western meta-analysis showed that the relative chance of CR was not improved for corticosteroid-treated patients [relative risk (RR): 1.55, 95% confidence interval (CI) 0.99–2.44; $p > 0.1$] compared to those receiving no treatment [23]. However, in Asia, it is quite different, and some Asian IMN patients were found to have a good treatment response [24]. In Japan, Shiiki et al. [24] showed that 374 patients with corticosteroid monotherapy (40–60 mg/day orally, tapered over a period of 4 weeks or more according to the response to therapy) induced CR and PR of proteinuria in 47.9 and 39.3% of IMN patients with NS. In addition, there was no significant difference in renal survival between the corticosteroid and cyclophosphamide combined groups. One

study with a small sample size (38 patients) from Hongkong, China, demonstrated that treatment with corticosteroids (0.5 mg/kg/day, orally) alone for 6–9 months (median 7 months) induced remission in 71% of IMN patients with NS [25]. Another study from Korea demonstrated that corticosteroids (1 mg/kg/day) alone led to remission and preserved the renal function after a median treatment time of 6.9 months in 72 IMN patients, with a 5-year CR rate of 88.5% [26]. These findings suggested that East Asian IMN patients responded well to corticosteroid monotherapy. However, corticosteroid monotherapy was not recommended by previous guidelines, and the studies available to date are all observational. As a result, this strategy still needs to be validated before its routine usage in clinical practice.

Corticosteroids and Alkylating Agents

KDIGO recommends that the initial therapy of IMN should consist of a 6-month course of alternating monthly cycles of oral and intravenous corticosteroids and oral alkylating agents. Chlorambucil is still used in Europe, while it has rarely been used in Asia in the last 2 decades. In addition, KDIGO suggests using cyclophosphamide rather than chlorambucil for the initial therapy [22].

A randomized controlled trial conducted in India compared the long-term effects of a 6-month treatment to alternating prednisolone and cyclophosphamide on untreated IMN patients. Patients were followed up for 10 years. Of the 47 patients receiving the experimental protocol, 34 (72.3%) achieved remission (15 CR and 19 PR), compared to 16 (5 CR and 11 PR) of 46 (34.8%) in the control group (not treated with immunosuppressants, only supportive treatment; $p < 0.0001$). The 10-year dialysis-free survival rate was higher in the study group than in the control group (89 vs. 65%; $p = 0.016$), and the likelihood of survival without death, dialysis and doubling of serum creatinine was also higher in the study group (79 vs. 44%; $p = 0.0006$) than that in the control group. The authors concluded that a 6-month therapy using cyclophosphamide and corticosteroids induced a higher remission rate and a delayed progression of renal insufficiency [27].

A long-term follow-up (8.5 years) of 103 IMN patients receiving cyclophosphamide and corticosteroids was conducted in Japan. Patients were treated with cyclophosphamide (50 mg/day for the first 3 months and 25 mg/day for the next 3 months) and prednisolone (30 mg/day for the first week, and then, the dosage was gradually tapered to withdrawal by 2 years). If the patients did not respond to the initial treatment or MN relapsed, additional treatment was allowed. The authors found that 90 patients (87.4%) achieved proteinuria <1 g/day, and 78 (75.7%) achieved CR. Twenty-seven patients did not respond to initial treatment, and 30 patients relapsed after remission. Of these patients, 39 received additional therapies. At the last observation, 12 patients had developed renal insufficiency (serum creatinine >1.5 mg/dl) but only 2 patients had reached ESRD. The authors concluded that low-dose cyclophosphamide and prednisolone was beneficial for a long-term renal prognosis in Japan with relatively few adverse effects [28].

Corticosteroids combined with cytotoxic agents is the first choice for IMN therapy in most renal centers in China. However, the protocols of IMN treatment from these centers do not match. Oral prednisone plus cyclophosphamide pulse therapy was adopted by most of these centers. A clinical trial with a small sample size has been conducted to study its efficacy. Twenty-six patients with urine protein excretion >5 g/day received oral prednisone plus cyclophosphamide pulse therapy in addition to ACEI and antiplatelet adhesion treatment. After a mean period of 28.1 months of follow-up, 31% of patients experienced CR, 27% PR and 42% were without remission [18]. Corticosteroids combined with cyclophosphamide pulse therapy are effective in inducing remission and are well tolerated in Chinese patients.

