Idiopathic Membranous Nephropathy Traditional Chinese Medicine Clinical Practice Guidelines (2021) Postprint

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Abstract

Idiopathic membranous nephropathy accounts for 24.9% of glomerular diseases in China, ranking second with a proportion that shows an increasing trend year by year. Traditional Chinese Medicine treatment has been widely applied in the clinical practice of idiopathic membranous nephropathy; however, there is currently no evidence-based practice guideline for the treatment of membranous nephropathy with Traditional Chinese Medicine. This guideline follows international guideline development methods and procedures, uses the GRADE methodology for evidence quality and strength of recommendations, and determines the scope of the guideline and forms a clinical question outline through interviews with National TCM Masters and Guangdong Provincial Renowned TCM Practitioners; based on the interview results and the systematic collation and review of existing Chinese and Western medicine nephrology guidelines, authoritative textbooks, and clinical research literature, drafts clinical questions, clinical efficacy evaluation indicators for membranous nephropathy, and a survey checklist for TCM syndrome patterns; and conducts a nationwide expert survey, ultimately forming 10 recommendations regarding the treatment of idiopathic membranous nephropathy with Traditional Chinese Medicine. This guideline focuses on the clinical practice of treating idiopathic membranous nephropathy with Traditional Chinese Medicine and is applicable to TCM (integrated Chinese and Western medicine) medical institutions at all levels, as well as medical institutions and healthcare workers that provide Traditional Chinese Medicine services.

Full Text

Preamble

Clinical Practice Guideline for Traditional Chinese Medicine Treatment of Idiopathic Membranous Nephropathy (2021)

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Abstract

Idiopathic Membranous Nephropathy (IMN) accounts for 24.9% of glomerular diseases in China, ranking second with a progressively increasing trend. Traditional Chinese Medicine (TCM) treatment has been widely applied in clinical practice for IMN; however, no evidence-based practice guideline currently exists for TCM management of this condition. This guideline was developed following international guideline development methodologies and procedures, utilizing the GRADE approach for assessing evidence quality and recommendation strength. Through interviews with national TCM masters and renowned TCM experts from Guangdong Province, the guideline scope was determined and clinical question outlines were formulated. Based on these interviews and systematic review of existing Chinese and Western nephrology guidelines, authoritative textbooks,

and clinical research literature, clinical questions, IMN clinical efficacy evaluation indicators, and TCM syndrome investigation checklists were developed. A nationwide expert survey was conducted, ultimately resulting in 10 recommendations for TCM treatment of IMN. This guideline focuses on clinical practice of TCM for IMN and is applicable to TCM (integrated Chinese-Western medicine) medical institutions at all levels, as well as medical institutions and healthcare workers providing TCM services.

Keywords: Idiopathic Membranous Nephropathy; evidence-based practice guideline; Traditional Chinese Medicine

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Introduction

Membranous Nephropathy (MN) is one of the most common pathological types of adult nephrotic syndrome. Cases without identifiable causes are termed Idiopathic Membranous Nephropathy (IMN) [**?**]. International reports indicate that IMN constitutes 30-40% of primary nephrotic syndrome [**?**], while domestic data show that MN accounts for 24.9% of glomerular diseases nationwide in China, ranking second with an increasing annual trend, reaching up to 51% in some regions [**?**]. Progressive renal function deterioration occurs in 8-15% of MN patients [**?**].

Modern medicine has established guidelines with clear recommendations for IMN diagnosis and treatment; however, these have limitations when applied in China. The evidence is primarily derived from non-Asian populations and lacks recommendations for TCM diagnosis and treatment. TCM has a long history in preventing and treating kidney diseases. Based on clinical manifestations, IMN falls under the TCM categories of "edema," "turbid urine," and "consumptive disease." Numerous clinical trials on TCM treatment for IMN have been published, yet no TCM clinical guideline for MN has been released. Therefore, developing an evidence-based practice guideline for IMN in the TCM domain is imperative.

The guideline working group followed international guideline development methods and procedures to establish the "Clinical Practice Guideline for Traditional Chinese Medicine Treatment of Idiopathic Membranous Nephropathy," aiming to assist healthcare workers at all levels of medical institutions in making clinical decisions.

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2 Guideline Purpose

To provide decision-making evidence for integrated Chinese-Western medicine diagnosis and treatment of idiopathic membranous nephropathy, and to guide clinical practice among relevant healthcare professionals.

3 Guideline Users and Target Population

This guideline includes recommendations for TCM syndrome differentiation and treatment. It applies to TCM (integrated Chinese-Western medicine) medical institutions at all levels, as well as medical institutions providing TCM services. The guideline is intended for use by licensed TCM physicians (integrated Chinese-Western medicine), licensed assistant TCM physicians, policymakers, and other relevant stakeholders.

4 Professional Terminology

Idiopathic Membranous Nephropathy (IMN) [**?**]: A group of diseases characterized by immune complex deposition beneath the glomerular basement membrane epithelial cells with diffuse thickening of the glomerular basement membrane, diagnosed as IMN after excluding secondary factors. IMN is a common type of adult nephrotic syndrome, with approximately 50-80% associated with anti-phospholipase A2 receptor (PLA2R) antibodies and 2-4% associated with thrombospondin type-1 domain-containing 7A (THSD7A). MN without identified secondary factors is termed Idiopathic Membranous Nephropathy (IMN), also known as Primary Membranous Nephropathy (PMN). This guideline adopts the term Idiopathic Membranous Nephropathy (IMN).

