KDIGO 2021 肾小球疾病管理临床实践指南

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参考按键

评定指南建议的术语和描述

在每个建议中，建议强度表示为1级或2级，支持性证据的质量表示为a、B、C或D。

	影响		
等级	患者	临床医生	政策
1级“强” “我们推荐”	在您的情况下，大多数人都希望采取推荐的行动方案，只有一小部分人不愿意。	大多数患者应接受推荐的疗程。	该建议可被评估为制定政策或绩效指标的候选人。
2级“弱” “我们建议”	在您的情况下，大多数人希望采取推荐的行动方案，但许多人不希望。	不同的选择将适用于不同的患者。每位患者都需要帮助才能做出符合其价值观和偏好的管理决策。	该建议很可能需要利益攸关方进行实质性辩论和参与，才能确定政策。

等级	证据质量	含义
A	高	我们确信真实效应接近效应估计值。
B	中度	真实效应可能接近效应的估计值，但可能存在实质性差异。
C	低	真实效应可能与效应估计值存在显著差异。
D	极低	对效果的估计是非常不确定的，往往会与真实的效果相去甚远。

KDIGO 使用的当前慢性肾病 (CKD) 命名

CKD 定义为肾脏结构或功能异常，存在 > 3 个月，提示健康。根据条款、GFR 类别 (G1–G5) 对 CKD 进行评估，和 A 白蛋白尿类别 (A1–A3)，简称为 CGA。

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	< 15			

绿色，低风险（如果没有其他肾病标志物，没有CKD）；黄色，中度风险增加；橙色，高风险；红色，极高风险。GFR，肾小球滤过率

常规单位与 SI 单位的换算系数

	常规单位	转换因子	SI 单位
白蛋白	g/dl	10	g/l
肌酐	mg/dl	88.4	m mol/l
肌酐清除率	ml/min	0.01667	ml/s
环孢霉素	ng/ml	0.832	nmol/l
麦考酚酸	m g/ml	3.12	m mol/l
蛋白质-肌酐比值	mg/g	0.113	mg/mmol
他克莫司	ng/ml	1.24	nmol/l

注：常用单位转换因子¼SI单位。

白蛋白尿和蛋白尿类别的关系

	类别		
测量	正常至轻度增加 (A1)	中度增加 (A2)	重度增加 (A3)
AER(mg/d)	< 30	30–300	> 300
PER(mg/d)	< 150	150–500	> 500
美国风湿病学会			
(mg/mmol)	< 3	3–30	> 30
(mg/g)	< 30	30–300	> 300
PCR			
(mg/mmol)	< 15	15–50	> 50
(mg/g)	< 150	150–500	> 500
蛋白试剂条	阴性至痕量	痕量至 +	+ 或更大

类别内测量方法之间的关系并不确切。例如，AER和 ACR 之间以及 PER 和 PCR 之间的关系是基于平均肌酐排泄率约为1.0 g/日或 10 mmol/d 的假设。出于语用原因，对转换进行了四舍五入。（对于从 mg/g 肌酐到 mg/mmol 肌酐的精确转换，乘以0.113。）肌酐排泄量随年龄、性别、人种和饮食而变化；因此，这些类别之间的关系仅为近似值。尿液试剂条结果和其他测量之间的关系取决于尿液浓度。ACR，白蛋白-肌酐比值；AER，白蛋白排泄率；PCR，蛋白-肌酐比值；PER，蛋白排泄率。

缩略语和首字母缩略词

AAV	抗中性粒细胞胞浆抗体相关血管炎
乙酰胆碱酯酶	血管紧张素转换酶抑制剂
美国风湿病学会	白蛋白-肌酐比值
活化凝血时间	以青蒿素为基础的联合治疗
非洲	非洲肾脏病学会
aHUS	非典型溶血性尿毒综合征
艾滋病	获得性免疫缺陷综合征
急性肾损伤	急性肾损伤
抗中性粒细胞胞浆抗体	抗中性粒细胞胞质抗体
aPLA	抗磷脂抗体
APS	抗磷脂综合征
ARB	血管紧张素 II 受体阻滞剂
抗逆转录病毒治疗	抗逆转录病毒治疗
ATE	动脉血栓栓塞
AUC	曲线下面积
卡介苗	溴甲酚绿
BCP	溴甲酚紫
体重指数	体重指数
BP	血压
C3G	C3 肾小球病
C4G	C4 肾小球病
丙磺舒	C3 肾小球肾炎
CCB	钙通道阻滞剂
CFH	补体因子 H
CFHR	补体因子 H 相关
CI	置信区间
慢性肾脏病	慢性肾病
CNI	钙调磷酸酶抑制剂
肌酐清除率	肌酐清除率
CV	心血管的
DDD	致密沉积物病
DNA	脱氧核糖核酸
DNAJB9	DnaJ 同源亚家族 B 成员9
多库酯钠	直接口服抗凝剂
直接呼吸指数	直接肾素抑制剂
双链 DNA	双链 DNA
深静脉血栓	深静脉血栓形成
eGFR	估计肾小球滤过率
ELISA 法	酶联免疫吸附试验
ERT	证据评审团队
终末期肾病	终末期肾病
FAS	完整老化范围
等级	建议评估分级，开发和评价
HAART	高效抗逆转录病毒治疗
乙型肝炎病毒	乙型肝炎病毒
丙型肝炎病毒	丙型肝炎病毒
HIV 病毒	人类免疫缺陷病毒
人类免疫缺陷病毒	HIV 相关肾病
HR	风险比
国际神经营养学会	免疫复合物介导肾小球肾炎
干扰素	干扰素
IgADIRGN	IgA 显性感染相关 GN
免疫球蛋白 A	免疫球蛋白 A 肾病
免疫球蛋白 V	免疫球蛋白 A 血管炎
免疫球蛋白 N	免疫球蛋白 A 血管炎相关肾炎
免疫球蛋白 E	免疫球蛋白 E
IgG	免疫球蛋白 G
IgM	免疫球蛋白 M
ISN/RPS	国际肾脏病学会和肾脏病理学会
国际医学协会	医学研究所
四分位距	四分位距
i.v.	静脉内
KDIGO	肾病：改善全球结果
LDL-C	低密度脂蛋白胆固醇
LN	狼疮肾炎
MCD	微小病变
MD	平均差异
MDRD	肾脏疾病饮食改良
MPA	麦考酚酸
MPAA	霉酚酸类似物
MMF	吗替麦考酚酯
MN	膜性肾病
甲丙氨酯	膜增生性肾小球肾炎
髓过氧化物酶	髓过氧化物酶
MRA	盐皮质激素受体拮抗剂
mTOR	哺乳动物雷帕霉素靶蛋白
NCGN	坏死性新月体肾小球肾炎
美国国立卫生研究院	美国国立卫生研究院
NS	肾病综合征

FDA	美国食品药品监督管理局
FR	经常复发
FRNS	经常复发的肾病综合征
FSGS	局灶节段性肾小球硬化
FSGS-UC	不明原因 FSGS
葡萄糖脱氢酶	葡萄糖-6-磷酸脱氢酶
肾小球基底膜	肾小球基底膜
肾小球滤过率	肾小球滤过率
GN	肾小球肾炎
GPA	肉芽肿性多血管炎
非甾体抗炎药	非甾体类抗炎药
OR	比值比
PCR	蛋白质-肌酐比值
PE	肺栓塞
依据	蛋白排泄率
PERR	主要疗效肾脏反应
PGNMID	增生性 GN 伴单克隆 Ig 沉积
吡美卡因	人群、干预、对照、结局，方法

PLA2R	M型磷脂酶 A2 受体
p.o.	口服
质子泵抑制剂	质子泵抑制剂
PR3	蛋白酶3
定量微核	石英疟疾性肾病
血管紧张素原	肾素-血管紧张素系统
RASi	肾素-血管紧张素系统抑制剂
红细胞	红细胞
随机对照试验	随机对照试验
RPGN	急进性肾小球肾炎RR 相对危险度
右室速	肾静脉血栓形成
血清肌酐	血清肌酐
SD	激素依赖性
系统性红斑狼疮	系统性红斑狼疮
SMP	麦考酚钠
标准误	结果总结
SRNS	激素抵抗型肾病综合征
SSNS	激素敏感性肾病综合征
TB	肺结核
羟乙基淀粉	血小板反应蛋白1型 含结构域 7A
三羟甲基氨基甲烷	血栓性微血管病
TMP-SMX	甲氧苄啶-磺胺甲恶唑
TTP	血栓性血小板减少性紫癜
UK	英国
超高分子量聚乙烯	尿蛋白排泄
US	美国
VTE	静脉血栓栓塞
世界卫生组织	世界卫生组织

通知

第 I 部分：临床实践指南的使用

本临床实践指南文件基于2018年10月最后进行的文献检索，并补充了截至2019年9月的其他证据。检索于2020年6月更新。其旨在帮助决策。其目的不是定义标准治疗，不应解释为处方专有的管理疗程。当临床医生考虑个体患者的需求、可用资源和机构或实践类型特有的局限性时，实践中的变化将不可避免且适当地发生。使用这些建议的医疗保健专业人员应决定如何将其应用于自己的临床实践。

第二部分：披露

肾病：改善全球预后组织 (KDIGO) 应尽一切努力避免因工作组成员的外部关系或个人、专业或商业利益而可能引起的任何实际或合理感知的利益冲突。所有工作组成员必须填写、签署并提交一份披露和证明表，显示所有可能被视为或实际利益冲突的此类关系。本文件每年更新一次，并对信息进行相应调整。所有报告的信息均完整发表在本文件结尾处的工作组成员“披露”部分，并在 KDIGO 存档。

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前言

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随着人们对慢性肾病（CKD）是全球主要健康问题的认识不断加深，2003年确立了肾病改善全球预后组织（KDIGO），其使命是"通过促进协调、协作和整合制定和实施临床实践指南的倡议，改善全球肾病患者的护理和预后。"

自2003年以来，KDIGO制定了临床实践指南目录，告知肾病患者或有发生风险的患者的护理。最近，KDIGO发表了关于CKD糖尿病管理的新指南，并更新了其CKD血压管理指南。最后一个系列是肾小球疾病管理指南的更新。所有3个指南将使用新的指南格式预先发布。

肾小球疾病（不包括糖尿病肾病）约占全球CKD病例的25%。考虑到肾小球疾病的长期发病率，尤其是其在年轻患者中的常见表现，有效地对其进行诊断以及优化管理以控制疾病和预防进展性肾病至关重要。

KDIGO于2012年发表了其肾小球肾炎（GN）临床实践指南。该指南来源于工作组根据截至2011年11月的现有证据总结的12种不同疾病的建议所做的重要工作。从那时起，出现了大量新的证据，对本原始指南中的建议声明具有重要影响。

2017年，KDIGO召开了肾小球疾病争议会议。会议的目的是召集多学科临床和科学专家组成的全球小组，以确定与原发性和继发性肾小球疾病最佳管理相关的关键问题。目的是确定肾小球疾病治疗的最佳实践治疗和不确定性领域，审查自KDIGO 2012 GN指南以来发表的关键相关文献，确定需要重新审查以进行未来指南更新的主题或问题，并概述改善GN管理所需的研究。该会议的结论于去年发表在*Kidney International*上。[1,2]基于该会议，建议更新指南。

根据KDIGO在指南制定过程中的透明度政策和严格的公众审查，2017年争议会议的范围在会议之前可供公开评论。准则工作组成员仔细考虑了收到的关于工作范围的反馈和会议的产出。该指南也可供公众审查，工作组对审查了公众意见，并酌情修订了最终出版物的指南。

我们感谢Jürgen Floege（医学博士）和Brad H. Rovin（医学博士）领导这一重要倡议，我们特别感谢所有工作组成员为这一努力提供了大量的时间和专业知识。此外，本工作组得到了Jonathan C. Craig,MBChB,DipCH,FRACP,M Med(Clin Epi) ,PhD,Martin Howell,PhD和David J. Tunnicliffe,PhD领导的独立证据审查团队（ERT）的同事的大力支持，他们使本指南成为可能。

KDIGO最近任命Marcello A. Tonelli,MD,SM,MSc,FRCPC为其第一份指南方法主席。他的任务是通过加强建议与相应证据之间的联系，规范指南格式，减少不必要的长度，加强指南对其用户的效用，改进KDIGO指南方法。

为了实现这些目标，Tonelli博士建议KDIGO与MAGICapp合作，MAGICapp是一个基于网络的循证指南出版平台。该计划使用预定格式，允许将证据与建议声明直接链接，并直接从用于支持指南的证据综合中生成患者决策辅助。此外，他还介绍了实践要点的概念，这是除建议外产生的一种新的指导形式。当未进行系统评价或进行系统评价但未发现足够的证据支持推荐时，使用实践点为临床医生提供指导。实践要点不一定遵循与建议相同的格式——例如，它们可能被格式化为表格、图或算法——并且不根据强度或证据质量进行分级。

在Tonelli博士的指导和专业知识下，使用MAGICapp，以及实践要点的采纳，KDIGO已经看到肾小球疾病指南的更新发展成为一个非常有用的文件，在保持KDIGO最著名的高质量标准和严谨性的同时，丰富了指导。Dr. Tonelli在下文更详细地讨论了KDIGO指南格式的更新（图1）。

总之，我们认为该指南将证明对全世界治疗肾小球疾病患者的临床医生有用。我们再次感谢工作组共同主席和成员以及为这一非常重要的KDIGO活动作出贡献的所有人员。

Michel Jadoul,MD Wolfgang C. Winkelmayer,MD,ScD
KDIGO联合主席

Updates to the KDIGO guideline format

KDIGO guidelines continue to use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, but we have strengthened the link between the recommendation statements and underlying evidence base.

Guidelines now include a mix of recommendations and "practice points" to help clinicians better evaluate and implement the guidance from the expert Work Group.

All recommendations follow a consistent and structured format and are similar in style to previous KDIGO recommendations.

Practice points are a new addition to KDIGO guidance, and may be formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Guidelines will be published in print form and posted online in MAGICapp; the online format will facilitate rapid updates as new evidence emerges.

Below are frequently asked questions outlining the rationale for this shift along with an example recommendation in the new format.

Practice Points are used when	Recommendations are provided when
• No systematic review was conducted • There is insufficient evidence • Evidence is inconclusive • The alternative option is illogical	• Systematic review was conducted • Ample/significant evidence is available • Evidence shows a clear preference for one action over the alternatives
• Guidance is discretionary for the physician	• Guidance is always actionable
• Consensus statements providing guidance are needed in the absence of evidence. Benefits and harms will not be explicitly discussed	• Consensus statements are supported with evidence and explicit discussion of their balance of benefits and harms, values and preferences is necessary
• Guidance does not require an explicit discussion of values and preferences or of resource considerations, although it is implied that these factors were considered	• Application of guidance requires explicit discussion of values and preferences or resource considerations
• The guidance may be more useful as a table, figure, or algorithm	• The guidance requires a more thorough explanation in text (i.e., rationale)

Information on Guideline Development Process

Who

- A Work Group of experts is convened to develop KDIGO guidelines based on evidence and clinical judgment.
- A designated Evidence Review Team systematically reviews and analyzes the evidence.
- The GRADE approach is used to analyze certainty in the evidence and strength of guideline recommendations.

图1|更新 KDIGO 指南格式。CNI，钙调磷酸酶抑制剂；eGFR，估计肾小球滤过率；FAQ，常见问题；GRADE，建议评估、开发和评价分

级；KDIGO，肾病：改善全球预后；MN，膜性肾病；PLA2R，M型磷脂酶 A2 受体；RCT，随机对照试验。（续）

How

- Where the Work Group determines that the quality of evidence or strength/ importance of the statement warrants a graded recommendation, the text will be organized into structured sections (see below).
- Strength, quality, and magnitude of evidence (published or empirical) will indicate grading of the recommendation.
- Where the Work Group judges that there is a lack of evidence or consensus-based clinical practice statements are more appropriate, they may choose to develop a practice point.

What are the structured sections that are included in a recommendation?

Following each recommendation, there is a short remark of one to two sentences **summarizing the most important factors** considered when making the recommendation statement.

Next, the **Key Information** write-up consists of five specific subsections representing factors that the Work Group considered both in developing and grading the recommendation. The sections are:

1. Balance of benefits and harms,
2. Quality of evidence,
3. Values and preferences,
4. Resource use and costs, and
5. Considerations for implementation.

The final section of the write-up is a **Rationale** section which serves two purposes. First, the rationale expands on the short remark that immediately follows the recommendation summarizing how the Work Group considered the five factors of the Key Information section when drafting the recommendation.

Second, the rationale may be used to describe any key differences between the current KDIGO recommendation and recommendations made in the previous guideline or by other guideline producers.

How should I use practice points when caring for my patients?

- As noted, practice points are consensus statements about a specific aspect of care, and supplement recommendations for which a larger quantity of evidence was identified.
- Note that practice points represent the expert judgment of the guideline Work Group, but may also be based on limited evidence.
- Unlike recommendations, practice points are not graded for strength of recommendation or quality of evidence.
- Users should consider the practice point as expert guidance, and use it as they see fit to inform the care of patients.

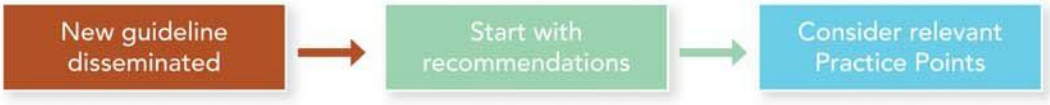


图1|（续）

What happened to the previous "ungraded statements"?

Ungraded statements were often useful to clinicians, but some were not strictly necessary, and their format (i.e., as imperative statements) was not suitable for every situation.

The added flexibility to present practice points in alternative formats such as tables, figures, and algorithms should make them more useful to clinicians. Since shorter documents are easier to use, we have tried to eliminate superfluous statements from the guideline and to retain only those that are necessary for providing patient care.

Why did KDIGO make these changes?

The main rationale for the changes was to improve rigor (better linkage of evidence to recommendations; standardized and consistent format), reduce unnecessary length, and enhance utility to practitioners (clinically useful guidance through practice points; visually appealing tables, figures and algorithms that are easier to use at point of care).

Example of new recommendation and practice point format

Treatment

Recommendation 1. For patients with MN and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or tacrolimus-based therapy for ≥6 months, with the choice of treatment depending on the risk estimate (1B).

Why was this formatted as a recommendation?

- Balance of benefits and harms (all based on published, scientific studies):
  - Benefits: Prevention of progressive kidney failure, complete and partial remission, reduction in the complications and risk of nephrotic syndrome.
  - Harms: Severe short- and long-term side effects with alkylating agents.
- Quality of evidence: This recommendation was based on clinical data extracted from RCTs and outcomes from observational studies were considered.
- Values and preferences: Most physicians and patients will prefer initial treatment with rituximab or CNI over treatment with cyclophosphamide and most well-informed patients with (very high risk of) kidney failure would choose to be treated with cyclophosphamide as compared to conservative treatment only.
- Resources and other costs: This recommendation is likely to be cost-effective to the extent that immunosuppressive treatment prevents progressive loss of kidney function and kidney failure. Cost-efficacy is less likely in patients with a predicted uneventful disease course.
- Considerations for implementation: The recommendation holds for all patients.

Practice Point 1. Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, serum albumin >30 g/l, and eGFR >60 ml/min per 1.73 m^2.

Why was this formatted as a practice point?

- Less robust data than recommendation; no systematic review was conducted.
- Few studies found; clinical experience and data from cohort studies show

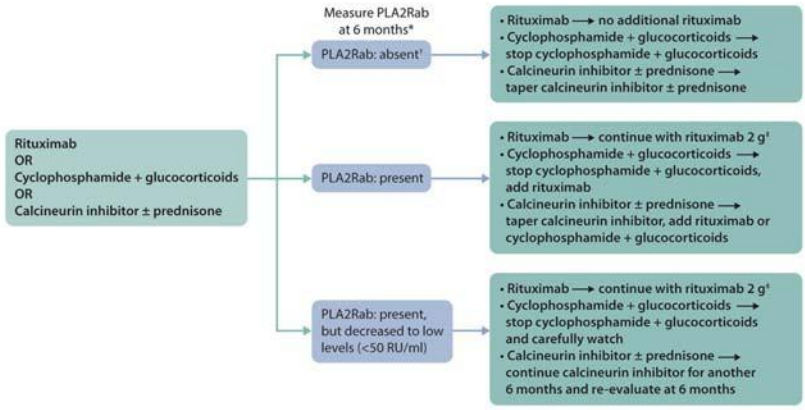
图1|（续）

favorable kidney outcomes in patients with MN who are persistently non-nephrotic, despite the absence of immunosuppressive treatment. This evidence cannot be considered conclusive.
- Based on the limited evidence available, the Work Group decided to base their guidance on the observation that immunosuppressive therapy adds risks without potential benefits for this population.

Practice Points may also have accompanying algorithms to aid in implementation

For example:

Practice Point 2. Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after start of therapy may be useful for evaluating treatment response in patients with membranous nephropathy, and can be used to guide adjustments to therapy.



Why was this formatted as a practice point?

- Limited evidence to support the guidance but monitoring anti-PLA2R antibody levels in these patients can be beneficial.
- No systematic review was conducted.
- The Work Group believes a graphic would be more useful to the reader since an algorithm offers a clearer visual presentation of the approach to monitoring than a series of statements.