Calcineurin Inhibitors

Cyclosporine, which is used effectively in the treatment of IMN, is preferable to alkylating agents in some countries, including Korea, where clinicians regard infertility as a serious disability even in the elderly [26].

In our study aimed to compare the efficacy of tacrolimus to cyclophosphamide in IMN patients, we found that the remission rate in the tacrolimus group ($n = 48$) was higher than that in the cyclophosphamide group ($n = 52$; 65.1 vs. 44.2%; $p = 0.02$). The mean time to PR or CR was faster in the tacrolimus group than in the cyclophosphamide group (2.20 vs. 3.92 months; $p < 0.001$). Although remission was faster and the remission rate was higher in the tacrolimus group (compared to the cyclophosphamide group) before 3 months, there was no superiority of tacrolimus after 6 months. All of the side effects were mild and controlled, and there were fewer side effects in the tacrolimus group, indicating a better treatment tolerance [29]. Although it is very effective, the large costs restrict its use in IMN patients in China.

The guidelines for the treatment of NS in Japan recommend a combination treatment with corticosteroids and cyclosporine as the first choice for IMN therapy [30]. One

clinical trial with a small sample size (13 patients receiving prednisolone 0.5 mg/kg/day and cyclosporine A 2 mg/kg/day) suggested that a single daily dose of cyclosporine combined with a low dose of prednisolone and ARB induced a high remission rate, a low incidence of relapse and a low risk of adverse effects in new-onset IMN patients who presented with NS [31]. Saito et al. [32] further demonstrated that 2 h after dose administration, the peak cyclosporine value should be at least 600 ng/ml to assure efficacy. They suggest that preprandial once-a-day administration of cyclosporine at 2–3 mg/kg with prednisolone may be the most appropriate option.

Mycophenolate Mofetil

A randomized controlled trial from China with a small sample size compared the efficacy and safety between cyclophosphamide and MMF. Sixty IMN patients were randomly divided into 2 groups: group A was treated with MMF + prednisone, and group B was treated with cyclophosphamide + prednisone. The remission rate in group A and group B was 70.0 and 56.7%, respectively. It suggested that MMF was superior to cyclophosphamide ($p < 0.05$) [33]. There are few data on MMF used for the treatment of IMN patients and it is not recommended by KDIGO. Further studies in this field are required.

In order to compare the effects among alkylant agents, calcineurin inhibitors and MMF, one Chinese group performed a meta-analysis by pooling data from 17 high-quality studies (involving 696 patients). This study found that calcineurin inhibitors had a better effect when compared to alkylating agents, including a higher CR rate (RR: 1.61, 95% CI 1.13–2.30), PR or CR rate (RR: 1.29, 95% CI 1.09–1.52) and less side effects. Among calcineurin inhibitors, tacrolimus achieved more remissions. MMF showed effectiveness with a higher PR or CR rate (RR: 1.41, 95% CI 1.16–1.72), but it was not significant for CR (RR: 1.38, 95% CI 0.89–2.13) [34].

Traditional Chinese Medicine

Traditional Chinese medicine is widely used for the treatment of IMN in China. Among all the agents, triptolide and Shenqi show promising data.

Triptolide is a Chinese traditional medicine herb. Recent studies showed that triptolide could probably have a protective effect on C5b-9-induced podocyte injury by inhibiting the P38 MAPK activation [35]. It is now used to treat IMN in China. One study compared 41 IMN patients treated with triptolide to 43 IMN patients treated with triptolide plus low-dose prednisone. After 12 months, the remission rates were 74.4, 79.1 and 76.7% after 3, 6 and 12 months of treatment in the triptolide plus low-dose prednisone group, while in the triptolide group, the remission rates were 51.2, 51.2 and 43.9%, respectively. The CR rate was 37.2% at 12 months in the triptolide plus low-dose prednisone group, which was higher than in the triptolide group 4.88% ($p < 0.01$). No severe adverse events were observed [36]. This study showed that triptolide plus low-dose prednisone could be an alternative treatment protocol for IMN.