Complete Remission [**?**]: Urinary protein excretion <0.3g/24h (urine protein-to-creatinine ratio <300mg/g or <30mg/mmol), measured on at least two occasions at least one week apart, with normal serum albumin and normal serum creatinine.

Partial Remission [**?**]: Urinary protein excretion <3.5g/24h (urine protein-to-creatinine ratio <3500mg/g or <350mg/mmol) with >50% reduction from peak value, measured on at least two occasions at least one week apart; with stable or normalized serum albumin and stable serum creatinine.

Composite Remission [**?**]: Achievement of either complete remission or partial remission.

Relapse [**?**]: Urinary protein excretion >3.5g/24h after complete remission, or >50% increase from the nadir after partial remission.

5 Risk Factors for Disease Progression

Persistent proteinuria, uncontrolled blood pressure and blood glucose, cardiovascular disease, use of nephrotoxic drugs, smoking, obesity, sleep deprivation, and other related conditions.

5.2 Risk Stratification

Low Risk: Normal estimated glomerular filtration rate (eGFR), proteinuria <3.5g/24h and serum albumin >30g/L; or normal eGFR, proteinuria <3.5g/24h with >50% reduction in proteinuria after 6 months of conservative treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB).

Medium Risk: Normal eGFR, proteinuria >3.5g/24h with <50% reduction in proteinuria after 6 months of conservative treatment with ACEI/ARB, without high-risk features.

High Risk: eGFR <60ml/min/1.73m^2 and/or proteinuria >8g/24h persisting for >6 months; or normal eGFR, proteinuria >3.5g/24h with <50% reduction in proteinuria after 6 months of ACEI/ARB treatment, combined with one or more of the following: serum albumin <25g/L, PLA2Rab >50RU/ml, urinary $ $1-microglobulin >40 g/min, urinary IgG >1 g/min, urinary $ $2-macroglobulin >250mg/24h, or selectivity coefficient >0.20.

Very High Risk: Life-threatening nephrotic syndrome or rapid renal function deterioration unexplained by other causes.

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6 TCM Syndrome Differentiation

6.1 Primary Syndromes

Qi-Yin Deficiency Syndrome: Generalized edema, eyelid and foot swelling, increased foamy urine, dull or sallow complexion, fatigue, susceptibility to common cold, lower back and knee weakness, hot palms and soles, dry mouth and throat, afternoon tidal fever. Tongue: red or pale red, thin or scanty coating. Pulse: thready or rapid and thready.

Lung-Spleen Qi Deficiency Syndrome: Generalized edema, eyelid and foot swelling, increased foamy urine, mental fatigue and reluctance to speak, poor appetite and abdominal distension, susceptibility to common cold, spontaneous sweating, loose stools. Tongue: pale red, enlarged body or with teeth marks on edges, thin white coating. Pulse: thready and weak.

Spleen-Kidney Yang Deficiency Syndrome: Generalized edema, eyelid and foot swelling, oliguria, increased foamy urine, pale complexion, aversion to cold and cold limbs, lower back and knee weakness, possibly accompanied by pleural effusion and ascites, mental fatigue, abdominal distension and poor appetite, loose stools, frequent nocturia, decreased sexual function or menstrual irregularities. Tongue: pale and enlarged with teeth marks, white slippery coating. Pulse: deep and thready or deep, slow and weak.

Liver-Kidney Yin Deficiency Syndrome: Generalized edema, eyelid and foot swelling, increased foamy urine, dry eyes, dizziness and tinnitus, dry throat

and mouth, lower back and knee weakness, tidal fever and night sweats, insomnia with vivid dreams, five-center heat, dry stools. Tongue: red, scanty coating. Pulse: rapid and thready, or wiry, rapid and thready.

6.2 Secondary Syndromes

Blood Stasis Obstruction Syndrome: Generalized edema, eyelid and foot swelling, increased foamy urine, stabbing pain in the lower back, or prolonged disease course refractory to treatment; possibly accompanied by dull or dark complexion, purple lips or petechiae, limb numbness. Tongue: dark, or with petechiae/ecchymosis, or with stagnant sublingual veins. Pulse: thready and choppy or choppy.

Wind-Dampness Complex Syndrome: Fatigue, foamy urine, generalized edema primarily affecting eyelids and face, or recurrence of aforementioned symptoms after external infection, or acute exacerbation, possibly accompanied by external infection symptoms. Tongue: red or pale red, thin greasy coating. Pulse: wiry, or wiry and thready, or deep.

Water-Dampness Retention Syndrome: Generalized edema, eyelid and foot swelling, increased foamy urine, heavy sensation in limbs, chest oppression and abdominal distension, poor appetite, loose stools. Tongue: pale and enlarged, white greasy coating. Pulse: soft or moderate.

Damp-Heat Accumulation Syndrome: Generalized edema, eyelid and foot swelling, increased foamy urine, chest and epigastric fullness, heavy head sensation, bitter taste and sticky mouth, poor appetite and nausea, thirst without desire to drink, sticky stools, scanty dark urine with burning pain. Tongue: red, yellow greasy coating. Pulse: soft and rapid or slippery and rapid.