图1|（续）

工作组成员

工作组共同主席

Jürgen Floege,MD
University Hospital,RWTH
Aachen Aachen,Germany

工作组

Sharon G. Adler,MD
洛杉矶生物医学研究所洛杉矶，加利福
尼亚州，美国

Jonathan Barratt,
MBChB，英国莱斯特莱斯特
大学博士

Frank Bridoux,MD,PhD
University Hospital
Poitiers Poitiers,France

Kelly A. Burdge，医学博士
Mass General Brigham-Salem
Hospital Salem,MA,USA

Tak Mao
Chan,MBBS,MD,DSc,FHKCP,FHKAM,
MD,FRCP,FASN
香港大学，中国

H. Terence Cook、MBBS、MRCP、
MRCPath、FRCPath、FMedSci
英国伦敦帝国理工学院

Fernando C.
Fervenza,MD,PhD梅奥诊所
美国明尼苏达州罗切斯特市

Keisha L. Gibson,MD,MPH
北卡罗来纳大学医学院教堂山，北卡罗来纳
州，美国

Richard J. Glassock,MD,MACP
加州大学洛杉矶分校 Geffen 医学院，
Laguna Niguel，CA，USA

David
R.W.Jayne,MD,FMedSci

Brad H. Rovin,MD,FACP,FASN
美国俄亥俄州哥伦布市俄亥俄州立大学医学院

University of Cambridge
Cambridge,英国

Vivekanand
Jha,MD,DM,FRCP,FAMS印度新德里
乔治全球健康研究所

Adrian
Liew,MD,MBBS,MRCP,FAMS,FASN,
FRCP，MClinEpid
Mount Elizabeth Novena Hospital
Singapore

Zhi-Hong Liu,MD
南京大学医学院中国南京

Juan Manuel Mejía-Vilet,MD,PhD
Instituto Nacional de Ciencias Médicas
yNutrición Salvador Zubirán
墨西哥墨西哥城

Carla M. Nester,MD,MSA,FASN
University of Iowa
美国爱荷华州爱荷华市

Jai Radhakrishnan，MD，MS，MRCP，
FACC，FASN哥伦比亚大学医学中心
New York,NY,USA

Elizabeth M.
Rave,MD Ohio
Kidney Associates
Columbus,OH,US
A

Heather N.
Reich,MD,CM,PhD,FRCPC
University of Toronto
加拿大多伦多

Pierre
Ronco,MD,PhD
Sorbonne
UniversitéParis,Fra
nce
Le Mans
Hospital Le
Mans,France

Jan-Stephan F.
Sanders,MD,PhD
University of Groningen
Groningen,荷兰

Sanjeev
Sethi,MD,PhD 梅 奥
诊所
美国明尼苏达州罗切斯特市

Yusuke
Suzuki,MD,PhD日本
东京顺天堂大学

悉尼
C.W.Tang,MD,PhD,FRCP,FACP,FHKCP,FHKAM
香港大学，中国

Vladimír Tesar,MD,PhD,FERA,FASN
Charles University
布拉格，捷克共和国
M

arina Vivarelli,MD
Ospedale Pediatrico Bambino
GesōRome,Italy

Jack F.M.荷兰内梅亨 Radboud
大学医学中心Wetzels，MD，
PhD

方法主席
Marcello A. Tonelli,MD,SM,MSc,FRCPC

证据审查小组

Cochrane 肾脏和移植，悉尼，澳大利亚
Jonathan C. Craig,MBChB,DipCH,FRACP,M Med(Clin Epi) ,PhD，证据审核团队总监
Suetonia C. Palmer,MBChB,FRACP,PhD，证据审核团队联合总监
Giovanni F.M.Strippoli,MD,MPH,M Med(Clin Epi) ,PhD，证据审查团队联合总监
Martin Howell,PhD，项目总监助理
David J. Tunnicliffe,PhD，证据审查项目团队负责人和项目经理Fiona
Russell,PhD，Cochrane Kidney and Transplant，总编辑
Gail Y. Higgins,BA,Grad Ed,Grad Dip LibSc,信息专家
Brydee Cashmore,MPH,研究助理

MAGICAPP LIAISON
Lyubov Lytvyn,BSc,MS

摘要

*肾脏疾病：改善全球预后 (KDIGO)2021 肾小球疾病管理临床实践指南*是对 KDIGO 2012 指南的更新。目的是协助临床医生护理成人和儿童肾小球疾病患者。范围包括各种肾小球疾病，包括 IgA 肾病 (IgAN) 和 IgA 血管炎 (IgAV)、膜性肾病、儿童肾病综合征、微小病变 (MCD)、局灶节段性肾小球硬化 (FSGS)、感染相关肾小球肾炎 (GN)、抗中性粒细胞胞浆抗体 (ANCA) 相关性血管炎、狼疮性肾炎、抗肾小球基底膜 (anti-GBM) 抗体 GN 等。此外，该指南将是第一个解决补体介导疾病亚型的指南。每一章遵循相同的格式，提供与诊断、预后、治疗和特殊情况相关的指导。该指南的目标是通过提供可操作的建议和基于严格的正式系统性文献综述的有价值的信息图，为临床医生和患者生成有用的资源。另一个目的是为知识存在差距的领域提出研究建议。该指南针对广泛的临床医生治疗肾小球疾病，同时注意对政策和成本的影响。本指南更新的制定遵循证据审查的明确过程。治疗方法和指南建议基于相关研究的系统评价和证据综合，证据质量和建议强度的评估遵循“建议评估、开发和评价分级”(GRADE) 方法。讨论了证据的局限性，还介绍了未来研究的领域。

关键词：AAV；ANCA；抗GBM；C3；补体；循证；FSGS；肾小球疾病；肾小球肾炎；指南；IgA肾病；IgA血管炎；感染相关肾小球肾炎；KDIGO；狼疮肾炎；膜性肾病；微小病变；MPGN；肾病综合征；系统综述

引用

在引用本文件时，应使用以下格式：肾病：改善全球结局 (KDIGO) 肾小球疾病工作组。KDIGO 2021肾小球疾病管理的临床实践指南。*肾脏国际*2021；100(4S)：S1-S276

本指南（包括所有声明和证据）也将在 MAGICapp 上发布 (https://kdigo.org/guidelines/gd/)。这种在线格式将有助于在新的视图出现时快速更新。

引言

在系统性自身免疫性疾病、感染、药物或恶性肿瘤背景下发生的肾小球疾病（原发性或继发性）影响所有年龄的个体。在大多数肾衰竭登记研究中，肾小球疾病约占现患病例的20%-25%。然而，在儿童、青少年和年轻成人中，肾小球疾病是不可逆肾损伤的最常见原因之一，因此，不仅是个人痛苦的来源，也是主要的社会经济问题。

2012年，KDIGO发布了其关于肾小球疾病管理的首次指南。在过去的8年中，已经取得了一些重大发现，与我们对肾小球疾病的发病机制、诊断和治疗的理解有关。原发性膜性肾病是一种自身免疫性疾病的明确证据，揭示了补体在肾小球病中的作用，从致密沉积物病到 ANCA 相关血管炎，以及证明靶向 B 细胞可有效治疗由致病性（自身）抗体介导的疾病是一些最重要的优势的例子。因此，2012年指南的更新是适当的，并且比以往任何时候都更加紧迫。

在本指南中，我们在很大程度上保持了主题
第1版涵盖的重点是最常见的成人和儿童肾小球肾炎（即，IgAN、膜性肾病、肾病综合征，包括微小病变疾病和 FSGS 以及感染相关肾小球肾炎 [GN]）以及全身性免疫疾病（即，狼疮肾炎、ANCA相关血管炎和抗 GBM 抗体GN）。我们已经扩展了关于*肾小球疾病管理的一般原则*的章节，其中讨论了适用于所有肾小球疾病的支持疗法，以补充每种疾病更具体的免疫抑制治疗。与疾病发病机制的新发现一致，更新的*膜性肾病*章节现在提供了疾病管理中致病性自身抗体监测的深入讨论。我们用题为*免疫球蛋白和补体介导的肾小球疾病伴 MPGN 损伤模式*的新章节替换了膜增生性 GN(MPGN) 的章节标题。关于*抗中性粒细胞胞浆抗体 (ANCA) 相关血管炎*的章节比较和对比了 B 细胞靶向治疗与传统细胞毒性药物。对关于*局灶节段性肾小球硬化* (FSGS) 的章节进行了重组，以帮助临床医生更准确地区分由可能适合免疫抑制的可溶性因子介导的 FSGS 与不应使用免疫抑制的 FSGS 样组织学疾病。*儿童肾病综合征*利用了多种定义免疫抑制持续时间的新试验，撰写本章的目的是与国际儿科肾病协会 (IPNA) 的建议保持一致。

尽管本指南是迄今为止最广泛的 KDIGO 指南，涵盖了大量疾病，但仍有少数肾小球疾病未得到解决。特别是，非常罕见的 GN 类型（例如，滤泡性GN、免疫细胞样 GN 和IgM GN）未被涵盖，部分与空间和资源限制相关，但尤其是因为缺乏对照试验来指导治疗。我们对免疫介导的肾小球疾病的关注导致排除了其他重要实体，如淀粉样变性和免疫球蛋白沉积病、Alport综合征和血栓性微血管病。

该指南主要考虑临床问题
可获得高质量科学证据的管理。它并不意味着取代教科书。相反，工作组与证据审查小组合作，重新评估了2012年指南版本中提出的问题，并确定了几个在临床上仍然紧迫的问题，目前至少有一些证据基础可以提出有根据的建议。关于*肾小球疾病管理的一般原则*的章节将本指南与其他 KDIGO 指南联系起来，其中最重要的包括慢性肾病相关高血压的管理（KDIGO CKD血压管理指南：https://kdigo.org/guidelines/blood-pressure-in-ckd/）。在每一章的末尾，还包括了一个研究议程，旨在根据我们对临床证据现状的全面综述，为未来的研究提供路线图。

大多数肾小球疾病被归类为罕见疾病
因此，缺乏基于 rm 建议的随机对照试验。鉴于这种情况，基于回顾性分析、注册登记数据和专家意见共识，已通过实践要点补充了循证建议，以填补因证据不足而无法提出正式建议的管理缺口。读者会注意到，本指南大部分由实践要点组成。对于肾脏病学界的临床研究者而言，这应该是一个挑战，即开发新型临床试验设计，例如篮子试验、伞形试验、生物标志物驱动试验和单病例随机对照试验，以便在没有足够数量的患者可开展传统前瞻性随机对照试验的情况下实施拟定的研究议程。

作为共同主席，我们非常感谢工作组、证据审查小组和 KDIGO 工作人员为建立这一广泛的

指南。工作组是多样化的、多国的、多学科的、有经验的、深思熟虑的和敬业的，并自愿花无数小时制定这一准则。最后，我们特别感谢 KDIGO 执行委员会，特别是Marcello Tonelli，他审查了准则，并对本项目的方法方面提出了非常有帮助的建议。

我们希望本文提供的指南能为免疫介导的肾小球疾病患者提供更好、更规范的治疗和改善结局。

Jürgen Floege,MD Brad H. Rovin,MD

肾小球疾病指南联合主席

二。建议说明和做法要点摘要

第1章：肾小球疾病管理的一般原则

1.1. 肾活检

操作要点1.1.1：肾活检是肾小球疾病诊断评估的“金标准”。然而，在某些情况下，治疗可以在没有肾脏活检确诊的情况下进行（图2）。

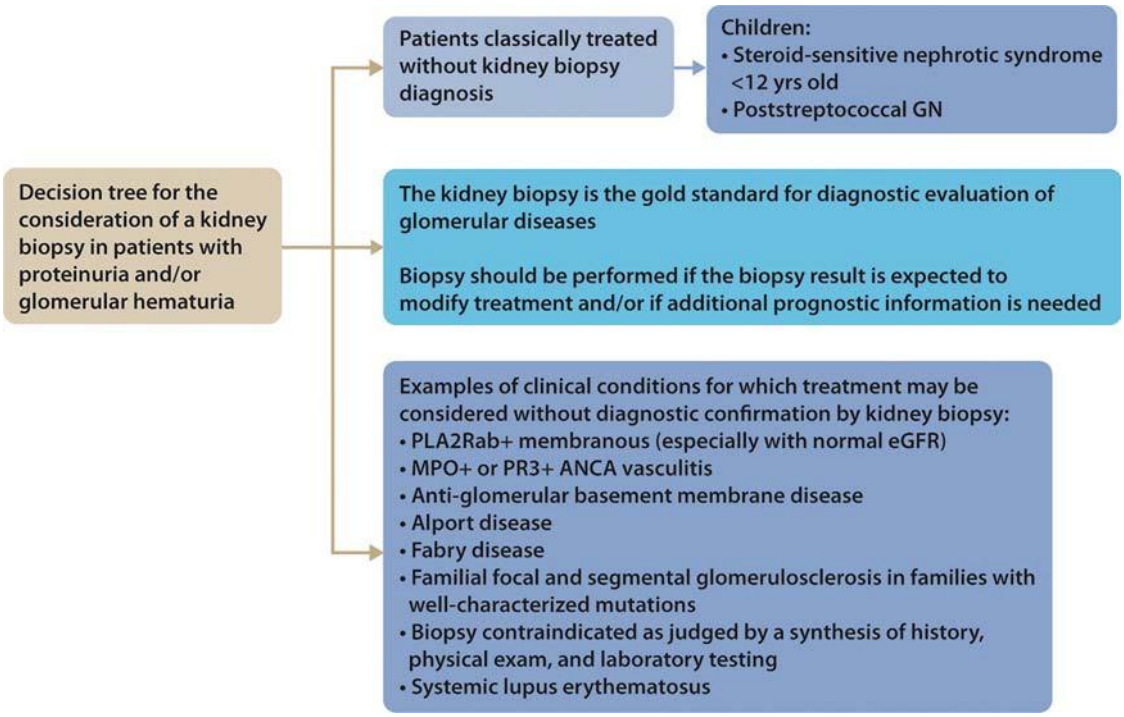


图2蛋白尿和/或肾小球性血尿患者肾活检的注意事项。ANCA，抗中性粒细胞胞浆抗体；eGFR，估计肾小球滤过率；GN，肾小球肾炎；MPO，髓过氧化物酶；PLA2Rab，M型磷脂酶 A2 受体抗体阳性；PR3，蛋白酶3。

实践要点1.1.2：肾组织评价应符合活检充分性标准（图3）。

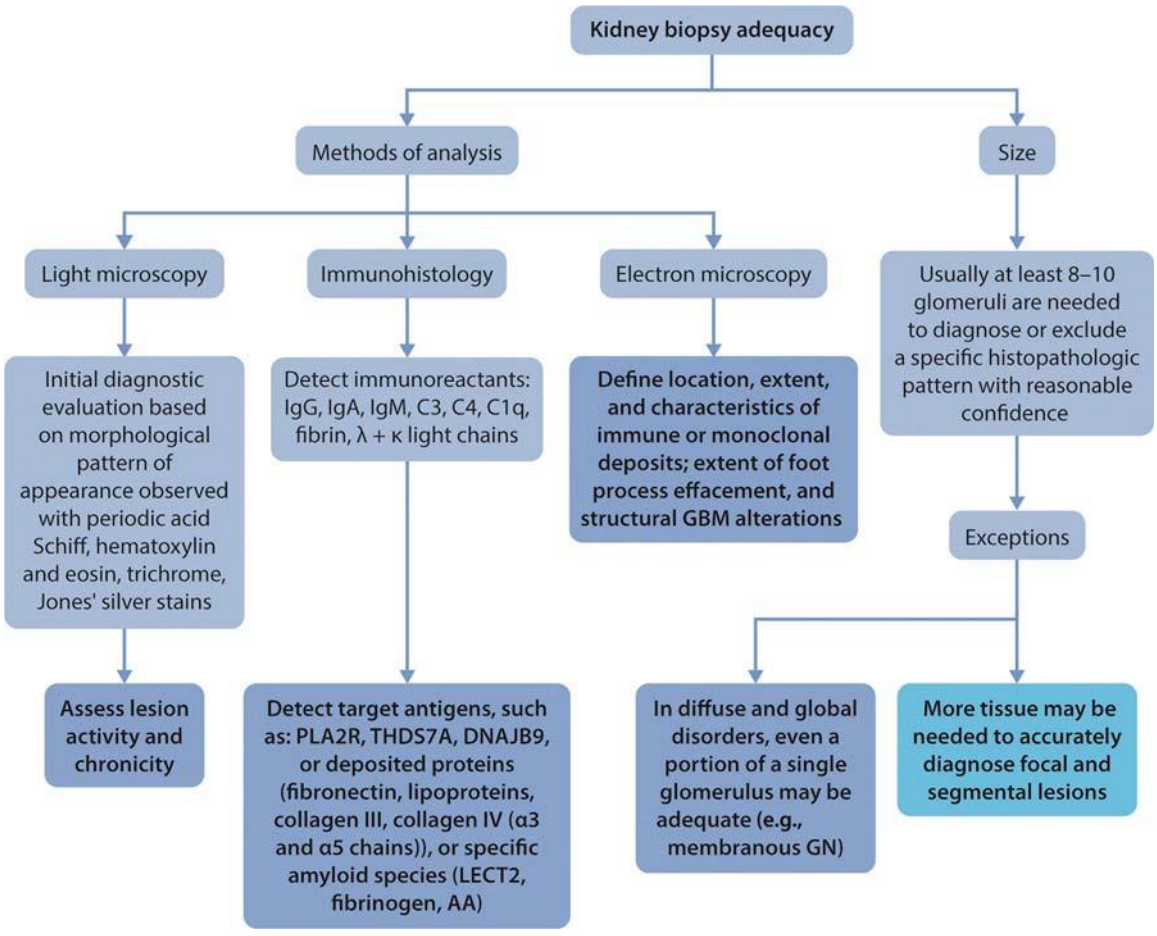


图3|肾组织评价。AA，淀粉样蛋白A；GBM，肾小球基底膜；DNAJB9，DnaJ同系物亚家族 B 成员9；GN，肾小球肾炎；IgA，免疫球蛋白A；IgG，免疫球蛋白g；IgM，免疫球蛋白M；LECT2，白细胞衍生趋化因子-2；PLA2R，M型磷脂酶 A2 受体；THDS7A，含 I 型血小板反应蛋白结构域的7A。

实践要点1.1.3：如果信息可能改变治疗计划或有助于估计预后，应重复进行肾活检。

1.2. 肾功能评估

实践要点1.2.1：在需要开始或强化免疫抑制治疗或临床状态发生变化的肾小球疾病患者中，采集24小时尿液，以测定总蛋白排泄。

实践点1.2.2：对于儿科，24小时尿液采集并不理想，因为可能不准确，采集繁琐。相反，应监测首次晨起蛋白–肌酐比值 (PCR)。

操作要点1.2.3：用于 PCR 的随机“点”尿液采集并不理想，因为蛋白和肌酐排泄均随时间发生变化。

实践要点1.2.4：首次晨尿采集可能低估了直立性蛋白尿中的24小时蛋白排泄。

规范点1.2.5：在可行的情况下，合理的折衷方法是采集“预期”的24小时尿液样本，并测量等份采集物中的PCR。

实践要点1.2.6：无需在每次尿液采集时同时和常规定量钠排泄量，除非有理由怀疑未能遵守关于饮食限钠的建议（图5以及实践要点1.4.2和1.5.9）。

Direct measures of kidney function	Indirect measures of kidney function: estimating equations	Limitations
• Creatinine clearance - 24 h urine creatinine	• eGFR	• No estimate of kidney function has been specifically validated for glomerular diseases and/or nephrotic syndrome • Ethnicity is often a confounding influence • In creatinine-based formulas, hypoalbuminemia may lead to overestimation of true GFR due to increased tubular creatinine secretion[8] • Glucocorticoids may increase serum cystatin C, potentially underestimating eGFR[9] • Low muscle mass overestimates eGFR using creatinine-based formulae[10] • AKI confounds all estimates, which are valid only in steady-state
• Measured GFR* - Inulin clearance (gold standard) - Radioisotopic plasma clearance[1] • ^{125}Iothalamate; ^{99m}Tc-DTPA; ^{51}Cr-EDTA - Non-radioisotopic plasma clearance • Iohexol[2]	**Adults** • Cockcroft–Gault[3] (140-age) (wt [kg]) x 0.85, if female/serum creatinine (mg/dl) x 72 • Modification of diet in renal disease (MDRD) equations[4] (not valid for eGFR >60 ml/min/1.73 m^2) - CKD-EPI creatinine equation (preferred) • Valid with eGFR >60 ml/min/1.73 m^2 - CKD-EPI-cystatin C equations[5] (valid for eGFR >60 ml/min/1.73 m^2) - Full Age Spectrum (FAS) equation[7] • Valid even in eGFR >60 ml/min/1.73 m^2 **Children** • Schwartz equation and its modifications[6] • Full-age spectrum (FAS) formulae[7]	

图5肾小球疾病的肾功能评估。*以ml/min/1.73 m ^{2}表示。GFR估计方程中人种的校正系数存在争议，关于该主题的讨论正在进行中。[20]更多信息请参考 KDIGO CKD 指南。[18]Perrone 等人[13]，[2]Gaspari 等人[12],[3]Cockcroft和Gault.[11],[4]Stevens 等人[16]，[5]Stevens 等人[17],[6]Schwartz 等人[15],[7]Pottel 等人[14],
[8]Branten *et al.*[19],[9]Zhai *et al.*[21],[10]Levey *et al.*[22]AKI，急性肾损伤；CKD-EPI，慢性肾病流行病学协作组；^{51}Cr-EDTA，铬-51标记的乙二胺四乙酸；eGFR，估计的肾小球滤过率 (ml/min)/1.73 m^2；^{99m}Tc-DTPA，锝-二乙烯三胺五乙酸。

实践要点1.2.7：定量肾小球疾病中的蛋白尿，因为其与疾病特异性预后和治疗决策相关。蛋白尿的定性评估在特定情况下可能有用。

实践要点1.2.8：在儿童中，定量蛋白尿，但疾病病因之间的治疗目标不应不同。任何肾小球疾病儿童的目标应是24小时尿液中PCR < 200 mg/g(< 20 mg/mmol) 或 < 8 mg/m ^{2}/小时。接受高于该值的基线值应仅有肾脏瘢痕的肾脏活检证据。

实践要点1.2.9：在成人肾小球疾病患者中首选慢性肾病流行病学协作组 (CKD-EPI) 估计的肾小球滤过率 (eGFR) 肌酐方程，在儿童中首选改良的 Schwartz 方程。成人和儿童均可使用全年龄范围 (FAS) 公式（图5）。

1.3. 血尿评价

实践要点1.3.1：在所有形式的肾小球疾病中，均应常规评价尿沉渣中的红细胞形态以及是否存在红细胞管型和/或棘红细胞。

实践要点1.3.2：监测血尿（程度和持续性）可能对多种形式的肾小球疾病具有预后价值。这尤其适用于免疫球蛋白 A 肾病 (IgAN) 和血管炎（IgAV；第2章）。

1.4. 肾小球疾病并发症的管理（图7）

Practice Point 1.4.1. Use loop diuretics as first-line therapy for treatment of edema in the nephrotic syndrome	• Twice daily dosing preferred over once daily dosing; daily dosing may be acceptable for reduced GFR • Increase dose of loop diuretic to cause clinically significant diuresis or until maximally effective dose has been reached • Switch to longer acting loop diuretic such as bumetanide or torsemide/torasemide if concerned about treatment failure with furosemide, or if concerned about oral drug bioavailability
Practice Point 1.4.2. Restrict dietary sodium intake	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d)
Practice Point 1.4.3. Use loop diuretics with other mechanistically different diuretics as synergistic treatment of resistant edema in the nephrotic syndrome	• All thiazide-like diuretics in high doses are equally effective. None is preferred. • Thiazide diuretics, administered with an oral or i.v. loop diuretic, will impair distal sodium reabsorption and improve diuretic response • Amiloride may provide improvement in edema/hypertension, and counter hypokalemia from loop or thiazide diuretics • Acetazolamide may be helpful for the metabolic alkalosis of diuresis • Spironolactone may provide improvement in edema/hypertension, and counter hypokalemia from loop or thiazide diuretics
Practice Point 1.4.4. Monitor for adverse effects of diuretics	• Hyponatremia with thiazide diuretics • Hypokalemia with thiazide and loop diuretics • Impaired GFR • Volume depletion, especially in pediatric/elderly patients • Hyperkalemia with spironolactone and eplerenone especially if combined with RAS blockade
Practice Point 1.4.5. Strategies for diuretic-resistant patient	• Amiloride • Acetazolamide • i.v. loop diuretics (bolus or infusion) alone • i.v. loop diuretics in combination with i.v. albumin • Ultrafiltration • Hemodialysis • Amiloride may reduce potassium loss and improve diuresis. Acetazolamide may help to treat metabolic alkalosis but is a weak diuretic

图7|NS中的水肿管理。GFR，肾小球滤过率；i.v.，静脉内；NS，肾病综合征；RAS，肾素-血管紧张素系统。

1.5. 肾小球疾病中高血压和蛋白尿减少的管理（图8）

Practice Point 1.5.1.	Use an ACEi or ARB to maximally tolerated or allowed dose as first-line therapy in treating patients with both hypertension and proteinuria	• Do not stop ACEi or ARB with modest and stable increase in serum creatinine (up to 30%) • Stop ACEi or ARB if kidney function continues to worsen, and/or refractory hyperkalemia • Combinations of ACEi and ARB may be used in young adults without diabetes or cardiovascular disease, but benefits and safety are uncertain Caveat: do not start ACEi/ARB in patients who present with abrupt onset of NS. These drugs can cause AKI especially in patients with MCD
Practice Point 1.5.2.	Target systolic blood pressure in most adult patients is <120 mm Hg using standardized office BP measurement. Target 24 h mean arterial pressure in children is ≤50th percentile for age, sex, and height by ambulatory blood pressure monitoring	• Refer to KDIGO BP Guideline (https://kdigo.org/guidelines/blood-pressure-in-ckd/) • Formally speaking, SBP <120 mm Hg has not been validated in GN. In practicality, we are able to achieve an SBP of 120–130 mm Hg in most patients with glomerular disease
Practice Point 1.5.3.	Uptitrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line therapy in treating patients with GN and proteinuria alone	• Indicated for persistent proteinuria despite treatment of primary GN with immunosuppression (where indicated) • Avoid use of an ACEi or ARB if kidney function is rapidly changing
Practice Point 1.5.4.	Proteinuria goal is variable depending on primary disease process; typically, <1 g/d	• It may be reasonable to delay initiation of ACEi or ARB for patients without hypertension with podocytopathy (MCD, SSNS, or primary FSGS) expected to be rapidly responsive to immunosuppression • Proteinuria goal is disease-specific in adults with GN
Practice Point 1.5.5.	Monitor labs frequently if on ACEi or ARB	• Titration of ACEi or ARB may cause acute kidney injury or hyperkalemia
Practice Point 1.5.6.	Counsel patients to hold ACEi or ARB and diuretics when at risk for volume depletion	• Increased risk for acute kidney injury and hyperkalemia • Counsel patients according to level of education in a culturally sensitive manner • Consider transiently stopping RASi during sick days
Practice Point 1.5.7.	Use potassium-wasting diuretics and/or potassium-binding agents to reduce serum potassium to normal, in order to use RAS blocking medications for BP control and proteinuria reduction Treat metabolic acidosis (serum bicarbonate <22 mmol/l)	• Loop diuretics • Thiazide diuretics • Patiromer • Sodium zirconium cyclosilicate (each 10 g of sodium zirconium cyclosilicate contains 800 mg of sodium) • Supplement with oral sodium bicarbonate
Practice Point 1.5.8.	Employ lifestyle modifications in all GN patients as synergistic means for improving control of hypertension and proteinuria	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d) • Normalize weight • Exercise regularly • Stop smoking
Practice Point 1.5.9.	Intensify dietary sodium restriction in those patients who fail to achieve proteinuria reductions, and who are on maximally tolerated medical therapy	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d). Consider using mineralocorticoid receptor antagonists in refractory cases (monitor for hyperkalemia)