Shenqi particle is a mixture of 13 different herbs. The exact active components responsible for the antiproteinuric effect are unclear. According to one animal study, Astragalus, a herbal component of Shenqi, could attenuate renal ischemia-reperfusion injury [37]. Chen et al. [38] conducted an open-label, multicenter, randomized controlled clinical trial to compare the efficacy of Shenqi to the standard therapy of corticosteroid plus cyclophoshamide. One hundred and thirty-two patients (63 in the Shenqi particle group and 69 in the control group) were included in the study. Two treatment protocols presented similar efficacy in reducing urine protein excretion: 3.01 g/day (95% CI 3.68–2.34) in the Shenqi particle group and 3.28 g/day (95% CI 3.98–2.58) in the control group. The mean difference between the 2 groups was 0.27 g/day (95% CI 0.70–1.23; $p = 0.6$). Shenqi was superior to standard therapy in enhancing the epidermal growth factor receptor: improved by 12.3 ml/min/1.73 $m^2$ (95% CI 4.99–19.6) in the Shenqi particle group and by 2.8 ml/min/1.73 $m^2$ (95% CI –10.32 to 4.77) in the control group. The mean difference between the two groups was 15.1 ml/min/1.73 $m^2$ (95% CI 4.56–25.55; $p = 0.005$). In addition, all severe adverse events occurred in the control group (14.5%), suggesting that Shenqi particle may be an effective and safe treatment for IMN patients.

Rituximab and ACTH

There are a few studies about the use of rituximab and ACTH for the treatment of IMN patients in Western countries and they all provided encouraging data [39–41]. However, in Asia, these are rarely used, and few data are available.

## Prognosis

MN is a disease with a relatively good prognosis. In one Japanese survey including 949 patients, Shiiki et al. [24] reported overall renal survival rates of 95.8, 90.3, 81.1 and 60.5% at 5, 10, 15 and 20 years after diagnosis, respectively. The renal survival rate in patients receiving corti-

costeroid therapy was significantly higher than in patients receiving supportive therapies only. In China, Liu and colleagues [42] reported overall renal survival rates of 96.9, 93.5 and 86.6% at 5, 10 and 15 years in 217 IMN patients from renal biopsies, respectively. Xie and Chen [19] reported that <5% of IMN patients progress to ESRD. The Chinese group found that hypertension and nephrotic-range proteinuria were predictors of a worse renal prognosis [42], while the Japanese researchers suggested that male, older age (≥60 years), a higher serum creatinine concentration (≥1.5 mg/dl) and tubulointerstitial lesions (≥20% of the biopsy sample area) were associated with a higher risk of progression to ESRD [24].

Japan, corticosteroid monotherapy or low-dose oral cyclophosphamide plus corticosteroids is widely used, leading to favorable outcomes. Corticosteroids combined with cytotoxic agents are commonly used in China to treat IMN patients. Of these protocols, cyclophosphamide pulse plus oral corticosteroid therapy has been considered a cost-effective treatment for IMN by most renal centers in China. Traditional Chinese medicine (especially triptolide and Shenqi) is generally preferred by the Chinese, and compelling results have recently been reported. In general, the prognosis of IMN in Asia is relatively benign, with fewer people progressing to ESRD compared to Westerners.

## Conclusion

MN is the leading cause of primary NS in adults. In recent years, its prevalence has dramatically increased by unknown reasons among the elderly people in Asia and other places in the world. The treatment strategies for IMN are not consistent in Asia. ACEI or ARB remains the first choice in IMN patients with non-nephrotic-range proteinuria. For patients with massive proteinuria and hypoalbuminemia, calcineurin inhibitors combined with corticosteroids are preferred in most Asian countries. In


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## Disclosure Statement

The authors declare no competing interests.

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