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7 Evidence Quality and Recommendation Strength Grading

Evidence quality and recommendation strength were assessed using the GRADE methodology. Evidence quality reflects the confidence in the estimated effect, with the GRADE system categorizing evidence into four levels: high (A), moderate (B), low (C), and very low (D). The meanings of GRADE evidence quality and recommendation strength grades are shown in Table 2 .

Table 2 GRADE Evidence Quality and Recommendation Strength Grading

Evidence Quality Level	Recommendation Strength Level	Description
Very Low (D)	Strong	Very confident that the observed effect is close to the true effect
Low (C)	Weak	Moderate confidence: observed effect may be close to true effect but could differ substantially
Moderate (B)		Limited confidence: observed effect may differ substantially from true effect
High (A)		Very little confidence: observed effect likely differs greatly from true effect
		Clear evidence that intervention benefits outweigh harms or vice versa

Evidence Quality Level	Recommendation Strength Level	Description
		Uncertain balance or evidence shows comparable benefits and harms regardless of quality Recommendations based on indirect evidence or expert opinion/experience

8 Clinical Questions and Recommendations

This guideline includes 10 clinical questions, forming 10 recommendations. A summary of recommendations is provided in Table 3 .

Table 3 Summary of Recommendations

1. Can combined TCM and immunosuppressive therapy on top of supportive care further improve outcomes in medium- and high-risk IMN patients?
2. Is TCM monotherapy effective for low-risk IMN patients on supportive care?
3. Can TCM improve fatigue symptoms in IMN patients?
4. Can TCM treatment improve edema symptoms in IMN patients?
5. Can TCM treatment improve quality of life in IMN patients?
6. Can TCM prevent or reduce IMN relapse?
7. What are the efficacy differences among various TCM formulas and patent medicines for IMN?
8. What is the safety of TCM/patent medicines with immunosuppressive effects?
9. Can TCM prevent secondary infections in IMN patients?
10. Can TCM prevent thrombosis or embolism in IMN patients?

Clinical Question 1

For medium- and high-risk IMN patients, can combined TCM and immunosuppressive therapy on top of supportive care further improve outcomes?

Recommendation:
For medium- and high-risk IMN patients, to further improve remission rates and renal function, combined TCM or patent medicine treatment may be considered on top of conventional immunosuppressive regimens, with a treatment duration of at least 6 months. Recommended TCM: Tripterygium preparations (1C), Huangkui Capsule (2C), Shenqi Dihuang Decoction (2C). Referential TCM: Kunxian Capsule, Huobahuagen Tablet, Yishen Huashi Granules (expert consensus).

Rationale:
IMN patients show considerable heterogeneity in prognosis. The 2021 KDIGO guideline recommends initiating immunosuppressive therapy for medium-, high-, and very high-risk groups with at least one disease progression factor. Commonly used drugs include alkylating agents (cyclophosphamide), glucocorticoids combined with calcineurin inhibitors (cyclosporine, tacrolimus), and rituximab, which can improve complete and partial remission rates [**?**]. In China, TCM also plays a valuable role in IMN treatment. In addition to the following evidence, one randomized controlled trial (RCT) showed that the TCM formula Shenqi Granules achieved similar overall remission rates compared with glucocorticoid plus cyclophosphamide for medium- and high-risk IMN patients (73% vs 78%), with no serious adverse events in the Shenqi Granules group [**?**]. As this study evaluated TCM monotherapy rather than combination therapy, it was not included in the recommendation.

Evidence Summary:
1. One RCT [**?**] showed that Tripterygium preparations combined with glucocorticoid and tacrolimus for 6 months in medium- and high-risk IMN patients further improved overall remission rate [RR=1.33 (1.04, 1.70), n=60], increased serum albumin [MD=5.98 (4.42, 7.54), n=60], and reduced serum creatinine [MD=-26.20 (-36.32, -16.08), n=60].
2. One RCT [**?**] demonstrated that Huangkui Capsule combined with glucocorticoid and tacrolimus for 3 months in medium- and high-risk IMN patients further increased serum albumin [MD=4.86 (2.83, 6.89), n=86].
3. A systematic review of 3 RCTs [**?**] showed that Shenqi Dihuang Decoction combined with glucocorticoid and cyclophosphamide for 3 months in medium- and high-risk IMN patients with Qi deficiency and blood stasis syndrome reduced 24-hour urinary protein [MD=-2.39 (-3.55, -1.24), n=170] and increased serum albumin [MD=6.19 (4.47, 7.91), n=170].

The included studies had unclear descriptions of randomization methods, blinding, and selective reporting, indicating risk of bias, and the precision of results was suboptimal; therefore, the evidence quality was rated as low.

Medication Instructions:
1. Tripterygium glycoside tablets: For wind-damp-heat stasis syndrome. Dosage: 1-1.5mg/kg, divided into 3 doses after meals. May also be used with concurrent water-dampness, damp-heat, wind-dampness, or blood stasis. Listed in the National Basic Medical Insurance, Work Injury Insurance, and

Maternity Insurance Drug Catalog and National Essential Medicines List.
2. Huangkui Capsule: For damp-heat syndrome. Dosage: 0.5g per capsule, 5 capsules per dose, orally, 3 times daily. Primarily for damp-heat accumulation syndrome or concurrent damp-heat. Listed in the National Basic Medical Insurance, Work Injury Insurance, and Maternity Insurance Drug Catalog.
3. Shenqi Dihuang Decoction: For Qi-Yin deficiency syndrome. Main ingredients: Ginseng, Astragalus, Rehmannia, Chinese Yam, Poria, Moutan, Cornus (from Shen Jin' ao' s *Zabing Yuanliu Xizhu* in Qing Dynasty). May also be used for Qi deficiency with blood stasis or Qi-Yin deficiency with blood stasis.