图8肾小球疾病中高血压和蛋白尿的管理。ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；BP，血压；FSGS，局灶节段性肾小球硬化；GN，肾小球肾炎；KDIGO，肾病：改善全球预后；MCD，微小病变；NS，肾病综合征；RAS，肾素-血管紧张素系统；RASi，肾素-血管紧张素系统抑制剂；SBP，收缩压；SSNS，类固醇敏感性肾病综合征。

1.6. 肾小球疾病中高脂血症的管理（图10）

Practice Point 1.6.1.	Treatment of hyperlipidemia may be considered in patients with the nephrotic syndrome, particularly for patients with other cardiovascular risk factors, including hypertension and diabetes	High quality data are lacking to guide treatment in these patients
Practice Point 1.6.2.	Use lifestyle modifications in all patients with persistent hyperlipidemia and glomerular disease: • Heart-healthy diet • Increased physical activity • Weight reduction • Smoking cessation	• Not well studied as primary means of reducing lipids in nephrotic syndrome • Can be used as primary therapy in low-risk individuals with mild to moderate hyperlipidemia • Additive to pharmacologic treatment of hyperlipidemia • Considered first-line treatment of hyperlipidemia in children • Consider a plant-based diet • Avoid red meat
Practice Point 1.6.3.	Consider starting a statin drug as first-line therapy for persistent hyperlipidemia in patients with glomerular disease: • Assess ASCVD risk based on LDL-C, Apo B, triglyceride and Lp (a) levels, age group, and ASCVD 'risk enhancers' • Align statin dosage intensity to ASCVD risk • Statins can be initiated in children aged > 8 years with concerning family history, extremely elevated LDL-C or Lp(a), in the context of informed shared decision-making and counselling with patient and family	• Reduced eGFR (<60 ml/min/1.73 m^2 not on dialysis) and albuminuria (ACR >30 mg/g) are independently associated with an elevated risk of ASCVD • ASCVD risk enhancers include chronic inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, history of preeclampsia, early menopause, South Asian ancestry, chronic kidney disease and human immunodeficiency virus/AIDS (accuracy of ASCVD risk estimators have not been well validated for adults with chronic inflammatory disorders or human immunodeficiency virus) • Adherence to changes in lifestyle and effects of LDL-C lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4–12 weeks after statin initiation/dose adjustment or inflammatory disease-modifying therapy/antiretroviral therapy, and every 3–12 months thereafter based on need to assess adherence or safety
Practice Point 1.6.4.	Consider initiation of non-statin therapy in those individuals who cannot tolerate a statin, or who are at high ASCVD risk and fail to achieve LDL-C or triglyceride goals despite maximally tolerated statin dose: • Bile acid sequestrants • Fibrates • Nicotinic acid • Ezetimibe • PCSK9 inhibitor • Lipid apheresis	• Bile acid sequestrants have a high rate of gastrointestinal side effects limiting their use • Bile acid sequestrants and fibrates have been shown in small studies to reduce serum cholesterol in nephrotic syndrome • Fibrates will increase serum creatinine level due to direct action on the kidney • Ezetimibe has limited vascular and clinical benefits, but is used in statin-intolerant patients as salvage therapy • Nicotinic acid and ezetimibe have not been studied in patients with nephrotic syndrome • PCSK9 inhibitors may be beneficial in nephrotic syndrome; trials ongoing

图10肾小球疾病中高脂血症的管理。ACR，白蛋白-肌酐比值；AIDS，获得性免疫缺陷综合征；Apo，载脂蛋白；ASCVD，动脉粥样硬化性心血管疾病；eGFR，估计的肾小球滤过率；LDL-C，低密度脂蛋白胆固醇；Lp，脂蛋白；PCSK9，前蛋白转化酶枯草溶菌素9。

1.7. 高凝状态和血栓形成

操作要点1.7.1：完全抗凝适用于在肾病综合征背景下发生血栓栓塞事件的患者。当血栓栓塞风险超过抗凝诱导的严重出血事件的患者特定风险估计值时，肾病综合征患者应采用预防性抗凝治疗（图11）。

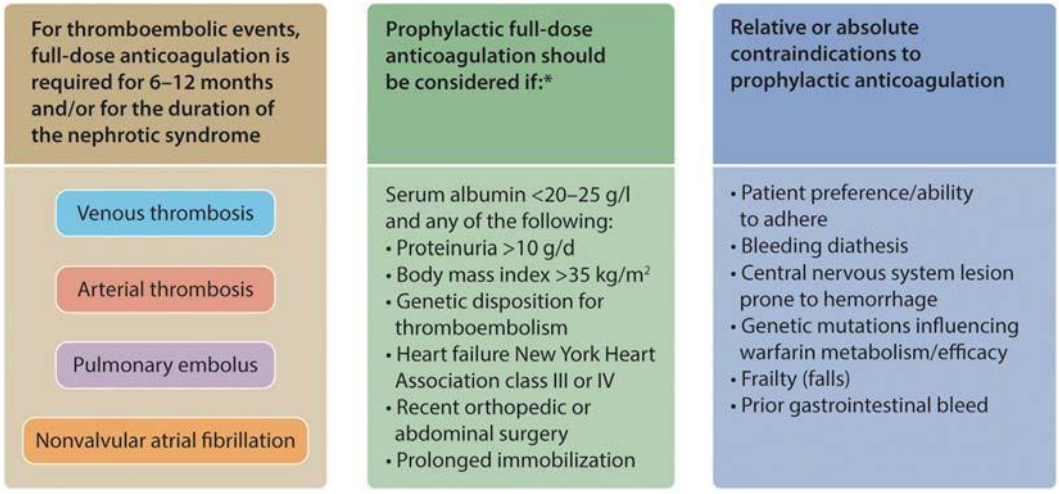


图11|NS中的抗凝治疗。*膜性 GN 发生血栓栓塞事件的风险特别高。NS，肾病综合征。

实践要点1.7.2：肾病综合征患者的抗凝剂给药考虑（图12和图13[44]）。

Prophylactic anticoagulation during transient high-risk events

- Low-dose anticoagulation (e.g., unfractionated heparin 5000 U subcutaneous twice per day)
- Low–molecular-weight heparin: dose reduction may be advised with creatinine clearance <30 ml/min (unadjusted for body surface area); avoid in kidney failure

Full warfarin anticoagulation for thromboembolic events

- Intravenous heparin followed by bridging to warfarin is preferred
- Higher than usual heparin dosing may be required in nephrotic syndrome due to antithrombin III urinary loss
- Long-term experience with warfarin makes it the anticoagulant of choice until pharmacokinetic studies are performed with newer agents
- International normalized ratio should be monitored frequently, since warfarin–protein binding may fluctuate with changing serum albumin
- Target international normalized ratio is 2–3
- These recommendations are not supported by randomized controlled trials
- Be watchful of interactions of warfarin with other medications

Factor Xa inhibitors (Xai): not systematically studied in patients with nephrotic syndrome

- Dosing in the general population is adjusted according to serum creatinine, creatinine clearance (estimated by Cockcroft–Gault equation), age, and weight. Urinary clearance of the Xa inhibitors varies:
  - Apixaban, 27%
  - Edoxaban, 50%
  - Rivaroxaban, 66%
- The effects of hypoalbuminemia on drug dosing have not been studied, and these drugs are heavily albumin-bound, which is likely to substantially affect their half-lives
- Protein binding:
  - Apixaban, 92%–94%
  - Edoxaban, 55%
  - Rivaroxaban, 92%–95%
- Despite a few favorable case reports, the pharmacokinetic properties of these drugs require additional study for both safety and efficacy before they can be generally recommended in nephrotic patients

Direct thrombin inhibitors (DTI): not systematically studied in patients with nephrotic syndrome

- Dosing in the general population is adjusted according to creatinine clearance for dabigatran. No adjustment is required for argatroban. The urinary clearance of the DTI varies:
  - Argatroban, 22% (6% metabolites; 16% unchanged drug)
  - Dabigatran etexilate, 7%
- The effects of hypoalbuminemia on drug dosing have not been studied, and these drugs are modestly albumin-bound, which is likely to affect their half-lives
- Protein binding:
  - Argatroban, 54%
  - Dabigatran etexilate, 35%
- Despite improved safety in the general population, the pharmacokinetic properties of these drugs require additional study for both safety and efficacy before they can be recommended in nephrotic patients

图 12 NS 患者的抗凝剂剂量考虑。NS，肾病综合征。

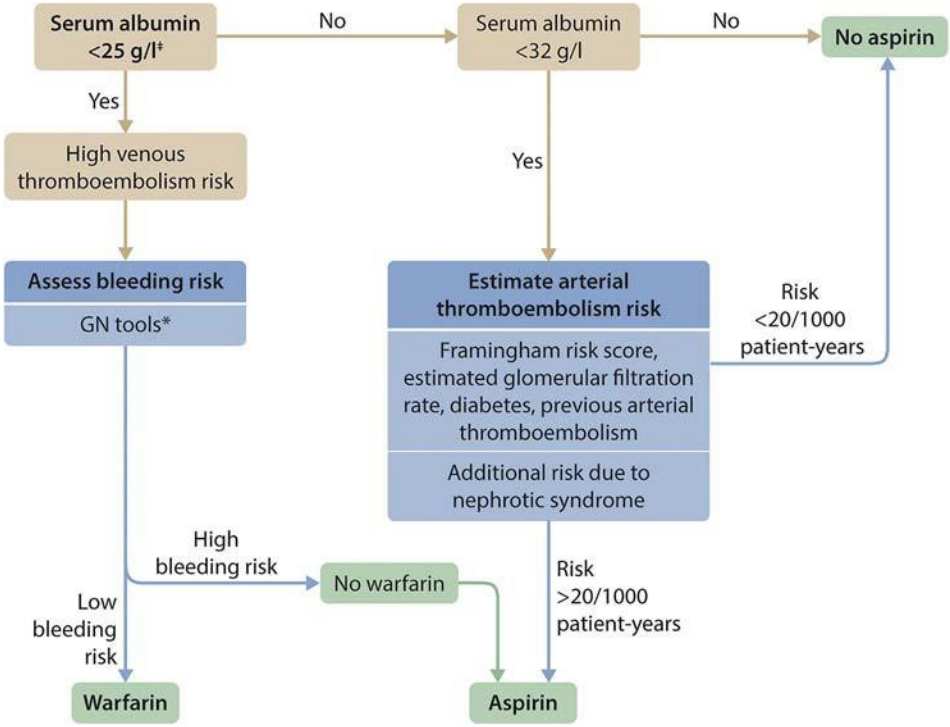


图13成人 GN/肾病综合征的预防性抗凝治疗。转载自*Kidney International*，第89卷，第5期，Hofstra JM，Wetzels JFM。阿司匹林是否应用于膜性肾病患者血栓事件的一级预防？第981-983页，版权ª2016，经国际肾脏病学会许可。[44]注：该算法适用于膜性肾病患者。对于其他基础疾病所致的肾病综合征 (NS) 患者，其价值尚不清楚。在肾小球肾炎 (GN) 儿童患者中，考虑正式血液学会诊，以评价静脉血栓栓塞 (VTE) 和出血风险。Framingham风险评分不适用于儿科患者。‡使用溴甲酚绿 (BCG) 测得白蛋白值为 25 g/L 或32 g/L（2.5 g/dL或3.2 g/dL）。当使用溴甲酚紫 (BCP) 或用于血清白蛋白水平的免疫测定时，应使用 20 g/L 或30 g/L（2 g/dL或3 g/dL）的值。*请转至 https://www.med.unc.edu/gntools/bleedrisk.html.

1.8. 感染风险

实践要点1.8.1：肾小球疾病和肾病综合征患者以及慢性肾病 (CKD) 患者接种肺炎球菌疫苗。患者和家庭接触者应接种流感疫苗。患者应接种带状疱疹疫苗 (Shingrix)。

实践要点1.8.2：在临床适当患者中筛查结核病 (TB)、乙型肝炎病毒 (HBV)、丙型肝炎病毒 (HCV)、人类免疫缺陷病毒 (HIV) 和梅毒（第7章）。

实践要点1.8.3：对于曾居住在地方性热带环境中并有嗜酸性粒细胞增多和血清免疫球蛋白 E(IgE) 水平升高的接受免疫抑制治疗的患者，应考虑类圆线虫二重感染。

实践要点1.8.4：在接受高剂量泼尼松或其他免疫抑制剂（利妥昔单抗、环磷酰胺）的患者中，应考虑预防性甲氧苄啶-磺胺甲恶唑 (TMP-SMX)。

1.9. 结局指标

实践要点1.9.1：治疗后蛋白尿减少的目标因肾小球疾病的各种特定原因而异。

实践点1.9.2：‡建议将2-3年期间 eGFR 较基线降低40%作为肾衰竭的替代结局指标。

1.10.年龄、性别、种族和遗传背景的影响
[无建议或实践要点]

1.11.基因组学、转录组学、蛋白质组学、代谢组学
[无建议或实践要点]

1.12.使用糖皮质激素和免疫抑制治疗
[更多信息请参见各章节。]

1.13.免疫抑制的药理学方面（图15）

Practice Point 1.13.1.	**Choose a glomerulonephritis treatment regimen that averts the immediate morbidity of the primary disease process**	• Intensity of induction therapy is predicated on the severity of presenting symptoms and type of glomerulonephritis • The level of GFR needs to be taken into account for determining safe dosage
Practice Point 1.13.2.	**Choose a glomerulonephritis treatment regimen that prevents disease progression**	• Complete clinical remission may not be possible in all forms of chronic glomerulonephritis • Prolonged immunosuppression or multiple rounds of immunosuppression may be required to prevent or delay chronic kidney disease progression or the development of kidney failure • Proteinuria reduction is a surrogate endpoint in the treatment of glomerulonephritis
Practice Point 1.13.3.	**Choose a glomerulonephritis treatment regimen that minimizes harmful side effects from immunosuppression**	• Disclose individual drug side effects (both short- and long-term) • Consider the patient's point of view in shared decision-making • Screen for latent infections, where appropriate, prior to initiation of certain immunosuppression protocols • Monitor therapeutic drug levels where clinically indicated • Prescribe prophylaxis for specific immunosuppressive drug side effects • Review vaccination status and update as required • Offer fertility preservation, where indicated • Monitor for development of cancers or infections • Prolonged immunosuppression or multiple rounds of immunosuppression is associated with more toxic drug exposure over time

图15|免疫抑制相关不良反应的最小化。GFR，肾小球滤过率。

1.14.肾小球疾病的饮食管理（图16）

Practice Point 1.14.1.	Restrict dietary sodium to reduce edema, control blood pressure, and control proteinuria	• Dietary sodium <2.0 g/d (<90 mmol/d)
Practice Point 1.14.2.	Restrict dietary protein based on degree of proteinuria	• Nephrotic-range proteinuria: 0.8–1 g/kg/d protein intake* • Add 1 g per g of protein losses (up to 5 g/d) • The safety of protein restriction in GN has not been established in children • Plant-based diets may be preferred
Practice Point 1.14.3.	Restrict dietary protein based on kidney function	• Estimated glomerular filtration rate <60 ml/min/1.73 m^2 with nephrotic-range proteinuria • Limit or target intake to 0.8 g/kg/d • Avoid <0.6 g/kg/d due to safety concerns and risk of malnutrition • Emphasis on vegetable (plant) sources of protein is appropriate
Practice Point 1.14.4.	Restrict caloric intake to achieve normal body mass index and limit central adiposity in order to reduce chronic kidney disease progression, development of kidney failure, cardiovascular events, and mortality	• Target caloric intake 35 kcal/kg/d • Estimated glomerular filtration rate <60 ml/min/1.73 m^2: 30–35 kcal/kg/d
Practice Point 1.14.5.	Restrict dietary fats in patients with elevated serum cholesterol to prevent cardiovascular complications	• Heart-healthy diet • Dietary fat <30% of total calories • Mono- or polyunsaturated fat 7%–10% of total calories

图16肾小球疾病的饮食建议。*理想体重。GN，肾小球肾炎。

1.15.肾小球疾病妇女的妊娠和生殖健康

实践要点1.15.1：肾小球疾病妊娠患者的护理需要肾内科和产科之间的协调，理想情况下，应在妊娠前考虑此类计划。

1.16.治疗费用及相关问题

实践要点1.16.1：应向肾小球疾病患者提供参加疾病登记研究和临床试验的机会（如可用）。

1.17.肾小球疾病治疗的目标

[无建议或实践要点]

1.18.移植后 GN

[更多信息请参见各章节。]

第2章：免疫球蛋白 A 肾病 (IgAN)/免疫球蛋白 A 血管炎 (IgAV) 免疫球蛋白 A 肾病

2.1 诊断

操作要点2.1.1：诊断免疫球蛋白 A 肾病 (IgAN) 的注意事项：

- IgAN 只能通过肾活检确诊。
- 根据修订后的 Oxford 分类确定 MEST-C 评分（系膜 [M] 和毛细血管内 [E] 细胞过多、节段性硬化 [S]、间质纤维化/肾小管萎缩 [T] 和新月体 [C]）。[80]
- 没有经验证的*诊断*血清或尿液 IgAN 生物标志物。
- 评估所有 IgAN 患者的次要原因。

2.2 预后

实践要点2.2.1：原发性 IgAN 预后的考虑因素：

- 活检时的临床和组织学数据可用于对患者进行风险分层。
- 国际 IgAN 预测工具是量化进展风险和告知与患者共同决策的宝贵资源。
  - 通过 QxMD 计算
- 国际 IgAN 预测工具结合了活检时的临床信息，不能用于确定任何特定治疗方案的可能影响。
- 除 eGFR 和蛋白尿外，没有经验证的 IgAN *预后*血清或尿液生物标志物。

2.3 治疗

实践要点2.3.1：治疗所有无变体形式原发性 IgAN 的 IgAN 患者的注意事项：

- 管理的主要重点应是优化支持治疗。
- 评估心血管风险，并在必要时开始适当的干预。
- 提供生活方式建议，包括饮食限钠、戒烟、控制体重和适当运动的信息。
- 除饮食限钠外，无特定饮食干预显示可改变 IgAN 结局。
- IgAN 的变异型：IgA沉积伴微小病变 (MCD)、IgAN伴急性肾损伤 (AKI) 和 IgAN 伴急进性肾小球肾炎 (RPGN) 可能需要特定的立即治疗。

实践要点2.3.2：*IgAN*患者的初始评估和管理算法（图21）

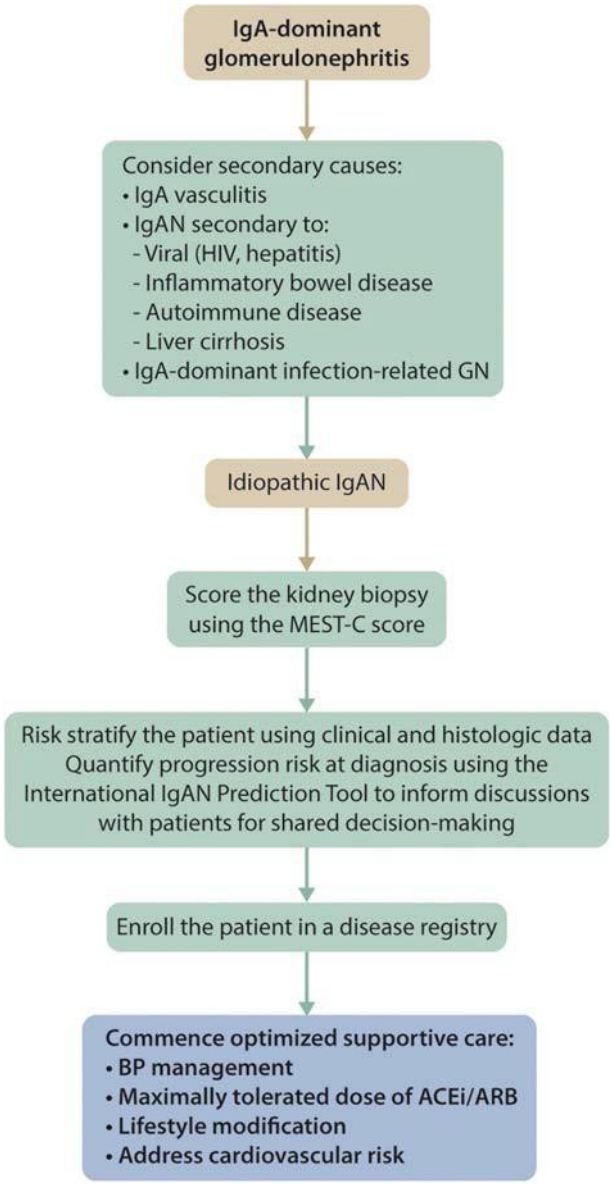


图 21 IgAN 患者的初步评估和管理。ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；BP，血压；GN，肾小球肾炎；HIV，人类免疫缺陷病毒；IgAN，免疫球蛋白 A 肾病；MEST-C，系膜 (M) 和毛细血管内 (E) 细胞过多、节段性硬化 (S)、间质纤维化/肾小管萎缩 (T) 和新月体 (C)。

建议2.3.1：我们建议对所有患者的血压进行管理，如第1章所述。如果患者蛋白尿 > 0.5 g/日，我们建议使用血管紧张素转换酶抑制剂 (ACEi) 或血管紧张素 II 进行初始治疗受体阻滞剂 (ARB)*(1B)*。

建议2.3.2：我们建议所有蛋白尿 > 0.5 g/日的患者（无论是否患有高血压）均接受 ACEi 或 ARB 治疗 *(1B)*。

2.3.1 尽管接受了最大程度的支持治疗，但仍存在进展性 CKD 高风险的 IgAN 患者

实践要点2.3.1.1：尽管进行了最大限度的支持治疗，但仍有进展性 CKD 高风险的 IgAN 患者的治疗考虑。

- IgAN 进展的高风险目前定义为蛋白尿 > 0.75–1 g/日，尽管‡进行了90天优化支持治疗。
- 免疫抑制药物应仅考虑用于尽管接受了最大程度的支持治疗但仍处于进展性 CKD 高风险的 IgAN 患者（入组唯一一项表明免疫抑制获益的大型随机对照试验 [RCT] 的患者的平均蛋白尿为2.4 g/日）。
- 鉴于现有免疫抑制治疗选择的安全性和有效性目前尚不确定，所有尽管接受了最大程度的支持治疗但仍处于进展性 CKD 高风险的患者均应被给予参加临床试验的机会。
- 在考虑免疫抑制的所有患者中，应详细讨论每种药物的风险和获益，患者应认识到eGFR < 50 mL/min/1.73 m ^{2}的患者更可能发生不良治疗作用。
- 没有足够的证据支持使用牛津分类 MEST-C 评分来确定是否应在 IgAN 中开始免疫抑制治疗。
- 没有足够的证据根据肾活检中新月体的存在和数量来做出治疗决策。
- 国际 IgAN 预测工具不能用于确定任何特定治疗方案的可能影响。
- 应动态评估患者风险随时间的变化，因为免疫抑制相关决定可能会发生变化。

实践要点2.3.1.2：蛋白尿降至 1 g/日以下是 IgAN 肾脏结局改善的替代标志物，降至 1 g/日以下是合理的治疗目标。

建议2.3.1.1：我们建议，尽管接受了最大程度的支持治疗，但仍处于进展性 CKD 高风险的患者应考虑接受6个月疗程的糖皮质激素治疗。必须与研究者讨论治疗期间毒性的重要风险患者，尤其是eGFR < 50 mL/min/1.73 m ^{2} *(2B)* 的患者。