Clinical Question 2

Is TCM monotherapy effective for low-risk IMN patients on supportive care?

Recommendation:
For low-risk patients, TCM monotherapy for 3-12 months can achieve favorable complete and overall remission rates. Consider using Tripterygium preparations (1D), Shenyan Kangfu Tablet (2D), Huangkui Capsule (2C), and Huobahuagen Tablet (2C).

Rationale:
Approximately 32% of IMN patients experience spontaneous remission, with higher spontaneous remission rates in those with lower proteinuria levels [**?**]. A meta-analysis also showed that serum PLA2R antibody-negative patients have higher spontaneous remission rates than PLA2R antibody-positive patients [**?**]. The 2021 KDIGO guideline [**?**] recommends optimized supportive treatment for low-risk patients, including sodium restriction, lifestyle modification, statin therapy for hyperlipidemia, and symptomatic diuresis. Studies show that IMN patients treated with renin-angiotensin-aldosterone system (RAAS) blockers achieve partial or complete remission at average times of 15 months and 39 months, respectively, with overall remission rates of 22% and 33% at 1 and 2 years.

Evidence Summary:
1. A systematic review of 3 RCTs [**?**] showed that compared with RAAS blockers, Tripterygium preparations for low-risk IMN patients over 6-12 months achieved higher complete remission [38.7% vs 15.1%, RR=3.17 (1.38, 7.24), n=98] and overall remission rates [38.7% vs 12.2%, RR=1.46 (1.03, 2.33), n=189], with no significant differences in eGFR and serum albumin. GRADE evidence rating: very low quality due to risk of bias, inconsistency, and imprecision.
2. One RCT [**?**] showed that compared with valsartan, Shenyan Kangfu Tablet for low-risk patients over 6 months achieved higher complete remission [43.3% vs 6.7%, RR=7.00 (1.74, 28.17), n=60]. GRADE evidence rating: very low quality.
3. A systematic review of 3 RCTs [**?**] showed that compared with RAAS blockers, Huangkui Capsule for low-risk patients over 2-3 months achieved higher overall remission [89.7% vs 67.1%, RR=1.34 (1.14, 1.58), n=173], with no significant

differences in serum creatinine and complete remission. GRADE evidence rating: low quality due to risk of bias and inconsistency.
4. One RCT [**?**] showed that compared with irbesartan, Huobahuagen Tablet for low-risk patients over 3 months achieved higher complete remission [76.6% vs 16.7%, RR=4.60 (2.02, 10.49), n=60] and overall remission [93.3% vs 63.3%, RR=1.47 (1.10, 1.97), n=60], and increased serum albumin [MD=3.47 (2.66, 4.28), n=60]. GRADE evidence rating: low quality due to risk of bias and imprecision.

Medication Instructions:
1. Tripterygium glycoside tablets: See Clinical Question 1 medication instructions (1).
2. Shenyan Kangfu Tablet: For Qi-Yin deficiency, spleen-kidney insufficiency, and water-dampness retention syndrome. Dosage: 0.3g per tablet, 5 tablets per dose, orally, 3 times daily. Listed in the National Basic Medical Insurance, Work Injury Insurance, and Maternity Insurance Drug Catalog and National Essential Medicines List.
3. Huangkui Capsule: See Clinical Question 1 medication instructions (2).
4. Huobahuagen Tablet: For wind-damp-heat stasis syndrome. Dosage: 0.18g per tablet, 3-5 tablets per dose, orally, 3 times daily. May also be used with concurrent damp-heat, wind-dampness, or blood stasis.

Clinical Question 3

Can TCM improve fatigue symptoms in IMN patients?

Recommendation:
TCM combined with angiotensin II receptor blockers for low-risk patients with Qi deficiency, dampness, and stasis syndrome for 3 months can improve fatigue symptoms (1D). TCM combined with immunosuppressants for medium- and high-risk patients with Qi deficiency-blood stasis syndrome and Qi-Yin deficiency-blood stasis syndrome for 3-6 months can improve fatigue symptoms (1D). Consider using Shenqi Dihuang Decoction for IMN patients with Qi deficiency-blood stasis syndrome (1D).

Rationale:
Fatigue is a common symptom in IMN patients [**?**], with 71-86.2% experiencing fatigue and weakness [**?**], often accompanied by shortness of breath, lower back and knee weakness, poor appetite, and dull complexion, which may fall under the TCM category of "consumptive disease." Fatigue is an important component of TCM syndrome scoring for Qi deficiency-dampness-stasis or Qi-Yin deficiency patterns; therefore, TCM syndrome scores were used as indirect evaluation indicators.

Evidence Summary:
1. One RCT [**?**] showed that for low-risk patients with Qi deficiency-dampness-stasis syndrome, Qi-supplementing, dampness-removing, and stasis-resolving herbal formula (self-designed) combined with benazepril for 3 months improved

TCM syndrome scores compared with benazepril alone [SMD=-5.13 (-7.00, -3.26), n=60].
2. A systematic review of 2 RCTs [**?**, **?**] showed that compared with tacrolimus or glucocorticoid plus tacrolimus, adding Shenqi Dihuang Decoction for 3-6 months improved TCM syndrome scores [SMD=-0.66 (-1.03, -0.29), n=120].

The included studies had high risk of bias, imprecise results, and indirect outcome measures, resulting in low-quality evidence.

Clinical Question 4

Can TCM treatment improve edema symptoms in IMN patients?

Recommendation:
TCM combined with immunosuppressants (glucocorticoid and cyclophosphamide or glucocorticoid and tacrolimus) for 6 months can improve edema in medium- and high-risk patients with edema symptoms (1C).

Rationale:
Edema is a primary symptom and sign in IMN patients [**?**], present in approximately 82% of patients [**?**], and may manifest as generalized edema and serous cavity effusions in severe cases, representing a major chief complaint prompting medical consultation.

Evidence Summary:
A systematic review of 2 RCTs [**?**, **?**] showed that TCM (Qi-supplementing and wind-dispelling method, spleen-kidney-tonifying and heat-clearing blood-activating method) combined with glucocorticoid and cyclophosphamide or glucocorticoid and tacrolimus for 6 months in medium- and high-risk patients with edema reduced edema symptom scores compared with immunosuppressants alone [SMD=-0.78 (-1.26, -0.31), n=74]. GRADE evidence rating: low quality due to risk of bias and imprecision.

Clinical Question 5

Can TCM treatment improve quality of life in IMN patients?

Recommendation:
TCM combined with angiotensin II receptor blockers for low-risk patients with Qi deficiency-dampness-stasis syndrome for 3 months can improve quality of life (1D). TCM combined with immunosuppressants (glucocorticoid and cyclophosphamide or glucocorticoid and tacrolimus) for medium- and high-risk patients with Qi deficiency-blood stasis syndrome and spleen-kidney deficiency syndrome for 6 months can improve quality of life (1D).

Rationale:
International reports indicate approximately 60% of IMN patients present with nephrotic syndrome at onset, increasing to 75% during disease course [**?**]. Chinese data show 57.3-79.2% of IMN patients present with nephrotic syndrome

[?, ?], often accompanied by severe edema and massive proteinuria, leading to decreased quality of life.

Evidence Summary:
1. One RCT [?] of 60 low-risk IMN patients with Qi deficiency-dampness-stasis syndrome showed that self-designed TCM formula combined with benazepril for 3 months reduced TCM syndrome scores compared with benazepril alone [SMD=-5.13 (-7.00, -3.26), n=60].
2. A systematic review of 6 RCTs [?, ?, ?, ?, ?, ?] showed that TCM combined with glucocorticoid and cyclophosphamide or glucocorticoid and tacrolimus for medium- and high-risk patients with Qi deficiency-blood stasis and spleen-kidney deficiency syndromes for 6 months reduced TCM syndrome scores compared with immunosuppressants alone [SMD=-1.46 (-2.27, -0.65), n=327].

No direct evidence using quality-of-life scales was available; indirect evidence from TCM syndrome scores reflecting partial quality-of-life aspects was used. Evidence quality was rated as very low due to risk of bias, imprecision, and inconsistency among studies. No clinical research evidence was found for therapies other than herbal medicine, such as acupuncture or moxibustion.

Clinical Question 6

Can TCM prevent or reduce IMN relapse?

Recommendation:
TCM combined with immunosuppressants (tacrolimus or cyclophosphamide) for medium-risk patients over 6-12 months can reduce disease relapse (1C). For medium-risk patients, TCM monotherapy showed no statistically significant difference in relapse rates compared with immunosuppressants (cyclosporine or glucocorticoid plus cyclophosphamide) (2C).

Rationale:
Relapse after remission is common in IMN [?], including in patients who discontinue cyclophosphamide, cyclosporine, tacrolimus, or rituximab. Short-course cyclosporine and tacrolimus treatment are associated with relapse rates up to 50% after drug discontinuation [?].

Evidence Summary:
1. A systematic review of 5 RCTs [?] showed that compared with immunosuppressants alone, TCM combined with immunosuppressants for medium-risk patients over 6-12 months reduced relapse rate by 17.5% [12.5% vs 30%, RR=0.42 (0.27, 0.67), n=320].
2. Subgroup analysis of 2 RCTs [?, ?] showed that compared with tacrolimus alone, TCM combined with tacrolimus for medium-risk patients over 12 months reduced relapse rate by 23.9% [17.4% vs 41.3%, RR=0.42 (0.21, 0.86), n=92].
3. Subgroup analysis of 2 RCTs [?, ?] showed that compared with cyclophosphamide alone, TCM combined with cyclophosphamide for medium-risk

patients over 12 months reduced relapse rate by 21.8% [1.4% vs 23.2%, RR=0.09 (0.02, 0.47), n=138].
4. A systematic review of 3 RCTs [**?**] showed that TCM monotherapy for medium-risk patients over 3-24 months reduced relapse rate by 7.5% compared with cyclosporine or glucocorticoid plus cyclophosphamide [9.3% vs 16.8%, RR=0.54 (0.30, 1.01), n=304], but the difference was not statistically significant.

All included studies had low GRADE evidence quality due to risk of bias and imprecision.