实践要点2.3.1.3：糖皮质激素在 IgAN 中的应用：

- 糖皮质激素治疗 IgAN 的临床获益尚不明确，在图23所列情况下应极其谨慎或完全避免使用：

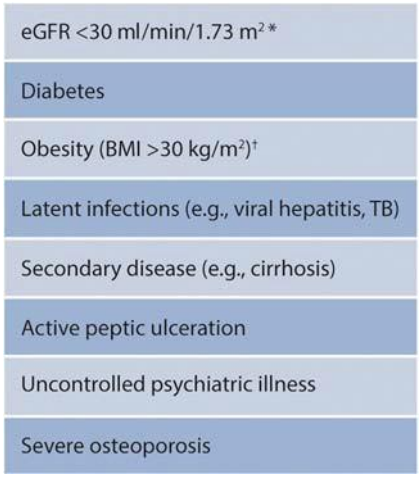


图23应避免使用糖皮质激素或慎用糖皮质激素的情况。*全球 IgA 肾病类固醇治疗评价 (TESTING)[109] 研究纳入 eGFR 为20-30 mL/min/1.73 m^2的患者，但总计仅26例患者具有该范围的肾功能。预先设定的疗效和毒性信号亚组分析效力不足，无法区分eGFR < 30 mL/min/1.73 m^2的患者。†TESTING研究中的高 BMI 未被特别视为排除标准，但平均 BMI < 24 kg/m^2。BMI，体重指数；eGFR，估计肾小球滤过率；TB，结核病。

- 没有足够的证据支持使用牛津分类 MEST-C 评分来确定何时应开始任何糖皮质激素治疗。
- 没有数据支持隔日糖皮质激素方案或减量方案的疗效或毒性降低。
- 根据当地指南，在适当情况下，糖皮质激素（泼尼松等效剂量‡0.5 mg/kg/d）治疗应包括预防*肺囊虫*肺炎以及胃保护和骨保护。

实践要点2.3.1.4：最大限度支持治疗后仍处于进展高风险的 IgAN 患者的管理（图24）

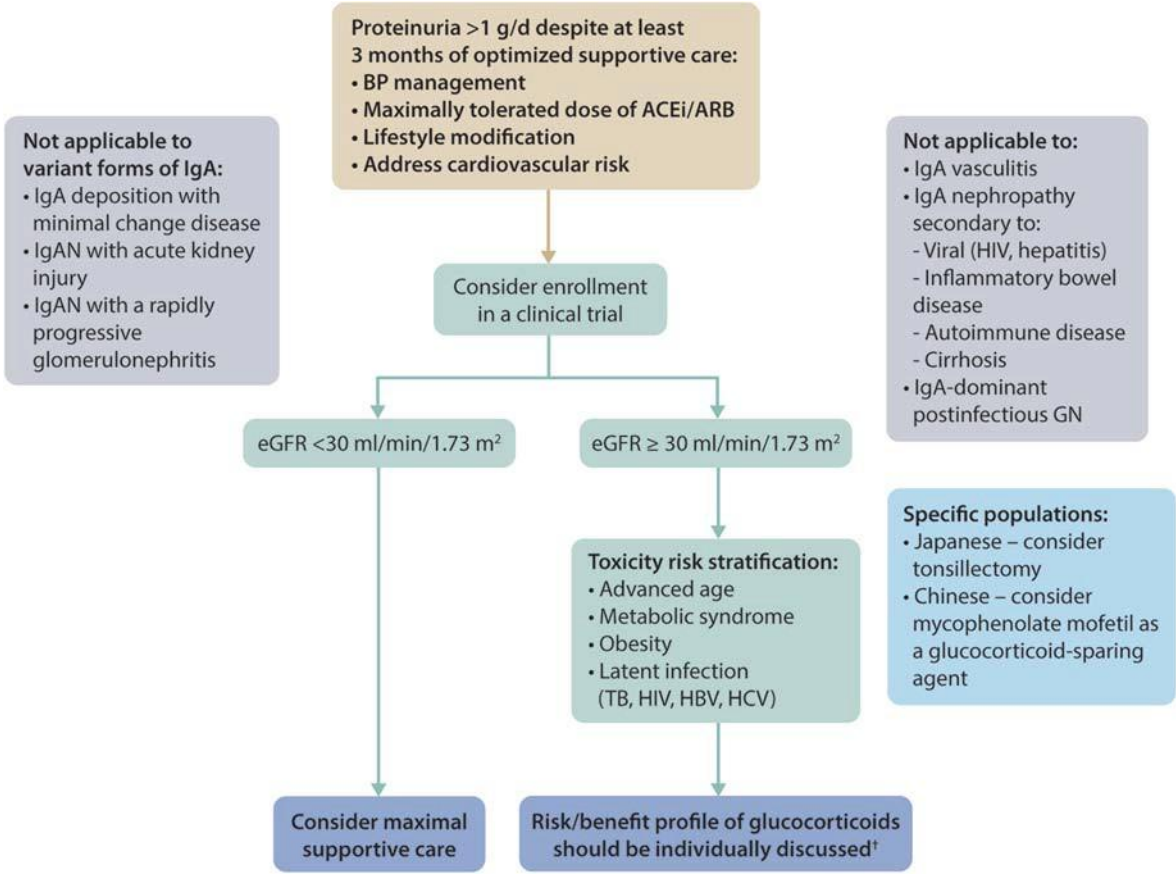


图24最大限度支持治疗后仍处于进展高风险的 IgAN 患者的管理。*IgAN伴急进性肾小球肾炎见操作要点2.4.3。†TESTING研究[109]显示了显著蛋白尿（平均2.4 g/日）患者疗效的早期证据，以牺牲治疗相关发病率和死亡率为代价。ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；BP，血压；eGFR，估计肾小球滤过率；GN，肾小球肾炎；HBV，乙型肝炎病毒；HCV，丙型肝炎病毒；HIV，人类免疫缺陷病毒；IgAN，免疫球蛋白 A 肾病；TB，结核病。

实践要点2.3.1.5：IgAN中评价的其他药物治疗（图25）

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No documented evidence of efficacy
Rituximab	Not recommended	No documented evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	In a single RCT conducted in China, MMF with low-dose glucocorticoids was noninferior to standard-dose glucocorticoids for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d. There were significantly fewer glucocorticoid-related side effects in the combination-therapy arm.[1, 5]
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy.[2–5]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[6]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

图25|IgAN中评价的其他药物治疗。[1]Hou *et al.*[115],[2]Hogg *et al.*[116],[3]Frisch *et al.*[117],[4]Maes *et al.*[118],[5]Vecchio *et al.*[119],[6]Liu *et al.*[120]ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；IgAN，免疫球蛋白 A 肾病；MMF，吗替麦考酚酯；RCT，随机对照试验。

实践要点2.3.1.6：IgAN中的扁桃体切除术：

- 在高加索患者中，不应进行扁桃体切除术治疗IgAN。
- 一些国家 IgAN 患者复发性扁桃体炎治疗指南建议行扁桃体切除术。
- 来自日本的多项研究报告，单独扁桃体切除术或联合脉冲式糖皮质激素治疗后，肾脏存活率提高，血尿和蛋白尿部分或完全缓解（图26；补充表S7 [95、121–124]）。

	Japanese IgAN	Chinese IgAN	Caucasian IgAN
Clinical practice	Performed routinely (often with pulsed glucocorticoids)	Not routinely performed	Not performed
Remarks	Multiple cohort studies,[1–5] including a large retrospective study with propensity matching,[5] report improved kidney survival following tonsillectomy. A single RCT failed to show a difference in eGFR at 1 year comparing tonsillectomy vs. tonsillectomy and pulsed glucocorticoids, and no longer term data are available from this study.[6]	Inconsistent data from small retrospective cohort studies and a small single-center RCT	Very few data available in this population. Available data do not support the efficacy of tonsillectomy as a treatment for IgAN in Caucasian patients

图26局部使用扁桃体切除术治疗IgAN。[1]Yang *et al.*[124],[2]Kawasaki *et al.*[123],[3]Hotta *et al.*[121],[4]Reid 等人[95]，[5]Hirano 等人[125]，[6]Kawamura *et al.*[122]eGFR，估计肾小球滤过率；IgAN，免疫球蛋白 A 肾病；RCT，随机对照试验。

2.4.特殊情况

实践要点2.4.1：IgAN伴肾病综合征：

- 罕见情况下，IgAN患者表现为肾病综合征（包括水肿以及低白蛋白血症和肾病范围蛋白尿 > 3.5 g/日）。
- 在这些病例中，系膜 IgA 沉积可能与光学和电子显微镜检查特征相关，否则与类似 MCD 的足细胞病一致。
- 目前尚不清楚这是 IgAN 的特异性足细胞病变变体还是 IgAN 患者存在MCD。
- 肾活检显示系膜 IgA 沉积以及光学和电子显微镜检查特征与 MCD 一致的患者应按照 MCD 指南进行治疗（第5章）。
- 对于肾活检同时具有系膜增生性肾小球肾炎 (MPGN) 特征的肾病综合征患者，尽管采取了最大程度的支持治疗，但仍应采用与进展性 CKD 高风险患者相同的方式进行治疗。
- 在 IgAN 中也可能观察到不伴肾病综合征的肾病范围蛋白尿，这通常反映了同时存在的继发性局灶节段性肾小球硬化 (FSGS)（例如，肥胖、不受控制的高血压）或广泛肾小球硬化和肾小管间质纤维化。

实践要点2.4.2：IgAN伴AKI：

- IgAN 患者可在重度可见血尿的背景下发生AKI，通常与上呼吸道感染相关。对于血尿停止后2周内肾功能未改善的患者，应考虑重复肾活检。伴有可见血尿的 AKI 的即刻处理应侧重于 AKI 的支持治疗。
- 由于 RPGN 伴广泛新月体形成（通常无可见血尿），IgAN也可能出现*新发* AKI 或在其自然病程中出现AKI。在无可见血尿且排除 RPGN 的其他原因（例如，抗中性粒细胞胞浆抗体 [ANCA] 相关血管炎 [AAV]、抗肾小球基膜 [GBM] 疾病）和可逆性原因（例如，药物毒性、常见的肾前和肾后原因）的情况下，应尽快进行肾活检。

练习点2.4.3：IgAN与RPGN：

- 快速进展的 IgAN 定义为‡eGFR在≤3个月内下降50%，其中排除了 RPGN 的其他原因（例如AAV、抗 GBM 疾病）和可逆性原因（例如药物毒性、常见的肾前和肾后原因）。
- 肾活检在这些病例中是必不可少的，通常会显示系膜和毛细血管内细胞过多，以及高比例的肾小球受到新月体累及并伴有局灶性坏死区域。
- 在血清肌酐 (SCr) 未伴随变化的情况下，肾活检中存在新月体并不构成快速进展的IgAN；然而，这些患者需要密切随访，以确保及时发现 GFR 的任何下降。如果发生这种情况，可考虑进行第二次肾活检。
- 应根据 AAV 指南（第9章）为快速进展的 IgAN 患者提供环磷酰胺和糖皮质激素治疗。

- 免疫抑制应伴随的预防措施在第1章中讨论。
- 没有足够的证据支持使用利妥昔单抗治疗快速进展的IgAN。

实践要点2.4.4：IgAN和妊娠计划：

- IgAN 是一种以青壮年为主的疾病，所有有生育能力的妇女均应酌情提供孕前咨询。
- 孕前咨询应包括停止肾素-血管紧张素系统 (RAS) 阻断的讨论。受孕前应使用替代抗高血压药物优化血压控制。
- 在最大程度支持治疗后仍有进展性 CKD 高风险的女性患者中（建议2.3.1.1），在受孕前进行优化免疫活性和减少蛋白尿的免疫抑制试验可能优于妊娠期间紧急启动免疫抑制。

操作要点2.4.5：儿童IgAN：

一般注意事项

- 出于本实践点的目的，将儿童定义为年龄 < 18岁的儿童。众所周知，青春期后儿童在某些方面的治疗过程和反应可能与 IgAN 成人相似，但目前尚无充分数据建议将其作为 IgAN 成人进行管理。
- 可见血尿在儿童中比成人中更常见，这可能解释了儿童早期诊断的原因。[126]
- 诊断时儿童一般 eGFR 高于成人，尿蛋白排泄量低于成人，血尿多于成人。[127]

儿童肾活检

- 通常在出现症状（血尿、蛋白尿、正常C3）时进行肾活检，以确诊（并排除其他诊断）并评估炎症/坏死的程度。
- 在儿童 IgAN 的肾活检中，炎症、系膜和毛细血管内细胞过多往往比成人更常见。[128–131]

治疗

- 有强有力的证据表明 RAS 阻断对儿童有益。[132]所有 IgAN 和蛋白尿儿童 > 200 mg/日或PCR > 200 mg/g(> 0.2 g/g[20 mg/mmol]) 应接受 ACEi 或 ARB 阻断治疗，建议低钠饮食，并采取最佳生活方式和血压控制（收缩压 [SBP] < 年龄、性别和身高的第90百分位数）。
- 众所周知，成人和儿童使用免疫抑制治疗 IgAN 不同，在儿童中，免疫抑制剂的使用更广泛，尤其是糖皮质激素的使用。然而，缺乏 RCT 和专家共识驱动的适应症。
- 主要来自回顾性研究的证据表明，糖皮质激素治疗（加二线免疫抑制）可改善肾脏存活率。[126,133]
- 在蛋白尿 > 1 g/日或PCR > 1 g/g(100 mg/mmol) 和/或系膜细胞过多的儿童中，大多数儿童肾病学家从诊断时开始除 RAS 阻断外，还将接受糖皮质激素治疗。尚未确定治疗持续时间，但通常采用4周 1-2 mg/kg/d 口服泼尼松龙（或等效药物），随后在4-6个月内隔日逐渐减量。还使用了包括静脉注射甲泼尼龙在内的方案。[127,128,130,134]
- 除糖皮质激素外使用非糖皮质激素免疫抑制剂的证据很少，但在更严重的病例中可考虑这种方法。
- 至于成人，可能发现伴有 MCD 的IgAN，应将其视为激素敏感性肾病综合征（SSNS；第4章）。
- 与成人一样，快速进展型 IgAN 儿童的结局较差，尽管证据有限，但仍应对该亚组提供糖皮质激素（通常为甲泼尼龙冲击）和环磷酰胺治疗。[128,130,135]

随访

- 针对蛋白尿£200 mg/日 (£400 mg/1.73 m²/d) 或PCR£200 mg/g(£0.2 g/g[£20 mg/mmol])。
- 针对年龄、性别和身高SBP < 第90百分位数时的血压。
- 即使在完全缓解后仍继续随访患者，因为即使在多年后也可能复发。[136]

免疫球蛋白 A 血管炎

2.5 诊断

操作要点2.5.1：诊断免疫球蛋白 A 血管炎 (IgAV) 的注意事项：

- 与儿童不同，国际上尚无一致的成人 IgAV 诊断标准，但通常根据儿童标准进行 IgAV 的临床诊断。[140,141]
- 对于具有 IgAV 典型血管炎性皮疹的成人，应在符合持续性和/或显著肾炎、RPGN、蛋白尿 > 1 g/日和/或肾功能受损特征的情况下进行肾活检。
- 评估所有 IgAV 成人患者的次要原因。
- 通过适合年龄和性别的筛查试验，评估所有 IgAV 成人患者的恶性肿瘤。

2.6 预后

实践要点2.6.1：IgAV预测的考虑因素：

- 来自有限数量的小型登记研究的回顾性数据已确定，不受控制的高血压和就诊时的蛋白尿量以及随访期间的高血压和平均蛋白尿是 IgAV 成人肾脏结局不良的预测因素[142–144]。
- 尚未对 IgAV 的 Oxford 分类进行验证[88]。
- 国际 IgAN 预测工具 非 IgAV 的预测指标。

2.7 治疗

2.7.1 IgAV 中肾炎的预防

并

建议2.7.1.1：我们建议不在肾外 IgAV 患者中使用糖皮质激素预防肾炎 (1B)。

实践要点2.7.1.1：治疗所有无 RPGN 的 IgAV 相关肾炎 (IgAVN) 患者的注意事项：

- 评估心血管风险，并在必要时开始适当的干预。
- 酌情提供生活方式建议，包括戒烟、控制体重和锻炼相关信息。
- 未显示特定饮食干预可改变 IgAVN 的结局。
- 治疗达到国家商定的血压目标。KDIGO建议治疗至 SBP 目标值 < 120 mmHg（使用标准化常规血压测量值测量）（图8）。
- 如果蛋白尿 > 0.5 g/日，则使用最大耐受剂量的 ACEi 或 ARB 进行治疗。
- 提供参与临床试验的机会（如果有）。

2.7.2 尽管接受了最大程度的支持治疗，但仍有进展性 CKD 高风险的 IgAVN 患者

实践要点2.7.2.1：尽管进行了最大程度的支持治疗，但仍存在进展性 CKD 高风险的 IgAVN 患者的治疗考虑因素：

- 没有足够的证据支持使用牛津分类 MEST-C 评分来确定 IgAVN 患者是否应开始免疫抑制治疗。
- 肾活检中新月体的存在本身并不是免疫抑制开始的自动指征。
- 在考虑免疫抑制的所有患者中，应与患者详细讨论每种药物的风险和获益，并认识到eGFR < 50 mL/min/1.73 m ^{2}的患者更可能发生不良治疗作用。
- 在那些希望尝试免疫抑制治疗的患者中，糖皮质激素的治疗如上所述用于IgAN。

2.8 特殊情况

操作要点2.8.1：IgAV和RPGN：

- 应在个体患者水平评价免疫抑制的潜在风险和获益，并与患者进行讨论。
- 同意治疗的患者应按照 AAV 指南进行治疗（第9章）。
- IgAV 伴 RPGN 以及其他 IgAVN 可能与显著的肾外受累（肺、胃肠道和皮肤）相关，这可能需要其他免疫抑制策略。
- 现有数据不足以确定 IgAVN 与 RPGN 血浆置换的疗效。然而，非对照病例系列描述了在糖皮质激素治疗的基础上加用血浆置换对 IgAV 危及生命或器官的肾外并发症患者加速恢复的潜在作用。[151]临床医生

参考了美国单采协会关于 IgAV 血浆置换建议的指南。[152]

2.8.1 儿童 IgAV 相关肾炎

练习点2.8.1.1：出于该练习点的目的，将儿童定义为年龄 < 18岁的儿童。众所周知，青春期后儿童在某些方面的治疗过程和反应可能与 IgAN 成人相似，但目前尚无充分数据建议将其作为 IgAN 成人进行管理。最近，根据欧洲联盟的倡议，公布了儿童 IgAVN 的管理适应症。[140]简报：

- 没有数据支持在 IgAV 儿童中使用糖皮质激素预防肾炎，但有轻度或无肾脏受累证据。[153,154]
- > 10岁儿童更常出现非肾病范围蛋白尿和肾功能损害，他们可能遭受更多的慢性组织学病变，活检延迟和治疗延迟超过30天。[155]
- 大多数将发生肾炎的儿童将在就诊后3个月内发生肾炎。‡6个月和最佳12个月（从首次出现全身性疾病起）需要进行尿液监测。
- IgAVN 和持续性蛋白尿 > 3个月的儿童应接受 ACEi 或 ARB 治疗。儿科应咨询肾病学家。
- 对于肾病范围蛋白尿、GFR受损或持续性中度（> 1 g/日）蛋白尿的儿童，应进行肾活检。
- 轻度或中度 IgAVN 患儿应口服泼尼松/泼尼松龙或静脉冲击甲泼尼龙。
- 伴有肾病综合征和（或）肾功能迅速恶化的 IgAVN 患儿治疗方法与急进性 IgAN 患儿相同。

第三章：膜性肾病

3.1 诊断

实践要点3.1.1：在肾病综合征和抗 PLA2R 抗体检测阳性的患者中，确认膜性肾病 (MN) 的诊断不需要肾活检。

实践要点3.1.2：应评价 MN 患者的相关疾病，无论是否存在抗 PLA2R 抗体和/或抗 THSD7A 抗体（图29）。

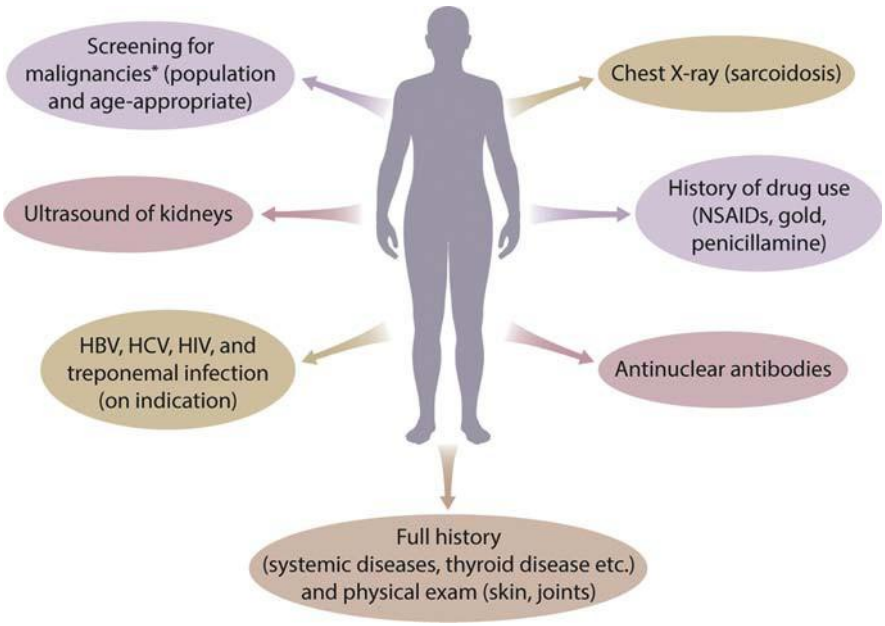


图29|MN患者相关疾病的评价。应评价 MN 患者的相关疾病，无论是否存在抗 PLA2R 抗体或抗 THSD7A 抗体。*因国家而异；癌症筛查率不是很高，尤其是年轻患者。许多中心将进行胸部 X 线或计算机断层扫描 (CT)，寻找铁缺乏，并要求患者参加国家乳腺癌和结肠癌筛查项目；在 > 50-60岁的成年男性中进行前列腺特异性抗原 (PSA) 检测。HBV，乙型肝炎病毒；HCV，丙型肝炎病毒；HIV，人类免疫缺陷病毒；NSAID，非甾体类抗炎药。

3.2 预后

实践要点3.2.1：在 MN 患者中，使用临床和实验室标准评估进行性肾功能丧失的风险（图30）。

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and serum albumin >30 g/l OR • Normal eGFR, proteinuria <3.5 g/d or a decrease >50% after 6 months of conservative therapy with ACEi/ARB	• Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND • Not fulfilling high-risk criteria	• eGFR <60 ml/min/1.73 m^{2*} and/or proteinuria >8 g/d for >6 months OR • Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND at least one of the following: • Serum albumin <25 g/l† • PLA2Rab >50 RU/ml‡ • Urinary α_1-microglobulin >40 μg/min • Urinary IgG >1 μg/min • Urinary β_2-microglobulin >250 mg/d • Selectivity index >0.20§	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

图30评估进展性肾功能丧失风险的临床标准。eGFR和 PCR 用于常规临床护理。其他生物标志物可能并非在所有中心均可用；本表提供了有用生物标志物的概述。*大多数研究使用血清肌酐 (SCr) 值来指导管理，SCr值 > 1.5 mg/dL(133 mmol/l) 通常用于定义肾功能不全。eGFR值为60 mL/min/1.73 m^2（年轻成人的肾功能不全）。重要的是要认识到 eGFR 随年龄增长而降低，1.5 mg/dL(133 mmol/l) 的 SCr 值反映了60岁男性患者的 eGFR 为50 mL/min/1.73 m^2，60岁女性患者为37 mL/min/1.73 m^2。因此，当使用 eGFR 进行风险估计时，应考虑年龄。†应通过 BCP 或
免疫测定法。‡临界值未经验证。应每隔3-6个月测量一次抗 PLA2R 抗体，在基线时抗 PLA2R 抗体水平较高的患者中进行较短的间隔。随访期间抗 PLA2R 抗体水平的变化可能增加风险估计。抗 PLA2R 抗体的消失先于临床缓解，应导致避免额外的治疗。缺乏详细的数据。§选择性指数计算为 IgG 清除率/白蛋白清除率。ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；BCP，溴甲酚紫；eGFR，估计肾小球滤过率；IgG，免疫球蛋白G；PLA2Rab，抗 M 型磷脂酶 A2 受体抗体。