Clinical Question 7

What are the efficacy differences among various TCM formulas and patent medicines for IMN?

Recommendation:
On the basis of RAAS blocker therapy, Tripterygium preparations combined with Buyang Huanwu Decoction can further reduce proteinuria and increase serum albumin compared with Tripterygium preparations alone (2C). On the basis of glucocorticoid and cyclophosphamide therapy, Modified Shengjiang Powder is superior to Huangkui Capsule in reducing urinary albumin and increasing serum albumin (2C).

Rationale:
TCM treatment for IMN commonly employs patent medicines and herbal decoctions. Frequently used patent medicines include Tripterygium preparations, Huangkui Capsule, and Cordyceps preparations, while herbal decoctions include classical formulas and self-designed prescriptions. Clinical studies have reported varying efficacies among different TCM prescriptions.

Evidence Summary:
1. One RCT [**?**] in medium-risk patients with Qi deficiency-blood stasis syndrome showed that on RAAS blocker therapy, Tripterygium preparations combined with Buyang Huanwu Decoction for 3 months had similar overall remission rates compared with Tripterygium preparations alone [83.3% vs 86.2%, RR=0.97 (0.78, 1.20), n=59], with no difference in serum creatinine [MD=-2.52 (-11.11, 6.07), n=59], but the combination further reduced 24-hour urinary protein excretion [MD=-1.03 (-1.97, -0.09), n=59] and increased serum albumin [MD=4.06 (1.71, 6.41), n=59].
2. One RCT [**?**] showed that on glucocorticoid and cyclophosphamide therapy, Modified Shengjiang Powder compared with Huangkui Capsule over 3 months resulted in greater proteinuria reduction [MD=-0.60 (-0.91, -0.29), n=111] and serum albumin increase [MD=4.14 (2.00, 6.28), n=111].

GRADE evidence rating: low quality for both studies due to risk of bias and imprecision.

Medication Instructions:

1. Tripterygium glycoside tablets: See Clinical Question 1 medication instructions (1).
2. Huangkui Capsule: See Clinical Question 1 medication instructions (2).
3. Buyang Huanwu Decoction: For Qi deficiency-blood stasis syndrome. Main ingredients: Astragalus, Angelica tail, Red Peony, Earthworm, Ligusticum, Safflower, Peach Kernel (from *Yilin Gaicuo*).
4. Shengjiang Powder: Raises clear yang, lowers turbid yin, disperses wind and clears heat. Main ingredients: Rhubarb, Silkworm, Turmeric, Cicada slough (from *Shanghan Wenyi Tiaobian*).

Clinical Question 8

What is the safety of TCM/patent medicines with immunosuppressive effects?

Recommendation:
Before using Tripterygium preparations, patients should be informed of potential side effects including reproductive system toxicity (menstrual irregularities), gastrointestinal symptoms, hepatic dysfunction, and hematologic system toxicity. Dosage should follow package instructions. Regular monitoring of liver function and blood counts is required when using Tripterygium alone or in combination; monitoring frequency should be intensified for continuous use exceeding 6 months (expert consensus).

Rationale:
In IMN treatment, TCM/patent medicines with immunosuppressive effects serve as important supplements and alternatives to immunosuppressive therapy, primarily for low- and medium-risk patients. Commonly used drugs include Tripterygium and its extracts, Huobahuagen Tablet, Kunming Shanhaitang, and Kunxian Capsule.

Evidence Summary:
1. A 2016 systematic review of 594 clinical studies [**?**] (264 RCTs, 100 non-randomized controlled trials, 156 prospective single-arm studies, and 74 case reports/series) showed that among 23,256 patients taking Tripterygium preparations, 7,616 adverse events occurred (26.7% incidence), most commonly gastrointestinal symptoms (13.3%), followed by reproductive system (11.7%), skin symptoms (7.8%), hematologic system (6.5%), and cardiovascular events (4.9%). Menstrual irregularities occurred in 11.7% of female patients, higher than control drugs [OR=4.65 (3.08, 7.03)].
2. A systematic review of 56 Tripterygium studies [**?**] showed total reproductive toxicity incidence of 17.9%, with menstrual irregularities (17.6%), amenorrhea (27.7%), and decreased sperm motility (20.3%).
3. A systematic review of 16 RCTs on Tripterygium for diabetic nephropathy [**?**] showed higher adverse event rates with Tripterygium plus RAAS blockers vs RAAS blockers alone [10.4% vs 2.9%, RR=0.07 (0.03, 0.11)], with 50% being hepatic injury that normalized after drug discontinuation or hepatoprotective therapy.

4. A systematic review of 79 Tripterygium studies for rheumatoid arthritis [**?**] showed total adverse event rate of 23%, with reproductive, gastrointestinal, skin, hematologic, and hepatobiliary systems being most common.
5. The same review [**?**] reported 14 case reports/series where 4 patients using doses exceeding package instructions developed serious adverse reactions, including 2 deaths. Symptoms resolved after drug discontinuation and symptomatic treatment in other cases.
6. The 2016 systematic review [**?**] showed higher adverse event rates with longer Tripterygium use: 23.4% for <3 months, 26.3% for 3-6 months, 31.0% for 6-12 months, and 31.2% for >12 months.
7. The systematic review of 56 studies [**?**] showed significantly higher adverse event rates with >12 months vs <6 months use [33.9% vs 9.4%; $ $12 months: RR=35.7 (22.4, 51.6); <6 months: RR=10.8 (5.9, 18.9)].
8. A 2018 evidence-based safety evaluation of 36 Tripterygium-containing patent medicines [**?**] (16 RCTs, 1 CCT, 6 case series, 13 case reports) showed nephrotoxicity incidence of 5.81% (4.43%, 7.57%) (n=1,999).

Clinical Question 9

Can TCM prevent secondary infections in IMN patients?

Recommendation:
Combined TCM and Western medicine treatment for IMN did not show significantly reduced pulmonary infection rates (2D).

Rationale:
Infection is the leading cause of all-cause mortality in MN patients and increases hospitalization rates. A Japanese cohort study [**?**] found that MN patients had an all-cause mortality rate of 21/1,000 person-years, with 41.7% due to infection and infection-related hospitalization rate of 16.2/1,000 person-years. Preventing secondary infections is crucial in IMN management.

Evidence Summary:
One RCT [**?**] showed that compared with Western medicine alone, Huangzhi Yishen Capsule combined with glucocorticoid and cyclophosphamide did not significantly reduce pulmonary infection rates [3.13% vs 12.5%, RR=0.25 (0.03, 2.12), n=64]. GRADE evidence rating: very low quality due to risk of bias, imprecision, and indirectness.

Clinical Question 10

Can TCM prevent thrombosis or embolism in IMN patients?

Recommendation:
TCM combined with immunosuppressants for 2-6 months did not significantly reduce deep vein thrombosis incidence (2C) but improved hypercoagulable state indicators including D-dimer (2D), coagulation time (2C), prothrombin time (2D), fibrinogen (2D), and thromboelastography parameters (2D). Used formu-

las included: Shenfukang Capsule, Buyang Huanwu Decoction, Zhenwu Decoction combined with Danggui Shaoyao Powder, Tripterygium preparations, and Maixuekang Capsule.

Rationale:
IMN patients often have hypercoagulable states, with blood stasis obstruction being a persistent pathological mechanism throughout the disease course. Approximately 7% of IMN patients experience at least one venous thrombotic event, with serum albumin <2.8g/dL being an independent predictor of venous thrombosis risk [**?**]. Prophylactic anticoagulation effectively prevents venous thrombotic events [**?**], but anticoagulant use is a double-edged sword that increases bleeding risk. Blood-activating and stasis-resolving TCM can reduce D-dimer and fibrinogen levels, prolong shortened coagulation and prothrombin times, and improve coagulation function.

Evidence Summary:
1. One RCT [**?**] in medium- and high-risk IMN patients with nephrotic syndrome showed that Huangzhi Yishen Capsule combined with glucocorticoid and cyclophosphamide for 6 months had no significant difference in deep vein thrombosis incidence compared with Western medicine alone [6.25% vs 9.38%, RR=0.67 (0.12, 3.73), n=64]. GRADE evidence rating: low quality due to risk of bias and imprecision.
2. A systematic review of 5 RCTs [**?**, **?**] showed that Qi-supplementing and blood-activating TCM combined with immunosuppressants reduced D-dimer levels [MD=-0.18 (-0.30, -0.07), n=390]. GRADE evidence rating: very low quality due to risk of bias, imprecision, and inconsistency.
3. A systematic review of 6 RCTs [**?**, **?**, **?**] showed that blood-activating TCM combined with Western medicine for 2-3 months prolonged shortened coagulation time [MD=0.93 (0.08, 1.78), n=452]. GRADE evidence rating: low quality due to risk of bias and inconsistency.
4. A systematic review of 3 RCTs [**?**, **?**, **?**] showed that blood-activating TCM combined with Western medicine for 2-3 months prolonged shortened prothrombin time [MD=3.21 (-2.40, 8.82), n=226]. GRADE evidence rating: very low quality due to risk of bias, imprecision, and inconsistency.
5. A systematic review of 11 RCTs [**?**, **?**, **?**, **?**, **?**] showed that blood-activating TCM combined with Western medicine for 2-6 months reduced plasma fibrinogen levels [MD=-0.67 (-0.91, -0.43), n=856].
6. One RCT [**?**] showed that Maixuekang Capsule combined with Western medicine for 4 weeks increased thromboelastography R-value [MD=0.69 (0.34, 1.04), n=73] and K-value [MD=0.36 (0.16, 0.56), n=73], and decreased α-angle [MD=-5.11 (-7.48, -2.74), n=73] and CI value [MD=-0.38 (-0.73, -0.03), n=73].

9.1 Guideline Development Methodology

This guideline was developed following international guideline development methods and procedures, with reference to GB/T 1.1-2020 *Directives for Standardization Work Part 1: Rules for the Structure and Drafting of Standardization Documents*. Evidence quality and recommendation strength were assessed using the GRADE methodology. Evidence quality reflects confidence in the estimated effect, with the GRADE system categorizing evidence into four levels: high (A), moderate (B), low (C), and very low (D).

Recommendation strength reflects the guideline' s certainty that benefits outweigh harms. This guideline' s recommendation strength considered the balance of benefits and harms, gaps between required clinical conditions and practice, and regional applicability, determined through comprehensive evaluation by consensus meeting experts.

9.2 Guideline Registration

This guideline is registered with the International Practice Guideline Registration Platform (Registration No.: IPGRP-2017CN016).