3.3 治疗

实践要点3.3.1：原发性 MN 患者的治疗考虑：

- 所有原发性 MN 伴蛋白尿的患者均应接受最佳支持治疗。
- 免疫抑制治疗应仅限于被认为有进展性肾损伤风险的患者（图31）。

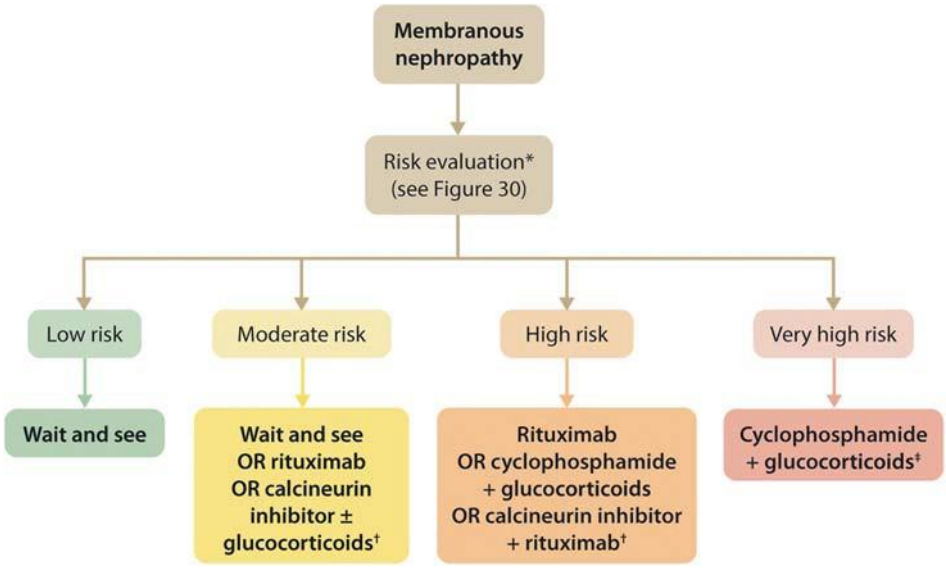


图31|基于风险的 MN 治疗。*风险评估的详细描述参见规范点3.2.1和图30。†钙调磷酸酶抑制剂 (CNI) 单药治疗被认为疗效较差。CNI治疗6-12个月，快速停药与高复发率相关。然而，可考虑在 eGFR 正常和中度进展风险的患者中使用，因为其中许多患者将发生自发缓解。使用 CNI 将缩短蛋白尿期。在进展风险高的患者中，建议在 CNI 治疗6个月后加用利妥昔单抗，CNI治疗后抗 PLA2R 抗体消失的患者可能除外。‡没有充分的证据表明使用标准剂量的利妥昔单抗可预防肾衰竭的发生。如果 eGFR 低于50 mL/min/1.73 m^2，环磷酰胺的剂量应减半。在不耐受或不能再使用环磷酰胺的患者中，可提供利妥昔单抗。建议咨询专家中心。eGFR，估计肾小球滤过率；MN，膜性肾病；PLA2R，M型磷脂酶 A2 受体。

实践要点3.3.2：MN、蛋白尿<3.5 g/日、血清白蛋白>30 g/L（溴甲酚紫 [BCP] 或免疫测定法）且 eGFR >60 mL/min的患者无需免疫抑制治疗 1.73 m^2。

实践要点3.3.3：MN、肾病综合征和 eGFR 正常的患者不需要免疫抑制治疗，除非至少存在一个疾病进展的风险因素或已发生肾病综合征的严重并发症（例如，AKI、感染、血栓栓塞事件）。

建议3.3.1：对于具有至少一种疾病进展风险因素的 MN 患者，我们建议使用利妥昔单抗或环磷酰胺和隔月糖皮质激素治疗6个月，或基于 CNI 的治疗‡6个月，治疗选择取决于风险估计（图30和图31）*(1B)*。

实践要点3.3.4：治疗开始后6个月时纵向监测抗 PLA2R 抗体水平可能有助于评价 MN 患者的治疗反应，并可用于指导治疗调整（图33[193]）。

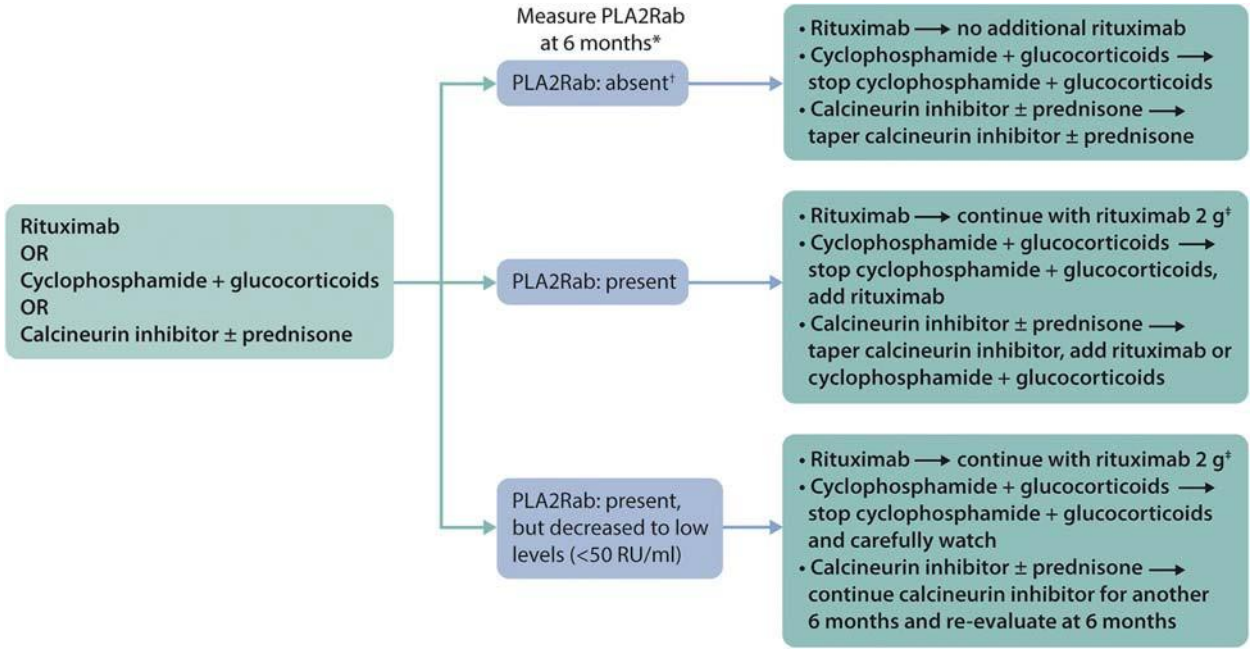


图33治疗开始后 MN 的免疫学监测。当前治疗方案见正文。注：考虑到恶性肿瘤的风险，环磷酰胺的累积剂量不应超过36 g（第1章）。为了保持安全，我们通常将累积剂量限制为25 g（在 80 kg 的男性中：6个月的环磷酰胺周期性给药，剂量为2.5 mg/kg/d，等于18 g，6个月的环磷酰胺每日给药，剂量为1.5 mg/kg/d，等于22 g）。希望怀孕的患者必须使用较低剂量（最多10 g）。CNI不太可能诱导晚期免疫缓解；在持续存在抗 PLA2R 抗体的患者中，这些药物可与利妥昔单抗联合使用。B细胞耗竭不足以判断利妥昔单抗治疗的疗效；即使外周血中 B 细胞不存在或非常低，也可考虑额外给药。但是，在这些患者中，建议咨询专家中心。eGFR应保持稳定；如果不稳定，则始终需要评价其他原因，如果 eGFR 降低归因于 MN 活性，则始终提供额外治疗。*一些中心将在第3个月测量抗 PLA2R 抗体，并在当时调整治疗。在大多数患者中，缓解发生在治疗开始后3个月内。†免疫荧光试验阴性表示免疫缓解。如果通过酶联免疫吸附试验测定，则应使用 2 RU/ml 的临界值来定义完全免疫学缓解。‡利妥昔单抗再治疗的给药方式应与利妥昔单抗1或2次输注（每次1 g，间隔2周）的初始治疗相似。[182]CNI，钙调磷酸酶抑制剂；eGFR，估计肾小球滤过率；MN，膜性肾病；PLA2Rab，抗 M 型磷脂酶 A2 受体抗体。

3.4 特殊情况

实践要点3.4.1：*MN*和治疗后初始复发患者的治疗算法（图34）

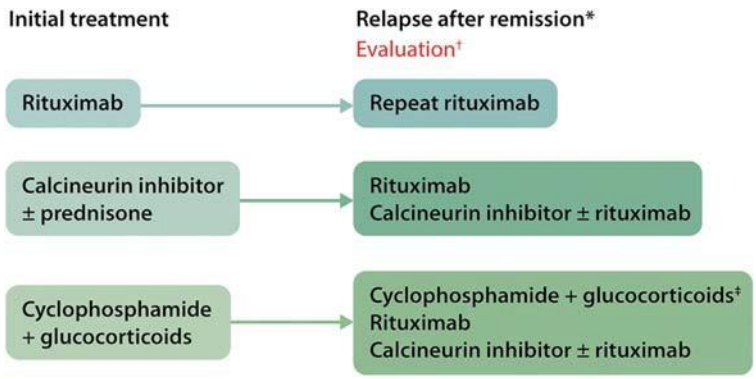


图 34 MN 治疗后初始复发的管理常用治疗方案的详细信息见图32。*复发的定义是可变的。一些作者将缓解后复发定义为出现部分或完全缓解的患者蛋白尿增加 > 3.5 g/日。我们建议在评估中应使用血清白蛋白和 PCR 的过程。如果 PCR 降至2-3.5 g/d之间，血清白蛋白未升高至正常，则后续 PCR 升高应视为耐药疾病，而不是缓解后复发。
在部分缓解（以血清白蛋白正常化为特征）的患者中，复发应定义为蛋白尿增加伴随血清白蛋白水平降低。†在这些情况下，免疫学监测特别重要。如果在"临床缓解"期间，抗 PLA2R 抗体仍为阳性，则表明疾病耐药。因此，在抗 PLA2R 抗体阳性的患者中，建议在缓解和复发时评价抗 PLA2R 抗体。抗 PLA2R 抗体的病程应先于临床病程。在极早期复发的患者中，重要的是要考虑既往治疗失败的原因（例如，依从性、药物水平低、B细胞耗竭不足、存在抗利妥昔单抗抗体）。‡可重复环磷酰胺给药；但医生必须考虑最大耐受剂量：如果需要保留生育能力，累积剂量不应超过10 g。累积剂量不应超过36 g，以限制恶性肿瘤风险。MN，膜性肾病；PCR，蛋白-肌酐比值；PLA2R，M型磷脂酶 A2 受体。

实践要点3.4.2：难治性 *MN* 患者的管理算法（图35）

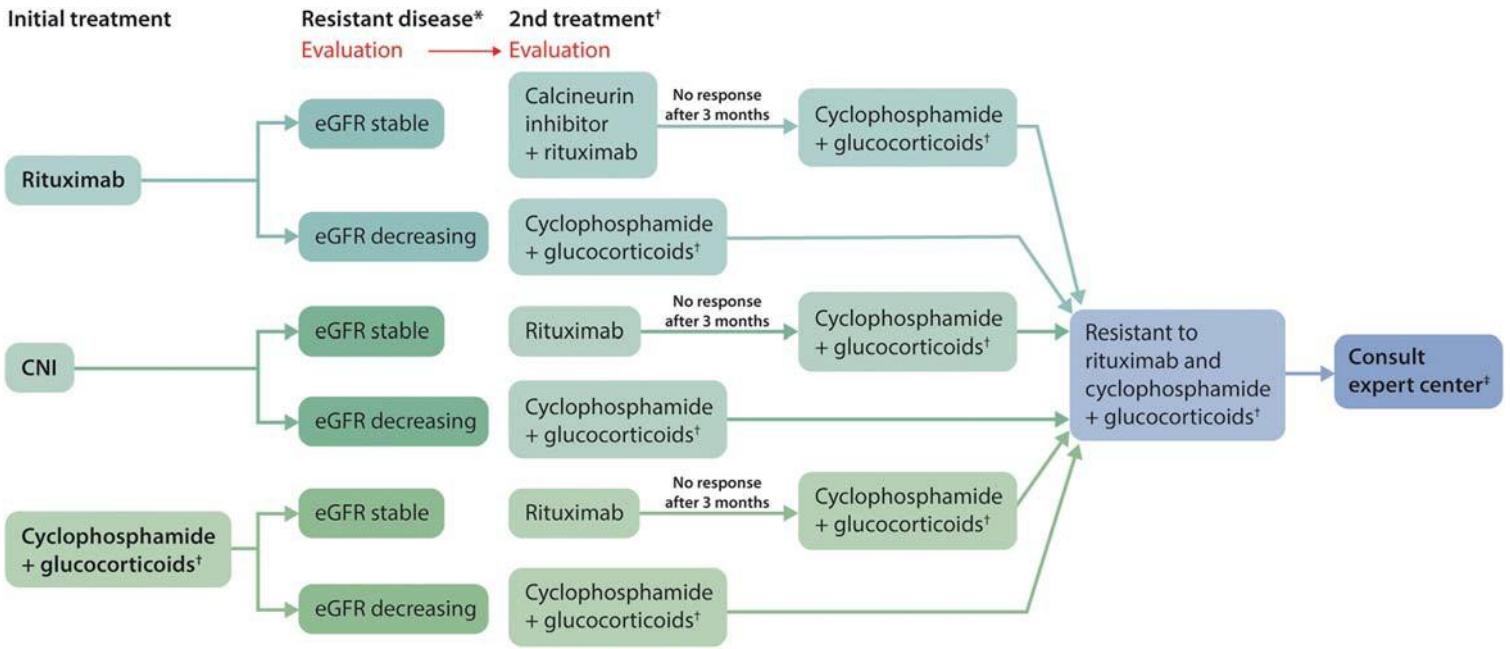


图35|MN耐药疾病的管理。常用治疗方案的详细信息见图32。*评价：在耐药性疾病患者中，应检查依从性并监测疗效（例如，B细胞应答、抗利妥昔单抗抗体、IgG水平、环磷酰胺治疗期间的白细胞减少症、CNI水平）。持续性蛋白尿不足以定义耐药性。如果蛋白尿持续存在，而血清白蛋白升高，应考虑继发性局灶节段性肾小球硬化 (FSGS)。抗 PLA2R 抗体的消失进一步支持了这一点。在血清白蛋白水平正常或接近正常的持续性蛋白尿患者或尽管抗 PLA2R 抗体丢失但仍有持续性蛋白尿的患者中，应考虑进行肾活检以记录活动性 MN。†第二次治疗取决于 eGFR 恶化的严重程度。当选择利妥昔单抗作为第二种治疗时，应在3个月后评价蛋白尿和抗 PLA2R 抗体的缓解。环磷酰胺治疗应考虑最大耐受剂量：如果需要保留生育能力，累积剂量不应超过10g。累积剂量不应超过36 g，以限制恶性肿瘤风险。根据权衡风险和获益，专家中心可能仍会使用更多。‡对利妥昔单抗或环磷酰胺无应答的患者应咨询专家中心。这些中心可以选择试验性治疗（硼替佐米、抗 CD38 治疗和贝利尤单抗）或更高剂量的常规免疫抑制治疗。CNI，钙调磷酸酶抑制剂；eGFR，估计肾小球滤过率；FSGS，局灶节段性肾小球硬化；MN，膜性肾病；PLA2R，M型磷脂酶 A2 受体。

实践要点3.4.3：*MN*肾移植受者的评价（图36）

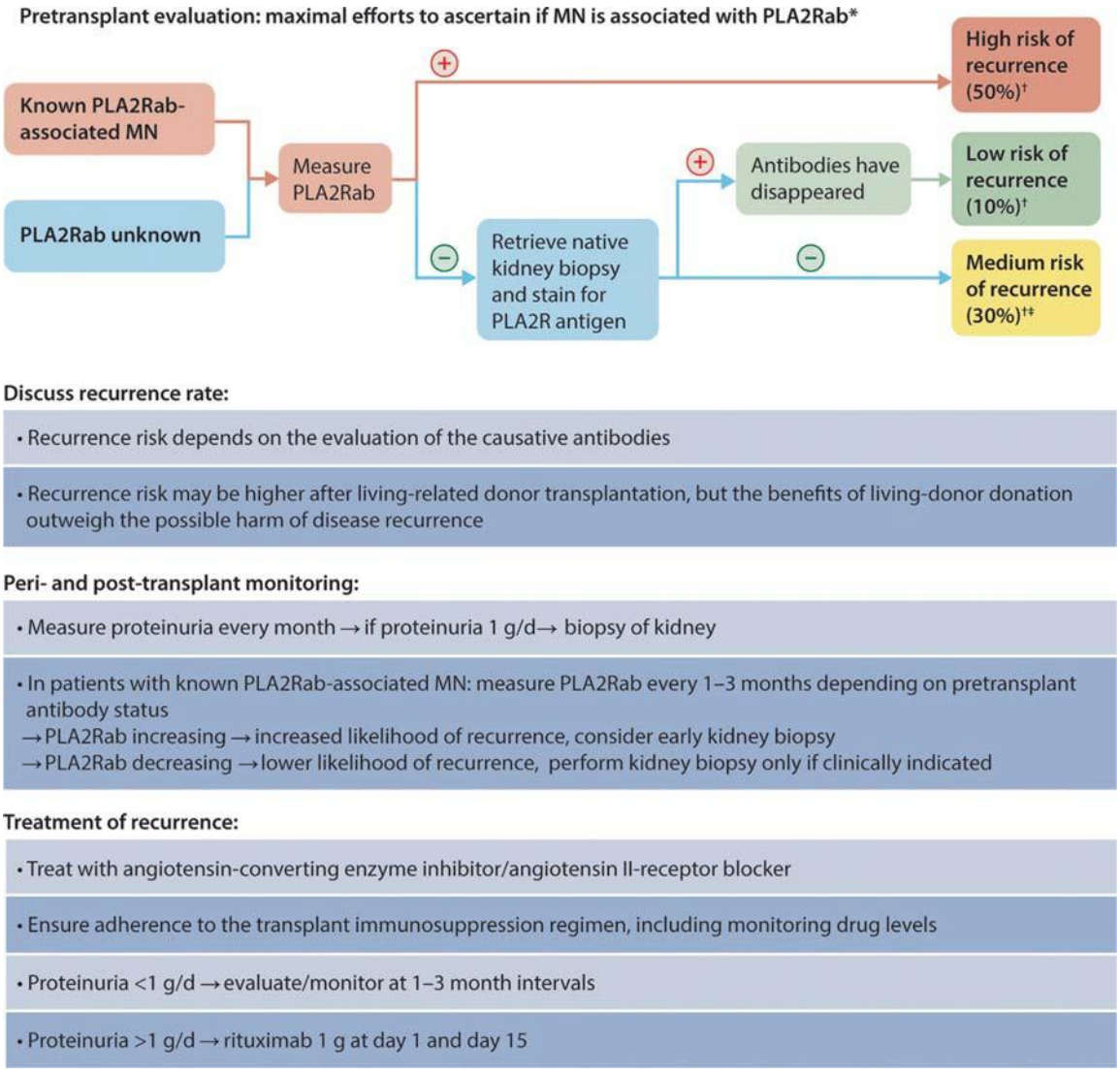


图 36 MN 肾移植受者的评估*可用数据有限，但相同算法可能适用于抗 THSD7A 相关MN。†临床复发。‡这是 MN 和未鉴定抗原患者的估计平均复发率。我们建议在这些患者中，通过评价患者的 THSD7A 抗原/抗体可以更好地估计复发率。MN，膜性肾病；PLA2Rab，抗 M 型磷脂酶 A2 受体抗体；THSD7A，含血小板反应蛋白1型结构域的7A。

实践要点3.4.4：*MN*儿童的管理算法（图37）

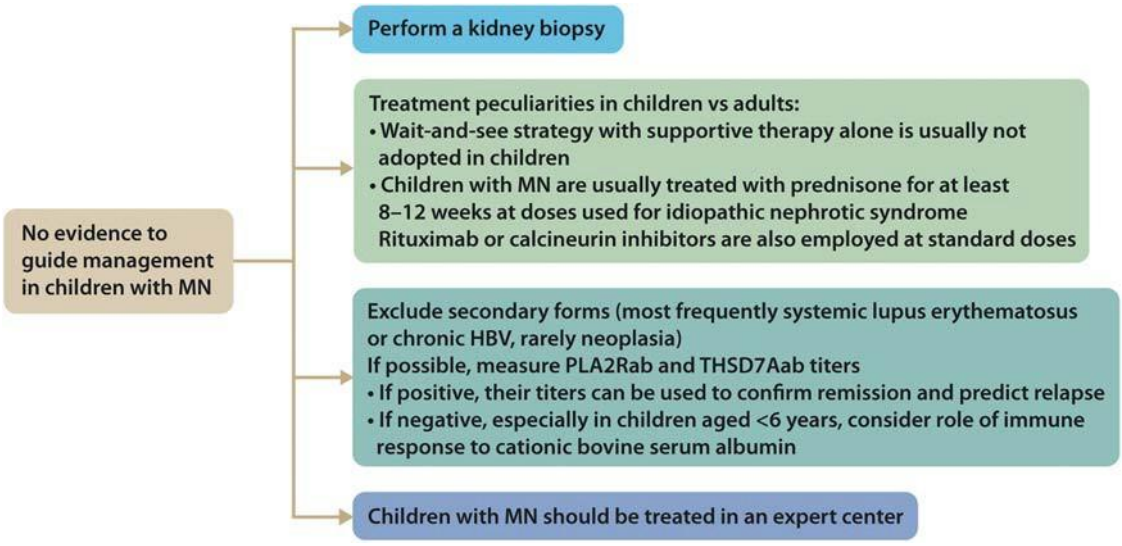


图37|MN儿童的管理。HBV，乙型肝炎病毒；MN，膜性肾病；PLA2Rab，抗 M 型磷脂酶 A2 受体的抗体；THSD7Aab，抗含血小板反应蛋白1型结构域的抗体7A。

实践要点3.4.5：*MN*和肾病综合征患者的预防性抗凝治疗应基于血栓事件风险和出血并发症风险的估计值（图38）。

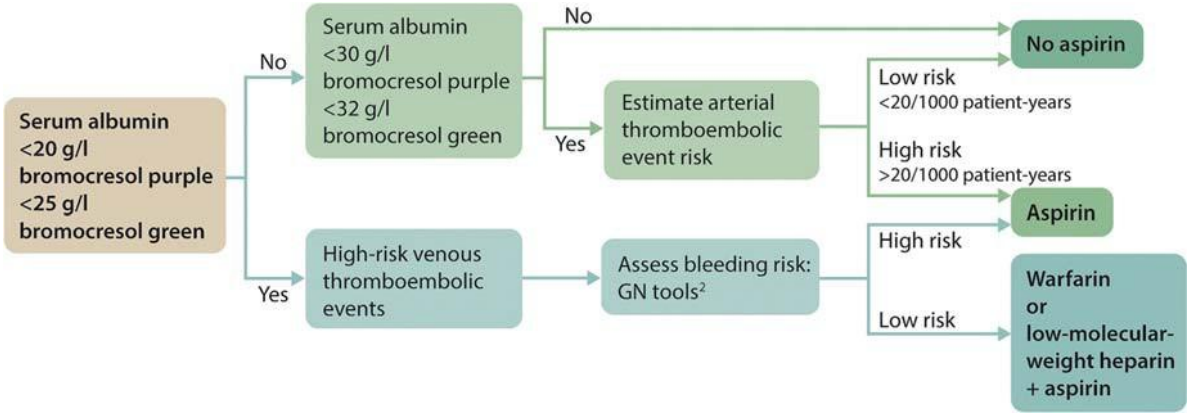


图 38 MN 患者的抗凝治疗摘自*Kidney International*，第89卷，第5期，Hofstra JM，Wetzels JFM。阿司匹林是否应用于膜性肾病患者血栓事件的一级预防？第981-983页，版权2016，经国际肾脏病学会许可。[44]膜性肾病 (MN) 患者抗凝治疗的拟定算法。该算法为临床医生提供指导。拟定临界值基于专家意见。在考虑抗凝治疗时，重要的是平衡获益和风险。以下是重要的考虑因素：