9.3 Guideline Working Group

The guideline drafting group was convened by the guideline leader and comprised experts in nephrology and methodology from 18 tertiary-grade institutions, including specialists in TCM and integrated Chinese-Western medicine nephrology and methodology.

Guidance Committee Experts: Zhang Daning (Tianjin Academy of Traditional Chinese Medicine Nephrology), Huang Chunlin (Guangdong Provincial Hospital of Chinese Medicine Nephrology), Yang Nizhi (Guangdong Provincial Hospital of Chinese Medicine Nephrology), Zhang Peiqing (Heilongjiang Provincial Academy of Chinese Medicine Nephrology)

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Yang Hongtao, Yang Lihong, Zhang Shoulin, Zhang Yu, Rao Xiangrong, Zhong Yifei, Zhao Wenjing, Guo Xinfeng, Xu Peng, Cheng Xiaohong, Lu Ying, Jian Guihua, Zhan Jihong, Li Chuang

Evidence Evaluation Group Members: Yang Lihong, Su Peiling, Liang Xing, Zhang La, Wang Lijuan, Liu Juan, Cai Fengdan, Hong Xiaofan, Zheng Jiaxuan, Yuan Yi, Qu Zhanhang, Wang Zhiwei, Liu Huoliang, Huang Jin, Liu Jinchu, Wang Xiaowan

Writers: Yang Lihong, Su Peiling, Bao Kun

9.4 Conflict of Interest Statement

No conflicts of interest were reported by any guideline drafting group members.

9.5 Clinical Question Selection and Determination

Through interviews with national TCM masters and renowned Guangdong TCM experts, the guideline scope was determined and clinical question outlines formulated. Based on interview results and systematic review of existing Chinese and Western nephrology guidelines, authoritative textbooks, and clinical research literature, clinical questions, IMN clinical efficacy evaluation indicators, and TCM syndrome investigation checklists were developed. A nationwide expert survey was conducted among TCM and integrated Chinese-Western medicine nephrology professionals from secondary or tertiary hospitals across various provinces. The survey involved 24 secondary and tertiary Chinese or integrated medicine hospitals in Guangdong, Hainan, Guangxi, Heilongjiang, Hubei, Zhejiang, Shaanxi, Shanghai, Beijing, and other regions. Electronic questionnaires were distributed, and clinical questions were scored on a 1-5 scale (higher scores indicating greater importance). The top ten clinical questions were selected for inclusion in the guideline.

9.6 Evidence Retrieval, Extraction, and Synthesis

Databases searched included CNKI, CBM, Wanfang, VIP, and PubMed from inception to May 2020. Chinese and English literature of all publication types were included. A total of 4,356 articles were retrieved (CNKI 971, CBM 700, Wanfang 2,378, VIP 256, PubMed 51), with 2,644 remaining after deduplication.

Literature was included based on the determined clinical questions. Exclusion criteria: pediatric studies; studies with Western interventions inconsistent with current clinical practice guidelines (e.g., glucocorticoid monotherapy); studies with unavailable outcome data.

For clinical questions with multiple primary studies, meta-analysis was performed using a random-effects model with RevMan 5.3 software.

9.7 Recommendation Formulation

The "Clinical Practice Guideline for Traditional Chinese Medicine Treatment of Idiopathic Membranous Nephropathy" evidence recommendation consensus meeting was held in Guangzhou on December 12, 2020. The GRADE grid method was used for voting, with 28 participating experts. Initially, 22 recommendation items were drafted. After three rounds of discussion and scoring, 21 items reached consensus, ultimately forming 10 recommendations.

9.8 Guideline Draft Development and External Review

The guideline was primarily written by Yang Lihong, Su Peiling, and Bao Kun. The draft was completed in May 2021, revised in July 2021 based on feedback from other drafting group members, and finalized in December 2021 after external expert review.

External Reviewers: Zhang Lei, Qiu Yuliang, Wang Xiaoxiao, Li Ming, Wei Minggang, Zhao Jing, Liu Lichang, Yan Can, Zheng Rong, Xiong Guoliang, Jin Hua, Zhou Ke, Zhao Xianfeng, Chen Min, Zhong Dan, Leng Wei, Chen Gangyi, Liu Yanhua, Qi Airong, Xiong Youming, Duan Xiaojun, Li Shuju, Sun Shengyun, Liu Xin, Xu Wenjuan, Tan Qinxiang, Xu Yanqiu, Zhu Rong, Wang Xiaoxing, Yu Pengcheng, Chen Min, Zhao Dapeng, Wu Jing, Li Liang, Wang Lifan, Shu Yongbing, Tan Ping

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9.9 Guideline Dissemination, Promotion, and Update

The "Clinical Practice Guideline for Traditional Chinese Medicine Treatment of Idiopathic Membranous Nephropathy"was issued as a group standard (T/CACM 1376-2021) by the China Association of Chinese Medicine on December 21, 2021. The guideline will be promoted through training and publicity on the official websites and WeChat platforms of the China Association of Chinese Medicine and Guangdong Provincial Hospital of Chinese Medicine, as well as through relevant publications. This version will be updated and revised 3-5 years after publication if new clinical research evidence changes current recommendations or if new clinical questions emerge.

No conflicts of interest exist in this article.

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Note: Figure translations are in progress. See original paper for figures.