1. 血栓事件的风险与血清白蛋白水平有关。值得注意的是，血清白蛋白测定之间存在较大差异。[204]使用溴甲酚绿 (BCG) 时血清白蛋白浓度为25 g/L(2.5 g/dL)，使用溴甲酚紫 (BCP) 或免疫散射比浊法时血清白蛋白浓度为w20 g/L(2.0 g/dL)。很可能大多数研究使用了 BCG 测定法。使用 BCG 时，考虑使用25 g/L(2.5 g/dL) 作为阈值，使用 BCP 或免疫散射比浊法时，考虑使用20 g/L(2.0 g/dL) 作为阈值。
2. 评估静脉血栓形成风险和出血风险 (https://www.med.unc.edu/gntools/bleedrisk.html) .
3. MN 和肾病综合征患者也有发生动脉血栓事件的风险。动脉血栓栓塞 (ATE) 的风险取决于年龄、既往事件史、糖尿病、估计的肾小球滤过率 (eGFR)、吸烟和肾病综合征 (NS) 的严重程度。可使用 Framingham 风险评分进行风险评估，包括既往事件和蛋白尿。[44]
4. 使用阿司匹林不足以预防静脉血栓栓塞 (VTE)；使用华法林足以预防ATE。
5. 华法林治疗：肾病综合征和低 eGFR 的国际标准化比值 (INR) 变异性更高；在开始高剂量华法林治疗后立即出现血栓形成的风险增加。考虑使用低剂量低分子量肝素开始抗凝治疗，然后折叠华法林，治疗时停用肝素。一个很好的替代方案是在转换为华法林之前使用低剂量低分子量肝素阿司匹林3个月，以便判断蛋白尿的病程。[205]
6. 糖皮质激素可增加血栓形成的风险；因此，在开始泼尼松治疗的患者中不应忽略抗凝治疗。
7. 使用 Framingham 风险评分估计 ATE 风险，在 eGFR 较低或蛋白尿较高的情况下增加风险。Framingham风险评分考虑了年龄、吸

烟、血清胆固醇和血压。

第4章：儿童肾病综合征

4.1 诊断

操作要点4.1.1：与儿童肾病综合征相关的定义是基于图39[206]中概述的临床特征。

- **Nephrotic-range proteinuria:** First morning or *24-h PCR ≥2 g/g (or 200 mg/mmol or ≥3+ dipstick)
- **NS:** Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin <30 g/l (3 g/dl)) or edema when albumin level is not available
- **Complete remission:** First morning or *24-h PCR ≤200 mg/g (or 20 mg/mmol or negative or trace dipstick) on three or more consecutive occasions
- **Partial remission:** First morning or *24-h PCR >200 mg/g but <2 g/g (or >20 and <200 mg/mmol) and, if available, serum albumin ≥30 g/l (3 g/dl)
- **Relapse:** Recurrence of nephrotic-range proteinuria. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick ≥3+ for 3 consecutive days
- Typical dipstick results are expressed semiquantitatively as follows†, or as stated by manufacturer:
  Negative: 0 to <15 mg/dl
  Trace: 15 to <30 mg/dl
  1+: 30 to <100 mg/dl
  2+: 100 to <300 mg/dl
  3+: 300 to <1000 mg/dl
  4+: ≥1000 mg/dl

- **SSNS:** Complete remission after 4 weeks of prednisone or prednisolone at standard dose
- **Infrequent relapsing NS:** <2 relapses per 6 months within 6 months of disease onset or <4 relapses per 12 months in any subsequent 12-month period
- **Frequent relapsing NS:** ≥2 relapses per 6 months within 6 months of disease onset or ≥4 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** Two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission at 4 weeks of therapy with daily prednisone or prednisolone at standard dose
- **Late responder:** Complete remission at 6 weeks.
- **Calcineurin inhibitor-responsive SRNS:** Partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Calcineurin inhibitor-resistant SRNS:** Absence of partial remission after at least 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Multi-drug resistant SRNS:** Absence of complete remission after 12 months of treatment with 2 mechanistically distinct glucocorticoid-sparing agents at standard doses (see below)
- **Secondary SRNS:** A SSNS patient at disease onset who at a subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose

图39|1 –18岁儿童中与 NS 相关的定义。*为排除直立性蛋白尿，应单独采集第1次晨尿进行评估。†van der Watt *et al.*[206]NS，肾病综合征；PCR，蛋白-肌酐比值；SRNS，类固醇耐药性肾病综合征；SSNS，类固醇敏感性肾病综合征。

4.2 预后

实践要点4.2.1：儿童肾病综合征的预后最好通过患者对初始治疗的反应和治疗后第一年的复发频率来预测。因此，通常在初次就诊时不需要进行肾活检，而是保留用于对治疗耐药或临床病程不典型的儿童。

4.3 治疗

4.3.1 儿童 NS 的初始治疗

建议4.3.1.1：我们建议口服糖皮质激素8周（每日4周糖皮质激素，随后4周隔日糖皮质激素）或12周（每日6周糖皮质激素，随后6周隔日糖皮质激素）(1B)。

实践要点4.3.1.1：肾病综合征初始治疗的标准给药方案是每日口服泼尼松/泼尼松龙 60 mg/m ^{2}/d 或2 mg/kg/d（最大 60 mg/日），持续4周，然后隔日口服泼尼松/泼尼松龙 40 mg/m ^{2} 或1.5 mg/kg（最大50 mg），持续4周，或泼尼松/泼尼松龙60 mg/m ^{2}/d（最大 60 mg/日），持续6周，然后隔日口服泼尼松/泼尼松龙 40 mg/m ^{2} 或1.5 mg/kg（最大50 mg），其他6周。

4.3.2 儿童 NS 复发的预防和治疗

建议4.3.2.1：对于目前正在使用隔日糖皮质激素或停用糖皮质激素的频繁复发和激素依赖性肾病综合征儿童，我们建议在上呼吸道和其他感染发作期间给予糖皮质激素每日0.5 mg/kg/d，持续5-7天，以降低复发风险 (1C)。

实践要点4.3.2.1：复发的初始方法应包括口服泼尼松/泼尼松龙，每日单次给药 60 mg/m ^{2}/d 或2 mg/kg/d（最大剂量 60 mg/日），直至儿童‡完全缓解3天。

实践要点4.3.2.2：达到完全缓解后，将口服泼尼松/泼尼松龙剂量减少至 40 mg/m ^{2} 或1.5 mg/kg（最大50 mg），隔日一次，持续‡4周。

实践要点4.3.2.3：对于无糖皮质激素毒性的频繁复发的肾病综合征或激素依赖性肾病综合征儿童，后续复发可采用相同的糖皮质激素治疗方案。

实践要点4.3.2.4：对于无严重糖皮质激素相关不良反应的频繁复发性肾病综合征儿童，可处方低剂量隔日口服泼尼松/泼尼松龙（最佳£0.5 mg/kg/d）以预防复发。

建议4.3.2.2：对于发生严重糖皮质激素相关不良反应的频繁复发的肾病综合征儿童和所有激素依赖性肾病综合征儿童，我们建议预先使用糖皮质激素节制药物，而不是不治疗或仅继续糖皮质激素治疗 (1B)。

实践要点4.3.2.5：在开始使用糖皮质激素节制药物（如口服环磷酰胺、左旋咪唑、吗替麦考酚酯 (MMF)、利妥昔单抗或钙调磷酸酶抑制剂 (CNI)）之前，患者最好使用糖皮质激素达到缓解。建议在开始糖皮质激素减量治疗后‡2周内同时给予糖皮质激素。

实践要点4.3.2.6：从口服环磷酰胺、左旋咪唑、MMF、利妥昔单抗和 CNI 中选择最合适的糖皮质激素节制药物需要仔细考虑特定患者相关问题，如资源、依从性、不良反应和患者偏好。对于经常复发的肾病综合征，口服环磷酰胺和左旋咪唑可能是首选的糖皮质激素保留疗法。在类固醇依赖性

肾病综合征儿童中，*MMF*、利妥昔单抗、*CNI*以及口服环磷酰胺（在较小程度上）可能优于糖皮质激素减量治疗（图*41*[178]）。

Treatment	Dose and duration	Clinical tips
First line:		
• Oral cyclophosphamide	2 mg/kg/d for 12 weeks (maximum cumulative dose 168 mg/kg)	Cyclophosphamide should not be started until the child has achieved remission with glucocorticoids. Moreover, second courses of alkylating agents should not be given. Weekly CBCs are recommended during the treatment course to assess for severe leukopenia or overall bone marrow suppression prompting dose reduction or treatment cessation
• Oral levamisole	2.5 mg/kg on alternate days, with a maximum dose of 150 mg	Monitor CBC every 2–3 months and alanine and aspartate aminotransferases every 3–6 months during therapy with levamisole. Check ANCA titers every 6 months, if possible, and interrupt treatment in case of ANCA positivity, skin rash or agranulocytosis. Maintaining low-dose alternate-day glucocorticoid dosing on the days not taking levamisole may be effective in some children. Levamisole should be continued for at least 12 months
Alternative agents:		
• Mycophenolate mofetil	Starting dose of 1200 mg/m^2/d (given in two divided doses)	Target area under the curve >50 μg•h/ml.* Mycophenolate mofetil should be continued for at least 12 months, as most children will relapse when it is stopped. In children experiencing significant abdominal pain on mycophenolate mofetil, other mycophenolic acid analogs (MPAAs), such as sodium mycophenolate, may be employed at equivalent doses (360 mg of sodium mycophenolate corresponds to 500 mg of mycophenolate mofetil)
• Rituximab	375 mg/m^2 i.v. × 1–4 doses	Rituximab may be used as a treatment for steroid-sensitive nephrotic syndrome in children who have continuing frequent relapses despite optimal combinations of prednisone and glucocorticoid-sparing oral agents, and/or who have serious adverse effects of therapy. Current trials report 1 to 4 doses of rituximab. There are insufficient data to make a recommendation for specific number of needed doses. Where available, CD20 levels should be monitored. Hepatitis B surface antigen, hepatitis B core antibody, and a QuantiFERON test for tuberculosis must be checked prior to rituximab administration. Monitoring IgG levels both before and after rituximab therapy may allow for earlier identification of risk for developing significant infection and identify patients who may benefit from immunoglobulin replacement
• Calcineurin inhibitors†		CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– Cyclosporine	4 to 5 mg/kg/d (starting dose) in two divided doses	Cyclosporine may be preferable in patients at risk for diabetic complications. Target 12 hour trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity
– Tacrolimus	0.1 mg/kg/d (starting dose) given in two divided doses	Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side effects of cyclosporine are unacceptable. Target 12 hour trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity

图 41 SSNS 患儿的糖皮质激素减量治疗*Gellermann *et al.*[178]†CNI通常每日两次给药，但可以每日给药一次，具体取决于制剂。在体型较小的儿童（< 6岁）中，环孢素的日剂量可分为3次给药（每8小时一次），以获得稳定的血液水平。CNI的血液水平不能提供细胞内水平的信息。CNI的目标范围基于移植文献。KDIGO工作组承认肾小球疾病的靶点尚不清楚。大多数临床医生检查这些水平以验证依从性并避免 CNI 毒性。目前，CNI最合理的剂量可能是在个体患者中滴定以获得对蛋白尿的预期作用，平衡剂量递增与血清肌酐，并在以下情况下降低剂量
血清肌酐升高，但未达到平台期或升高超过基线的30%。如果减量后血清肌酐水平未下降，应停用CNI。ANCA，抗中性粒细胞胞浆抗体；CBC，全血细胞计数；CNI，钙调磷酸酶抑制剂。

儿童激素抵抗型肾病综合征

4.4 治疗

建议4.4.1：我们建议使用环孢素或他克莫司作为类固醇耐药肾病综合征儿童的初始二线治疗 *(1C)*。

4.5 特殊情况

实践要点4.5.1：图43[301、302]概述了肾病综合征儿童的一般原则。

Indication for kidney biopsy*	• Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to glucocorticoids in steroid-sensitive nephrotic syndrome (secondary steroid-sensitive nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, systemic symptoms of vasculitis, hypocomplementemia, etc.) • At onset, kidney failure not related to hypovolemia. Subsequently, decreasing kidney function in children receiving calcineurin inhibitors or prolonged exposure to calcineurin inhibitors (2 to 3 years)
Genetic testing	• Steroid-resistant nephrotic syndrome • Congenital and infantile forms of nephrotic syndrome (<1 year of age) • Nephrotic syndrome associated with syndromic features • Family history of steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis
Vitamin D/calcium	In patients with steroid-sensitive nephrotic syndrome and normal vitamin D levels, supplementation is not required. However, in frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome in children or in the presence of a known vitamin D deficiency, a reduction in bone mineral content can be prevented by oral supplementation with oral calcium and vitamin D.[1,2]
Gastroprotection	There is insufficient evidence of benefit to recommend prophylactic use of proton-pump inhibitors in children with nephrotic syndrome in the absence of risk factors for gastrotoxicity or of gastric symptoms.

图 43 NS 患儿的一般原则。*如果蛋白尿有明显的肾外原因（即淋巴瘤、溃疡性结肠炎的单克隆抗体治疗、人类免疫缺陷病毒），可能不需要进行肾活检。NS，肾病综合征。[1]Gulati 等人[301]，[2]Gruppen 等人[302]

第5章：成人微小病变 (MCD)

5.1 诊断

实践要点5.1.1：成人 *MCD* 只能通过肾活检进行诊断。

5.2 预后

实践要点5.2.1：对糖皮质激素有反应的 *MCD* 患者的长期肾脏存活率极佳，但对无反应的患者不太确定。

5.3 治疗

建议5.3.1：我们建议在 MCD *(1C)* 的初始治疗中使用高剂量口服糖皮质激素。

实践要点5.3.1：成人 MCD 的初始治疗算法（图44）

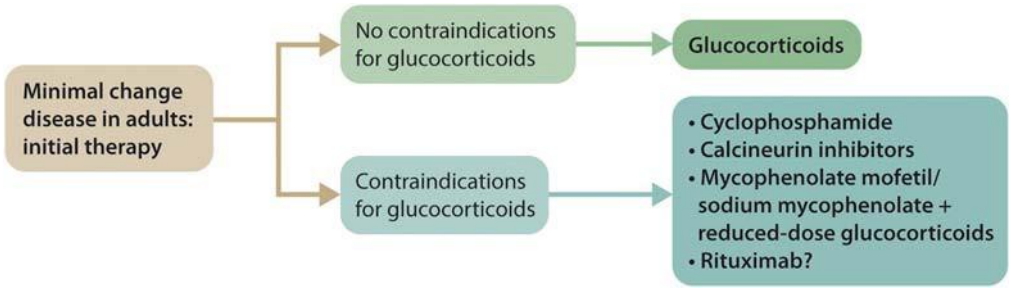


图44成人 MCD 的初始治疗。最佳糖皮质激素治疗方案尚不明确；但建议剂量见图45。药物的选择应基于医生和患者的偏好。MCD，微小病变。

实践要点5.3.2：MCD的高剂量糖皮质激素治疗应不超过16周。实践要点5.3.3：完全缓解后2周开始糖皮质激素逐渐减量。

实践要点5.3.4：尽管每日口服糖皮质激素最常用于治疗MCD，但给药途径和频率可根据患者需求进行个体化治疗。

实践要点5.3.5：对于糖皮质激素可能相对禁忌的患者，考虑环磷酰胺、CNI或 MMF 初始治疗。

5.3.1 复发的治疗（图46）

Complete remission
Reduction of proteinuria to <0.3 g/d or PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/l)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Steroid-resistant MCD
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for >16 weeks
Frequently relapsing MCD
Two or more relapses per 6 months (or four or more relapses per 12 months)
Steroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing glucocorticoid therapy

图 46 MCD 缓解、复发、耐药和依赖性的定义MCD，微小病变；PCR，蛋白-肌酐比值。

实践要点5.3.1.1：成人频繁复发 (FR)/激素依赖性 (SD)MCD 的治疗算法（图47）

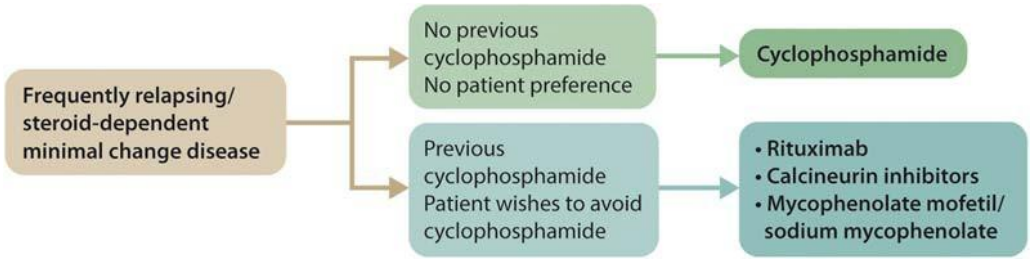


图47成人 FR/SD MCD 的治疗。应根据医生和患者的偏好选择药物。FR/SD，频繁复发/激素依赖性。

实践要点5.3.1.2：使用糖皮质激素治疗罕见复发（图46）。

建议5.3.1.1：我们建议使用环磷酰胺、利妥昔单抗、CNI或麦考酚酸类似物 (MPAA) 治疗频繁复发/类固醇依赖性MCD，而不是泼尼松单药或不治疗 (1C)。

第6章：成人局灶节段性肾小球硬化 (FSGS)

6.1 诊断

6.1.1 区分原发性和继发性 FSGS

实践要点6.1.1.1：应评价无肾病综合征的 FSGS 成人患者的次要原因（图51；图52）。

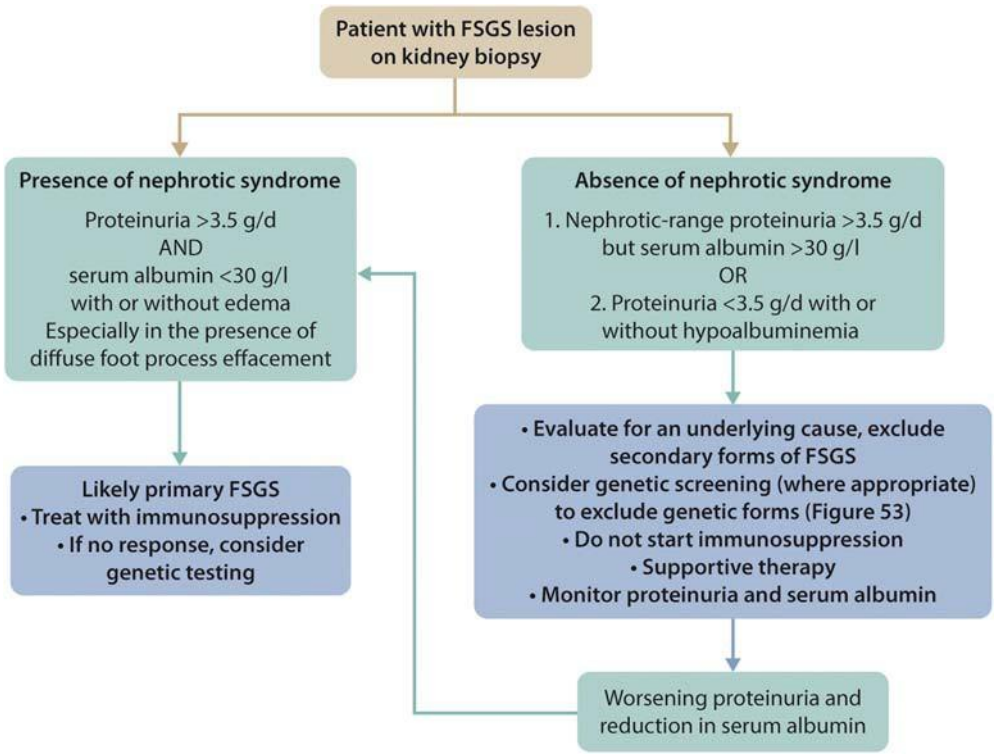


图51|肾活检显示 FSGS 病变且无其他肾小球病理证据的患者评价。FSGS，局灶节段性肾小球硬化。

Secondary to alterations of glomerular epithelial cells	
Viral infections	HIV (established) CMV (probably) Parvovirus B19, EBV, HCV (possibly) Hemophagocytic syndrome (possibly) SARS-COV-2 (with *APOL1* risk genotype)
Drug-induced	Direct-acting antiviral therapy mTOR inhibitors, CNIs Anthracyclines Heroin (adulterants) Lithium Interferon Anabolic steroids NSAIDs
Secondary to adaptive changes with glomerular hypertension	
Reduced nephron number	Reflux nephropathy Renal dysplasia Oligomeganephronia Sickle cell disease Age-related FSGS
Normal nephron number	Obesity-related glomerulopathy Primary glomerular diseases Systemic conditions, e.g., diabetic nephropathy, hypertensive nephrosclerosis

图52继发性 FSGS 的原因。*APOL1*，载脂蛋白L1；CMV，巨细胞病毒；CNI，钙调磷酸酶抑制剂；EBV，EB病毒；FSGS，局灶节段性肾小球硬化；HCV，丙型肝炎病毒；HIV，人类免疫缺陷病毒；mTOR，哺乳动物雷帕霉素靶蛋白；NSAID，非甾体抗炎药；SARS-CoV-2，重度急性呼吸综合征冠状病毒2。

6.1.2 基因检测

实践要点6.1.2.1：基因检测可能对选定的 *FSGS* 患者有益，这些患者应转诊至具有此类专业知识的专科中心（图53）。

Genetic forms of FSGS	
Genetic mutations of podocyte and glomerular basement membrane proteins	• Familial • Sporadic • Syndromic
Considerations for genetic testing in adults with FSGS	
• When there is a strong family history and/or clinical features suggestive of a syndromal disease • Aiding in diagnosis, especially if the clinical features are not representative of a particular disease phenotype • Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment • Determining the risk of recurrent disease in kidney transplantation • Allowing for risk assessment in living-related kidney donor candidate, or where there is a high suspicion for *APOL1* risk variants • Aiding in prenatal diagnosis	

图53|FSGS患者基因检测的实用性。*APOL1*，载脂蛋白-L1；FSGS，局灶节段性肾小球硬化。

6.2 治疗

6.2.1 *FSGS-UC* 和继发性 *FSGS* 的管理

实践要点6.2.1.1：免疫抑制不应用于不明原因 FSGS(FSGS-UC) 成人患者或继发性 FSGS 患者。

6.2.2 原发性 FSGS 的初始治疗

建议6.2.2.1：我们建议使用高剂量口服糖皮质激素作为原发性 FSGS 的一线免疫抑制治疗 (1D)。

实践要点6.2.2.1：原发性 FSGS 初始治疗中糖皮质激素的建议给药方案见下文图S4。

实践要点6.2.2.2：应继续初始高剂量糖皮质激素治疗，直至达到完全缓解，或患者耐受最长16周，以先发生者为准。

实践要点6.2.2.3：对糖皮质激素治疗有反应的原发性 FSGS 成人患者应接受糖皮质激素治疗≥6个月。

实践要点6.2.2.4：在存在糖皮质激素相对禁忌症或对糖皮质激素不耐受的成人中，应考虑将 CNI 替代免疫抑制作为原发性 FSGS 患者的初始治疗（图S4）。

Treatment	Dose and duration
Glucocorticoids	**Starting dose:** • High-dose glucocorticoid therapy with prednisone at daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg)
	High-dose glucocorticoid treatment duration: • Continue high-dose glucocorticoid therapy for at least 4 weeks and until complete remission is achieved, or a maximum of 16 weeks, whichever is earlier • Patients who are likely to remit will show some degree of proteinuria reduction before 16 weeks of high-dose treatment • It may not be necessary to persist with high-dose glucocorticoid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side effects
	Glucocorticoid tapering: • If complete remission is achieved rapidly, continue high-dose glucocorticoid treatment for 2 weeks or after the disappearance of proteinuria, whichever is longer. Reduce prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If partial remission is achieved within 8 to 12 weeks of high-dose glucocorticoid treatment, continue until 16 weeks to ascertain whether further reduction of proteinuria and complete remission may occur. Thereafter, reduce the dose of prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If the patient proves to be steroid-resistant or develops significant toxicities, glucocorticoids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI should be considered
Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 4–6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated

图S4|原发性 FSGS 的初始治疗。*CNI通常每日使用两次，但可以每日给药一次，具体取决于具体制剂。CNIs的血液水平不能提供细胞内水平的信息。CNI的目标范围基于移植文献。KDIGO工作组承认肾小球疾病的靶点尚不清楚。大多数临床医生检查这些水平以验证依从性并避免 CNI 毒性。目前，CNI最合理的剂量可能是在个体患者中滴定以获得对蛋白尿的预期作用，平衡剂量递增与血清肌酐，如果血清肌酐升高但未稳定或升高超过基线的30%，则降低剂量。如果减量后血清肌酐水平未下降，应停用CNI。CNI，钙调磷酸酶抑制剂；FSGS，局灶节段性肾小球硬化。

6.3 特殊情况

6.3.1 类固醇耐药性原发性 FSGS

建议6.3.1.1：对于类固醇耐药的原发性 FSGS 成人患者，我们建议环孢霉素或他克莫司给药≥6个月，而不是继续糖皮质激素单药治疗或不治疗 (1C)。

6.3.2 环孢素和他克莫司的给药方案

实践要点6.3.2.1：类固醇耐药性原发性 FSGS 的治疗：环孢素和他克莫司的推荐给药方案（图55）。

Treatment	Dose and duration
Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated • Consider discontinuing cyclosporine or tacrolimus if the eGFR continues to decline to <30 ml/min per 1.73 m^2
Inability to tolerate or contraindications to calcineurin inhibitors	• Lack of quality evidence for any specific alternative agents • Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered • Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression • Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

图55糖皮质激素抵抗的原发性 FSGS 的治疗*CNI通常每日使用两次，但可以每日给药一次，具体取决于具体制剂。CNI的血液水平不能提供细胞内水平的信息。CNI的目标范围基于移植文献。KDIGO工作组承认肾小球疾病的靶点尚不清楚。大多数临床医生检查这些水平以验证依从性并避免 CNI 毒性。目前，CNI最合理的剂量可能是在个体患者中滴定以获得对蛋白尿的预期作用，平衡剂量递增与血清肌酐，如果血清肌酐升高但未稳定或升高超过基线的30%，则降低剂量。如果减量后血清肌酐水平未下降，应停用CNI。ACTH，促肾上腺皮质激素；CNI，钙调磷酸酶抑制剂；eGFR，估计肾小球滤过率。

6.3.3 CNI 治疗持续时间

实践要点6.3.3.1：对 CNI 治疗有反应的类固醇耐药原发性 FSGS 成人患者应接受 CNI 治疗至少12个月，以将复发风险降至最低（图55）。

6.3.4 对 CNI 耐药或不耐受的患者

实践要点6.3.4.1：对 CNI 耐药或不耐受的类固醇耐药原发性 FSGS 成人患者应转诊至专门中心，考虑重新活

检、替代治疗或入组临床试验（图55）。

6.3.5 复发的管理

实践要点6.3.5.1：既往对类固醇敏感的原发性 FSGS 复发成人患者可采用与 MCD 复发成人患者相同的方法进行治疗（图47）。

第7章：感染相关肾小球肾炎

7.1 细菌感染相关 GN

7.1.1 诊断

实践要点7.1.1.1：肾活检可用于疑似细菌感染相关肾小球肾炎 (GN)，尤其是当感染的培养证据难以捉摸或诊断存在疑问时，以评估预后和/或出于潜在的治疗原因。在某些情况下，活检可能对得出正确诊断至关重要，因为合并症可能导致混杂效应（图56）。

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Risk and risk features	Children, elderly, immuno-compromised hosts, sub-sanitary living conditions	Highest: Ventriculo-atrial Mid: Ventriculo-jugular Least: Ventriculo-peritoneal	Prosthetic valve or structural heart valve lesion; substance abuse; elderly; diabetes mellitus; hepatitis C; HIV; immuno-compromised host	Diabetes mellitus, hypertension, heart disease, malignancy, alcohol or substance abuse, or kidney transplantation
History	Seek evidence of antecedent resolved pharyngitis (1–2 wks) or impetigo (4–6 wks)	May present within months or decades of shunt placement, sometimes after shunt revision. Diagnosis may be confounded and difficult in the 40% with occult infection	Echocardiographic evidence of cardiac valvular vegetations	Demonstration of active blood or tissue infection in a patient with acute GN
Physical exam	In some, active skin or tonsil infections present	Non-specific signs/ symptoms of infection, lethargy, fever, clinical signs of bacteremia	Fever, new or changed cardiac murmur; splenomegaly; characteristic skin lesions	Frequent hypertension. Exam mostly reflects the location/severity of the infection
Laboratory kidney	• Urinalysis (assess for glomerular hematuria and red blood cell casts); ACR; PCR • Measure serum creatinine/eGFR			
Laboratory infection	Culture skin or tonsils if infected Measure anti-streptolysin O, anti-DNAse B, and anti-hyaluronidase antibodies	Organism culture in blood, cerebrospinal fluid, shunt tip (after removal)	Blood culture positive 90%–98%; negative 2%–10%. Fastidious infections, such as *Candida, Coxiella burnetii, Borrelia,* and *Bartonella* may be difficult to culture. Serological tools for diagnosis may be required in such cases	Culture blood/tissues to identify bacterial infection (mostly staphylococcal)
Laboratory immunology	• Assess for low complement (C3, C4), rheumatoid factor, cryoglobulins, factor B antibody levels • Rule out other causes of nephritis if diagnosis in doubt: ANA, ANCA (occasionally PR3-ANCA in shunt nephritis and endocarditis), anti-GBM antibody			
				Serum IgA may be high

图56典型细菌感染相关 GN 综合征的评估。ACR，白蛋白-肌酐比值；ANA，抗核抗体；ANCA，抗中性粒细胞胞浆抗体；eGFR，估计肾小球滤过率；GBM，肾小球基底膜；GN，肾小球肾炎；HIV，人类免疫缺陷病毒；PCR，蛋白质-肌酐比值；PR3，蛋白酶3。

7.1.2 预后和治疗

实践要点7.1.2.1：细菌感染相关 GN 的预后和建议治疗（图57[401-403]）

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Prognosis	Short-term prognosis in children is excellent. In endemic regions, persistent albuminuria may occur and some adults develop low eGFR. In the elderly, kidney prognosis is poor for those who develop persistent albuminuria; mortality may be up to 20%	Outcome is good with early diagnosis and treatment of infection. Most patients recover some kidney function but are left with residual chronic kidney disease	Immediate prognosis is good with prompt infection eradication. Some may require valve replacement	Dialysis is frequently required in the acute setting. Recovery is guarded, with <20% returning to pre-morbid levels of kidney function
Treatment	• No randomized controlled trials guide the treatment in any of these conditions • Antibiotics for underlying infection (although this will not alter GN course in postinfectious GN) per local guidelines. Antibiotics can be given in poststreptococcal GN if streptococci are cultured from any site. This is primarily done to prevent the spread of infection within community sites • Treat edema, hypertension, etc. as well as persistent proteinuria and/or progressive GFR decline as per Chapter 1			
	Value of high dose glucocorticoids remains unproven [1]	Most shunts have been replaced with a shunt with a lesser likelihood of infection. Rarely ventriculocisternostomy has been performed after shunt removal	Utility of glucocorticoids and immunosuppression unproven and carries serious potential risks, even in cases with crescentic GN [2]	For severe kidney functional impairment, weigh risks and benefits of immunosuppression. The risk of infection and glucocorticoid-induced complications in this often elderly population with comorbidities can be substantial. A role for immunosuppression remains unproven and these agents should generally not be used
Course	• Follow kidney function, serum C3 and C4, urinalysis, ACR, and proteinuria at appropriate intervals until complete remission or return to baseline			
	Persistently low C3 beyond 12 weeks may be an indication for kidney biopsy to particularly exclude C3GN.[3] Prevention of epidemic poststreptococcal GN may include socioeconomic interventions and mass antimicrobial use to improve living conditions and limit the spread of infection in populations where Group A streptococcus infection and scabies are highly prevalent	The natural history of the PR3-ANCA seen in some patients is unclear and requires follow-up	If the infection can be identified and promptly eradicated, the prognosis is favorable	The prognosis for recovery is poor, especially in diabetic subjects

图57典型细菌感染相关 GN 综合征的预后和治疗。[1]Kapadia 等人[401]，[2]Okuyama 等人[402]，[3]Khalighi *et al.*[403]ACR，白蛋白-肌酐比值；

ANCA，抗中性粒细胞胞浆抗体；C3GN，C3肾小球肾炎；eGFR，估计肾小球滤过率；GN，肾小球肾炎；PR3，蛋白酶3；RCT，随机对照试验。

7.2 病毒感染相关 GN

7.2.1 丙型肝炎病毒 (HCV) 感染–相关 GN

工作组完全同意 *KDIGO 2018 年慢性肾病丙型肝炎预防、诊断、评估和治疗临床实践指南的建议5.1–5.2.3*[405]。有关具体建议、具体治疗药物的选择和给药以及研究建议，请参见本出版物。

7.2.2 乙型肝炎病毒 (HBV) 感染相关 GN

7.2.2.1 诊断

实践要点7.2.2.1.1：蛋白尿性肾小球疾病患者应接受 HBV 感染检测。

7.2.2.2 预后

实践要点7.2.2.2.1：应将慢性 HBV 感染成人患者视为存在发生肾衰竭的风险。

7.2.2.3 治疗

建议7.2.2.3.1：我们建议复制型 HBV 感染（通过 HBV DNA 水平 > 2000 IU/mL表示）和 GN 患者按照标准临床实践指南对一般人群的建议接受核苷（酸）类似物治疗用于 HBV 感染 *(1C)*。

实践要点7.2.2.3.1：聚乙二醇干扰素方案不应用于治疗复制型 HBV 感染和 GN 患者。

实践要点7.2.2.3.2：免疫抑制剂（如环磷酰胺或利妥昔单抗）可加速 HBV 再增殖，应避免用于未经治疗的复制型 HBV 感染和 GN 患者。

7.2.2.4 特殊情况

实践要点7.2.2.4.1：在同时存在 HBV 感染和抗 PLA2R 抗体介导的 MN 的患者中，应避免使用利妥昔单抗和环磷酰胺，直至通过核苷（酸）类似物治疗获得持续病毒学缓解。

实践要点7.2.2.4.2：在伴有冷球蛋白血症性血管炎的患者中可尝试血浆置换。实践要点7.2.2.4.3：HBV感染和 MN 儿童应保守治疗，不进行免疫–由于肾脏疾病自发缓解的可能性较高而受到抑制。

7.2.3 人类免疫缺陷病毒 (HIV) 相关 GN

7.2.3.1 诊断

实践要点7.2.3.1.1：如可行，应进行肾活检，以评价 HIV 相关肾病的形态学。应使用基于病理学的 HIV 相关肾病描述帮助定义和指导治疗。

7.2.3.2 预后

实践要点7.2.3.2.1：导致 GN 相关 HIV 感染长期结局的因素很多，包括病毒复制持续存在、抗病毒治疗应答、肾小球损伤的遗传易感性（例如，*APOL1*风险等位基因）、与其他病毒合并感染以及发生免疫复合物疾病或血栓性微血管病。因此，个体患者的预后判断可能非常困难。

7.2.3.3 治疗

建议7.2.3.3.1：我们建议所有 HIV 和 CKD 患者均开始抗逆转录病毒治疗，尤其是经活检证实的 HIV 相关肾病 (HIVAN)，无论 CD4 计数如何，根据肾功能程度调整 *(1C)*。

实践要点7.2.3.3.1：必须根据具体情况决定使用糖皮质激素作为 HIVAN 的辅助治疗，因为长期风险和获益尚不确定。

7.3 血吸虫病、线虫病和疟疾感染引起的肾病

7.3.1 血吸虫性肾病

7.3.1.1 诊断

实践要点7.3.1.1.1：检测适当的地方性混合感染（*沙门氏菌*、HBV、HCV、HIV），因为靶向治疗可能改变基础 GN 的侵袭性或血吸虫病后遗症。

实践要点7.3.1.1.2：在存在病毒合并感染 (HCV、HBV、HIV) 的情况下，对疑似患有血吸虫性 GN 的患者进行肾活检。

7.3.1.2 治疗

实践要点7.3.1.2.1：使用适当的抗寄生虫药物以足够的剂量和持续时间治疗血吸虫感染和 GN 患者，以根除微生物。目前尚无免疫抑制剂用于血吸虫性肾病的适应症。

7.3.1.3 特殊情况

实践要点7.3.1.3.1：监测血吸虫病肝纤维化患者是否出现肾病。

实践要点7.3.1.3.2：评价有血吸虫病史和 SCr 升高和/或血尿的膀胱癌和/或尿路梗阻患者。

7.3.2 丝虫病和肾小球疾病

7.3.2.1 治疗

实践要点7.3.2.1.1：使用适当的抗寄生虫药物以足够的剂量和持续时间治疗口腔感染和 GN 患者，以根除微生物。

7.3.3 疟疾性肾病

7.3.3.1 治疗

实践要点7.3.3.1.1：使用适当的抗寄生虫药物以足够的剂量和持续时间治疗疟疾感染和 GN 患者，以从血液和肝脾部位根除微生物。目前尚无免疫抑制剂用于疟疾肾病的适应症。

第8章：免疫球蛋白和补体介导的膜增生性肾小球肾炎 (MPGN) 损伤模式肾小球疾病

8.1 诊断

实践要点8.1.1：评价免疫复合物介导的 *GN(ICGN)* 患者的基础疾病（图68）。

Immunoglobulin-/ immune complex-mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** • Viral: hepatitis C (including HCV-associated mixed cryoglobulinemia), hepatitis B • Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis • Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, histoplasmosis **Deposition of immune complexes as a result of an autoimmune disease:** • SLE • Sjögren's syndrome • Rheumatoid arthritis • Mixed connective tissue disease **Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder** **Fibrillary glomerulonephritis** **Idiopathic** • None of the conditions above are present
Complement-mediated	**C3 glomerulonephritis and C3 DDD:** • Mutations in complement regulatory proteins: CFH, CFI, CFHR5 • Mutations in complement factors: C3 • Antibodies to complement factors: C3, C4, and C5 nephritic factors • Antibodies to complement regulatory proteins: CFH, CFI, CFB **C4 glomerulonephritis and C4 DDD**
Membranoproliferative pattern without immune complexes or complement	• Healing phase of HUS/TTP • Antiphospholipid (anticardiolipin) antibody syndrome • POEMS syndrome • Radiation nephritis • Nephropathy associated with bone marrow transplantation • Drug-associated thrombotic microangiopathies • Sickle cell anemia and polycythemia • Dysfibrinogenemia and other pro-thrombotic states • Antitrypsin deficiency

图68膜增生性损伤的原因。CFB，补体因子B；CFH，补体因子H；CFHR5，补体因子 H 相关蛋白5；CFI，补体因子I；DDD，致密物沉积病；HCV，丙型肝炎病毒；HUS，溶血性尿毒症综合征；Ig，免疫球蛋白；MPGN，膜增生性肾小球肾炎；POEMS，多发性神经病变、器官肿大、内分泌病、单克隆蛋白、皮肤改变；SLE，系统性红斑狼疮；TTP，血栓性血小板减少性紫癜。

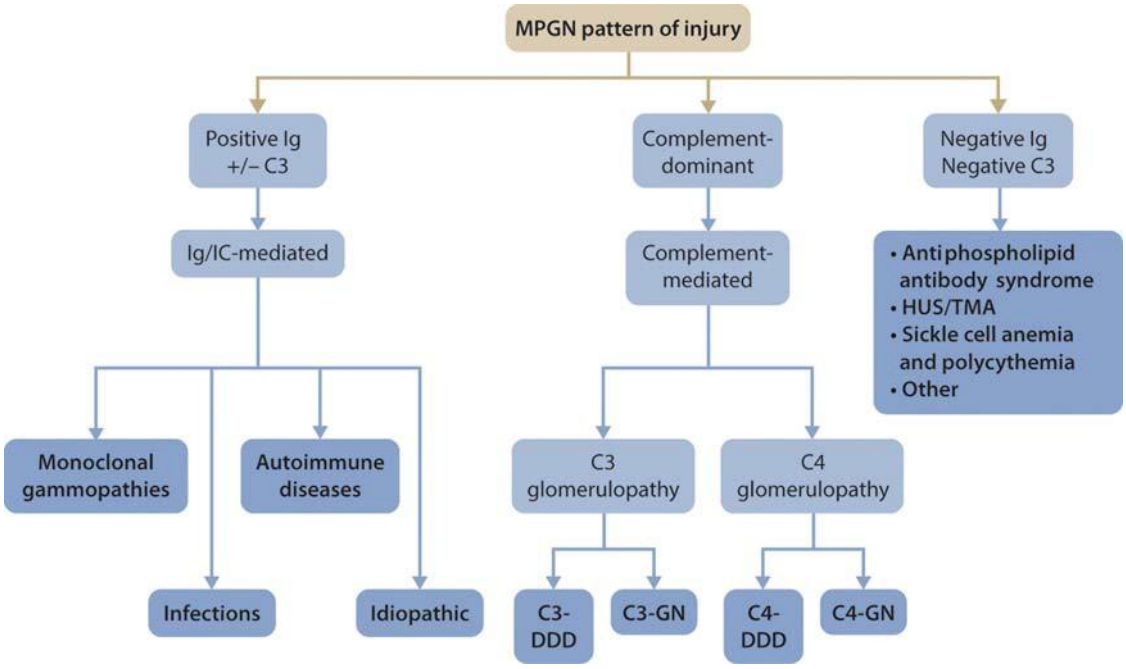


图69膜增生性病变的病理生理学。DDD，致密沉积物疾病；GN，肾小球肾炎；HUS，溶血性-尿毒症综合征；IC，免疫复合物；Ig，免疫球蛋白；MPGN，膜增生性肾小球肾炎；TMA，血栓性微血管病。

实践要点8.1.2：评价 *GN* 和单克隆免疫球蛋白沉积患者的血液恶性肿瘤。实践要点8.1.3：如果经过大量检查后未发现 *ICGN* 的基础病因，则评价补体失调和补体失调驱动因素（图70）。

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, and CFHR1-5 MLPA
Plasma cell disorders‡	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

图70补体替代途径异常的评价。摘自*Kidney International*,volume 89,issue 2,Angioi A,Fervenza FC,Sethi S,et al.补体替代途径疾病的诊断，第278–288页，版权所有[a]2016，经国际肾脏病学会许可。[539]‡50岁以下循环单克隆丙种球蛋白病较少见。检测单克隆蛋白的能力将取决于所用试验的灵敏度。†一些补体检测可能需要转诊至专家/研究实验室，解释补体检测可能需要专家咨询。AP50，补体替代途径激活50%；Bb，活化因子B；C3d，补体成分3d；C4d，补体成分4d；CFB，补体因子B；CFH，补体因子H；CFHR1-5，补体因子 H 相关蛋白1-5；CFI，补体因子I；CH50，补体溶血活性50%；FB，因子B；FH，因子H；FI，因子I；Ig，免疫球蛋白；IgA，免疫球蛋白A；IgG，免疫球蛋白G；IgM，免疫球蛋白M；MLPA，多重连接依赖性探针扩增；sMAC，可溶性膜攻击复合物。

实践要点8.1.4：在诊断 *C3* 胶性脑病 (*C3G*) 之前，排除感染相关 *GN* 或感染后*GN*。

操作要点8.1.5：评估首次诊断为 C3G 的≥50岁患者是否存在单克隆蛋白（图69）。

8.2 治疗

8.2.1 国际神经营养学会

实践要点8.2.1.1：当确定 ICGN 的原因时，治疗的初始方法应集中于潜在的病理过程。

实践要点8.2.1.2：惰性ICGN，无论是特发性还是与原发性疾病过程相关，最好通过支持性治疗进行管理，并仔细考虑使用免疫抑制。

实践要点8.2.1.3：对于蛋白尿 < 3.5 g/日且无肾病综合征的特发性 ICGN 患者，eGFR 正常，我们建议仅用 RAS 抑制进行支持治疗。

实践要点8.2.1.4：对于特发性ICGN、肾病综合征和 SCr 正常或接近正常的患者，尝试糖皮质激素的有限疗程。

实践要点8.2.1.5：对于特发性ICGN、肾功能异常（但无新月体受累）、活动性尿沉渣、伴或不伴肾病范围蛋白尿的患者，在支持治疗的基础上加用糖皮质激素和免疫抑制治疗。

实践要点8.2.1.6：对于表现为快速进展的新月体特发性 ICGN 的患者，使用高剂量糖皮质激素和环磷酰胺治疗。

实践要点8.2.1.7：对于大多数eGFR < 30 mL/min/1.73 m ^{2}的特发性 ICGN 患者，仅支持治疗。

实践要点8.2.1.8：对8.2.1.4和8.2.1.5中讨论的治疗方法无反应的患者应考虑参加临床试验（如可用）。

8.2.2 C3 肾小球病

实践要点8.2.2.1：在没有单克隆丙种球蛋白病的情况下，中重度疾病患者的 C3G 应最初接受 MMF 加糖皮质激素治疗，如果治疗失败，应考虑使用eculizumab。

实践要点8.2.2.2：对8.2.2.1中讨论的治疗方法无反应的患者应考虑参加临床试验（如可用）。

第9章：抗中性粒细胞胞浆抗体 (ANCA) 相关血管炎

9.1 诊断

实践要点9.1.1：在临床表现符合小血管炎且髓过氧化物酶 (MPO) 或蛋白酶 3(PR3)-ANCA 血清学阳性的情况下，等待进行或报告肾活检不应延迟开始免疫抑制治疗，尤其是在快速恶化的患者中（图71）。

实践要点9.1.2：ANCA相关血管炎 (AAV) 患者应在具有 AAV 治疗经验的中心接受治疗。

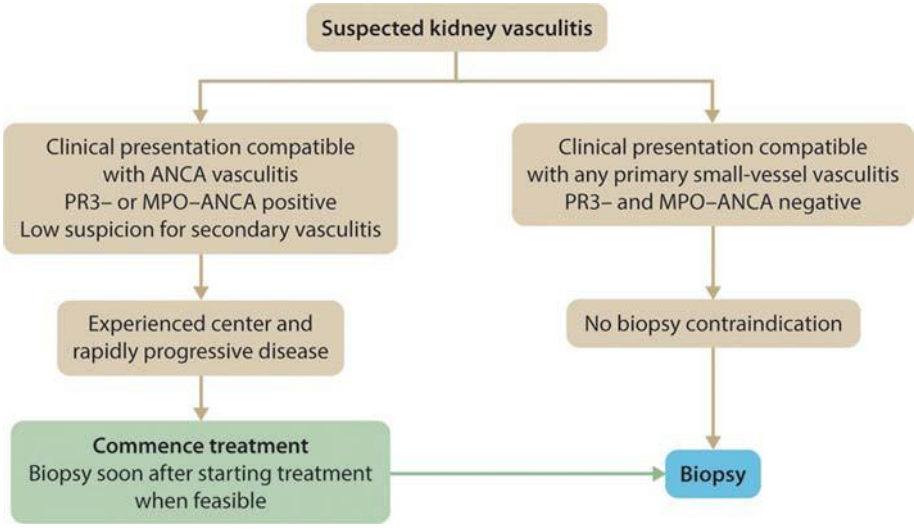


图71疑似肾血管炎的活检策略。ANCA，抗中性粒细胞胞浆抗体；MPO，髓过氧化物酶；PR3，蛋白酶3。

9.2 预后

9.2.1. 生存期
[无建议或实践要点]

9.2.2. 肾脏预后和治疗反应
[无建议或实践要点]

9.2.3 复发

实践要点9.2.3.1：ANCA阳性持续存在、ANCA水平升高以及 ANCA 从阴性变为阳性仅能适度预测未来疾病复发，不应用于指导治疗决策。

9.3 治疗

9.3.1 诱导

建议9.3.1.1：我们建议使用糖皮质激素联合环磷酰胺或利妥昔单抗作为新发 AAV 的初始治疗 *(1B)*。

实践要点9.3.1.1：推荐的累及肾脏的 AAV 治疗方案见图76。

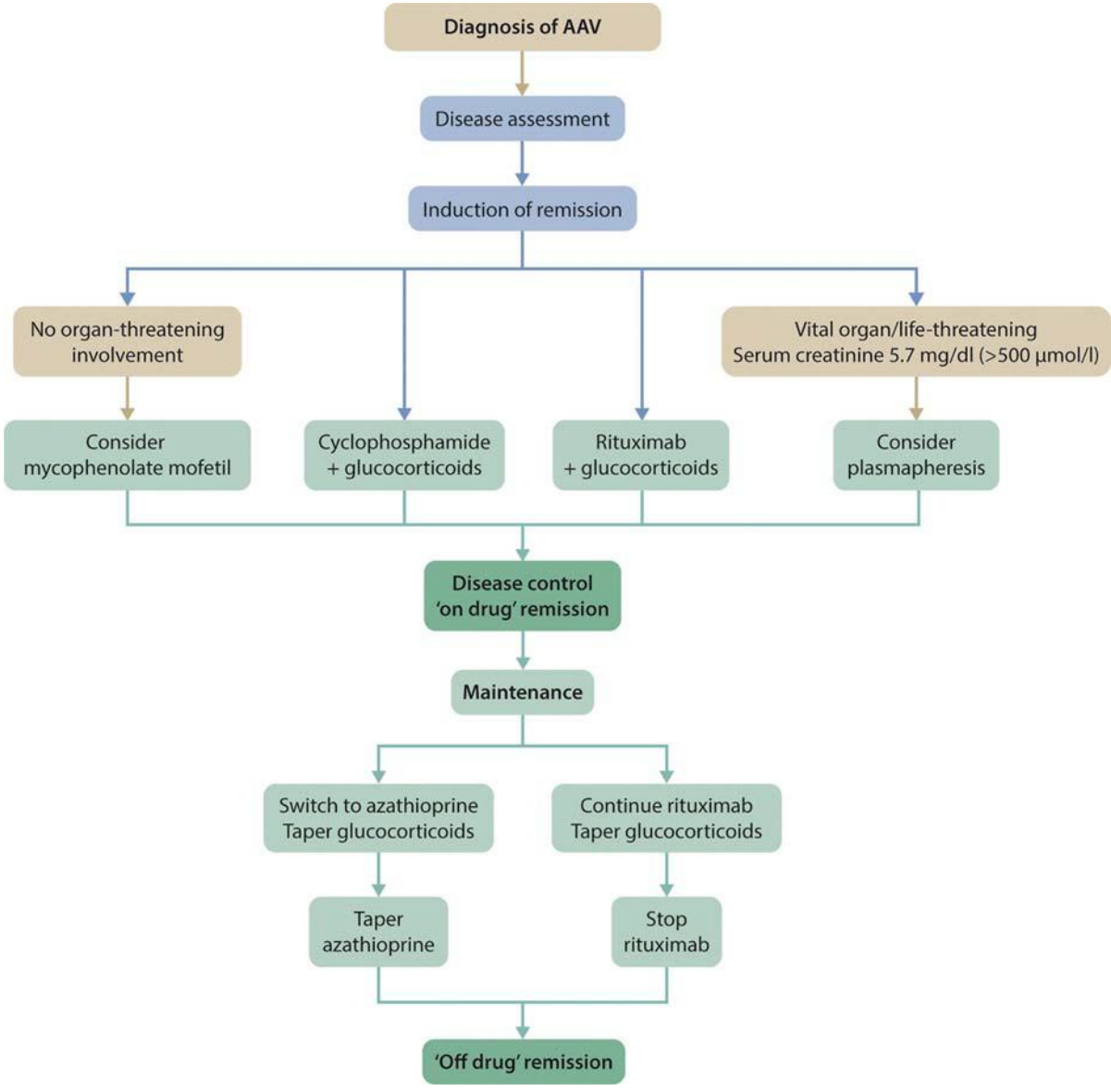


图76|推荐的 AAV 治疗方案。AAV，ANCA相关血管炎。

实践要点9.3.1.2：在 GFR 显著降低或快速下降 (SCr > 4 mg/dL[> 354 mmol/l]) 的患者中，支持利妥昔单抗和糖皮质激素的数据有限。诱导治疗首选环磷酰胺和糖皮质激素。利妥昔单抗联合环磷酰胺
在这种情况下也可以考虑。

实践要点9.3.1.3：在图77中给出了选择利妥昔单抗和环磷酰胺作为诱导治疗的考虑因素。

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 μmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered

图77选择利妥昔单抗和环磷酰胺诱导治疗 AAV 时的考虑因素。AAV，ANCA相关血管炎；ANCA，抗中性粒细胞胞浆抗体；GN，肾小球肾炎；PR3，蛋白酶3；SCr，血清肌酐。

实践要点9.3.1.4：在图78中给出了选择环磷酰胺给药途径的考虑。

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

图78|环磷酰胺治疗 AAV 的给药途径考虑。AAV，ANCA相关血管炎。

实践要点9.3.1.5：对于仍在接受透析且无任何肾外疾病表现的患者，在3个月后停止免疫抑制治疗。

实践要点9.3.1.6：图79给出了口服糖皮质激素逐渐减量的建议。

Week	'Reduced-corticosteroid dose' in PEXIVAS trial		
	<50 kg	50–75 kg	>75 kg
1	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–16	5	5	7.5
17–18	5	5	7.5
19–20	5	5	5
21–22	5	5	5
23–52	5	5	5
>52	Investigators' local practice		

图79|AAV的泼尼松龙逐渐减量方案。AAV，ANCA相关血管炎。

实践要点9.3.1.7：免疫抑制给药的建议见图80。

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m^2/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m^2/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m^2	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m^2			

图 80 AAV 的免疫抑制药物剂量。AAV，ANCA相关血管炎；GFR，肾小球滤过率；i.v.，静脉内；MMF，吗替麦考酚酯。

实践要点9.3.1.8：对于需要透析或 SCr 快速升高的SCr > 5.7 mg/dL(500 mmol/l) 的患者以及伴有低氧血症的弥漫性肺泡出血患者，考虑血浆置换。

实践要点9.3.1.9：为 ANCA 血管炎和抗 GBM 重叠综合征患者增加血浆置换。

9.3.2 维持治疗

建议9.3.2.1：我们建议在诱导缓解后使用利妥昔单抗或硫唑嘌呤和低剂量糖皮质激素进行维持治疗 *(1C)*。

实践要点9.3.2.1：环磷酰胺诱导后，应使用硫唑嘌呤加低剂量糖皮质激素或利妥昔单抗不加糖皮质激素预防复发。

实践要点9.3.2.2：在利妥昔单抗诱导后，大多数患者应给予维持免疫抑制治疗。

实践要点9.3.2.3：硫唑嘌呤加低剂量糖皮质激素的最佳持续时间未知，但应在诱导缓解后18个月至4年之间。

实践要点9.3.2.4：尚不清楚利妥昔单抗维持治疗的最佳持续时间，但迄今为止的研究评价了缓解后18个月的持续时间。常规使用口服糖皮质激素或口服免疫抑制剂与利妥昔单抗维持治疗无作用。

实践要点9.3.2.5：当考虑停止维持治疗时，应考虑复发风险，并告知患者如果症状复发需要及时关注（图82）。

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Lower serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

图82增加 AAV 复发风险的因素。AAV，ANCA相关血管炎；ANCA，抗中性粒细胞胞浆抗体；PR3，蛋白酶3。

实践要点9.3.2.6：对于甲氨蝶呤诱导后或对硫唑嘌呤和 MMF 不耐受的患者，考虑使用甲氨蝶呤进行维持治疗，但GFR < 60 mL/min/1.73 m ^{2}时不考虑。

实践要点9.3.2.7：选择利妥昔单抗或硫唑嘌呤进行维持治疗的考虑见图83。

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Hepatitis B exposure (HBsAg positive) • Limited availability of rituximab

图83|使用利妥昔单抗或硫唑嘌呤进行 AAV 维持治疗的注意事项。AAV，ANCA相关血管炎；ANCA，抗中性粒细胞胞浆抗体；HBsAg，乙型肝炎表面抗原；IgG，免疫球蛋白g；PR3，蛋白酶3。

实践要点9.3.2.8：维持治疗的给药和持续时间建议见图84。

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at months 6, 12 and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at months 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until one yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yrs
	Extend azathioprine at complete remission until 4 yrs after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yrs after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yrs and then slowly reduced by 1 mg every 2 mo	

图 84 AAV 维持治疗的免疫抑制剂量和持续时间。*RITAZAREM治疗复发性AAV。MAINRITSAN，在系统性 ANCA 相关血管炎中使用利妥昔单抗维持缓解；MMF，吗替麦考酚酯；RITAZAREM，利妥昔单抗与硫唑嘌呤作为抗中性粒细胞胞浆抗体相关血管炎 (AAV) 缓解的维持治疗。

9.3.3 疾病复发

实践要点9.3.3.1：复发疾病（危及生命或器官）的患者应重新诱导治疗（建议9.3.1.1）。），最好用利妥昔单抗。

9.4 特殊情况

9.4.1 难治性疾病

实践要点9.4.1.1：难治性疾病可通过增加糖皮质激素（静脉注射或口服）、加用利妥昔单抗（如果既往使用过环磷酰胺诱导治疗）进行治疗，反之亦然。可考虑血浆置换。

实践要点9.4.1.2：在弥漫性肺泡出血伴低氧血症的情况下，除糖皮质激素联合环磷酰胺或利妥昔单抗外，还应考虑血浆置换。

9.4.2 移植

实践要点9.4.2.1：延迟移植，直至患者达到6个月的完全临床缓解‡。ANCA的持续存在不应延迟移植。

第10章：狼疮肾炎

10.1 诊断

实践要点10.1.1：系统性红斑狼疮 (SLE) 肾脏受累的诊断方法（图85）

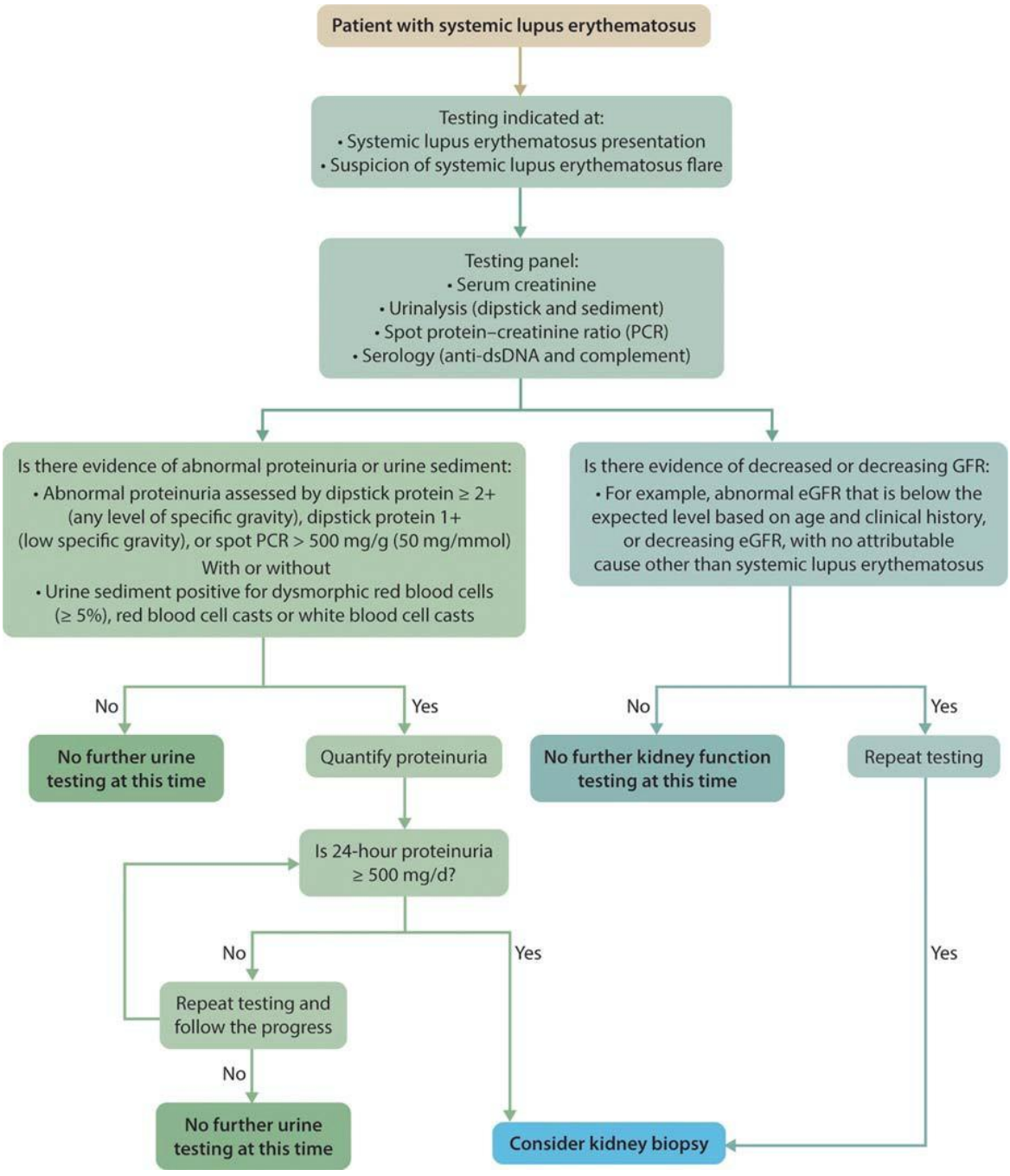


图 85 SLE 肾脏受累的诊断eGFR，估计肾小球滤过率。

10.2 治疗

10.2.1 狼疮肾炎患者的一般管理

建议10.2.1.1：我们建议 SLE 患者（包括狼疮肾炎 (LN) 患者）接受羟氯喹或等效抗疟药治疗，除非存在禁忌症 *(1C)*。

实践要点10.2.1.1：如图87所示，所有患者均应考虑使用辅助治疗来管理 *LN* 并减少疾病并发症或其治疗。

Risk	Risk attenuation
Cardiovascular risk	• Lifestyle modifications – smoking cessation, body weight optimization, exercise • Dyslipidemia management • Low-dose aspirin during pregnancy
Proteinuria (Chapter 1)	• Avoidance of high-sodium diet • Blood pressure control • RAS blockade
Infection risk	• Assess medical history of herpes zoster and tuberculosis • Screening for HBV, HCV, HIV, and HBV vaccination • *Pneumocystis jirovecii* prophylaxis (issue of potential adverse drug reaction discussed below) • Influenza and pneumococcal vaccination • Individualized consideration for recombinant zoster vaccine • Individualized consideration for other infectious organisms as dictated by public health concerns at the time of treatment
Bone injury	• Bone mineral density and fracture risk assessment • Calcium and vitamin D supplementation • Bisphosphonates when appropriate
Ultraviolet light exposure	• Broad-spectrum sunscreen • Limit ultraviolet light exposure
Premature ovarian failure	• Gonadotropin-releasing hormone agonists (i.e., leuprolide) • Sperm/oocyte cryopreservation
Unplanned pregnancy	• Individual evaluation and counselling for contraception type (preference, thrombosis risk, age)
Cancer	• Evaluate individual risk factors for malignancies • Age-specific malignancy screening • Limit lifetime cyclophosphamide exposure to <36 g

图87减少 LN 或其治疗相关并发症风险的措施。HBV，乙型肝炎病毒；HCV，丙型肝炎病毒；HIV，人类免疫缺陷病毒；LN，狼疮肾炎；RAS，肾素-血管紧张素系统。

10.2.2 I 类或 II 类狼疮肾炎

实践要点10.2.2.1：I类或 II 类 LN 患者的免疫抑制治疗方法（图88）

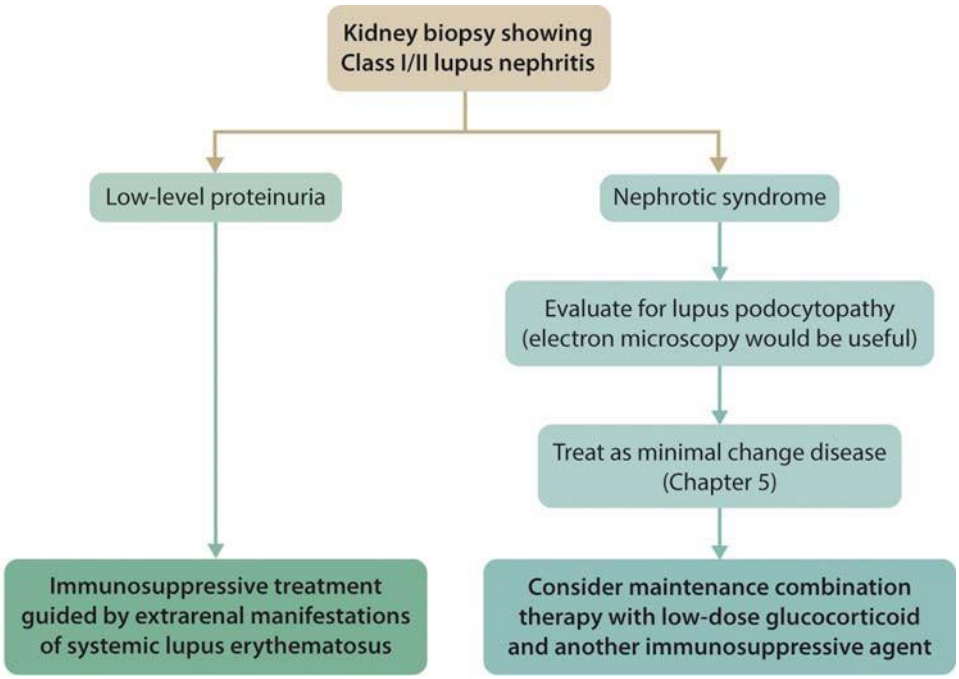


图 88 I 型或 II 型 LN 患者的免疫抑制治疗LN，狼疮肾炎。

10.2.3 III 类或 IV 类狼疮肾炎

10.2.3.1 活动性 III/IV 类狼疮肾炎的初始治疗

建议10.2.3.1.1：我们建议有或无膜性成分的活动性 III 或 IV 型 LN 患者最初接受糖皮质激素加低剂量静脉注射环磷酰胺或 MPAA 治疗 *(1B)*。

实践要点10.2.3.1.1：在活动性 LN 的初始治疗期间，当肾脏和肾外疾病表现均显示令人满意的改善时，可考虑在短疗程甲泼尼龙冲击后给予减量糖皮质激素的方案（图90）。

	Standard-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

图90|LN的糖皮质激素治疗方案示例。LN，狼疮肾炎。

实践要点10.2.3.1.2：对于可能难以依从口服方案的活动性 III 类和 IV 类 LN 患者，应使用静脉注射环磷酰胺作为初始治疗。

实践点10.2.3.1.3：基于 MPAA 的方案是高不育风险患者、既往环磷酰胺暴露为中度至高度的患者以及亚洲、西班牙裔或非洲血统患者的首选初始疗法。

实践要点10.2.3.1.4：包含CNI（他克莫司或环孢素）与减量 MPAA 和糖皮质激素的三联免疫抑制方案的初始治疗适用于不能耐受标准剂量 MPAA 或不适合或不会使用基于环磷酰胺的方案的患者。

实践点10.2.3.1.5：在基线 eGFR 至少为45 mL/min/1.73 m^2的患者中，可以在 MPAA 和糖皮质激素的基础上加用伏孢霉素作为初始治疗1年。

实践点10.2.3.1.6：B淋巴细胞靶向生物制剂在 LN 治疗中的新作用。在活动性 LN 的标准治疗中可加用Belimumab。疾病活动持续或反复发作的患者可考虑使用利妥昔单抗。

实践点10.2.3.1.7：在患者不耐受、缺乏可用药物和/或标准药物费用过高的情况下，可以考虑使用其他疗法代替推荐的增生性 LN 初始药物，如硫唑嘌呤或来氟米特联合糖皮质激素，但这些替代药物可能疗效较差，包括疾病发生率增加和/或药物毒性发生率增加。

10.2.3.2 III 类和 IV 类狼疮肾炎的维持治疗

建议10.2.3.2.1：我们建议在完成初始治疗后，患者应接受 MPAA 维持治疗 *(1B)*。

实践点10.2.3.2.1：对于不耐受MPAA、无法获得 MPAA 或考虑妊娠的患者，在完成初始治疗后，硫唑嘌呤是 MPAA 的替代药物。

实践要点10.2.3.2.2：在维持治疗期间，糖皮质激素应逐渐减量至可能的最低剂量，除非因肾外狼疮表现而需要使用糖皮质激素；在患者维持完全临床肾脏缓解‡12个月后，可考虑停用糖皮质激素。

实践点10.2.3.2.3：维持治疗早期 MMF 的剂量约为750–1000 mg，每日两次，MPA约为540–720 mg，每日两次。

实践要点10.2.3.2.4：如果 MPAA 和硫唑嘌呤不能用于维持治疗，则应考虑使用 CNI 或咪唑立宾。

实践要点10.2.3.2.5：增殖性 LN 的初始免疫抑制加联合维持免疫抑制的总持续时间不应 < 36个月。

10.2.4 V 类狼疮肾炎

实践要点10.2.4.1：推荐的单纯 V 类 LN 患者管理方法见图94。

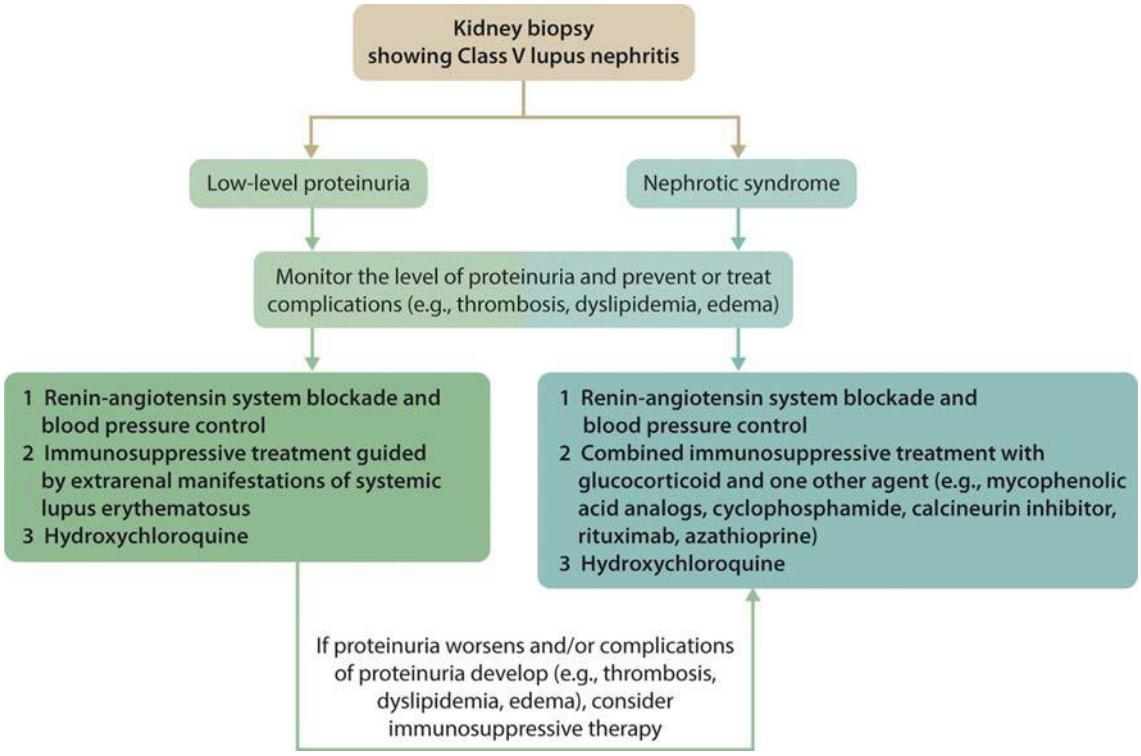


图94单纯 V 型 LN 患者的治疗。LN，狼疮肾炎。

10.2.4.1 评估 LN 的治疗反应

实践点10.2.4.1.1：LN治疗反应的定义见图95。

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

图 95 LN 治疗反应的常用定义*对于 < 18岁的儿童，完全缓解定义为蛋白尿 < 0.5 g/1.73 m ^{2}/d或 < 300 mg/m ^{2}/d，基于 24 h 尿液样本。LN，狼疮肾炎；PCR，蛋白-肌酐比值。

10.2.4.2 对治疗反应不满意的管理

实践点10.2.4.2.1：对治疗反应不满意的患者的算法见图96。

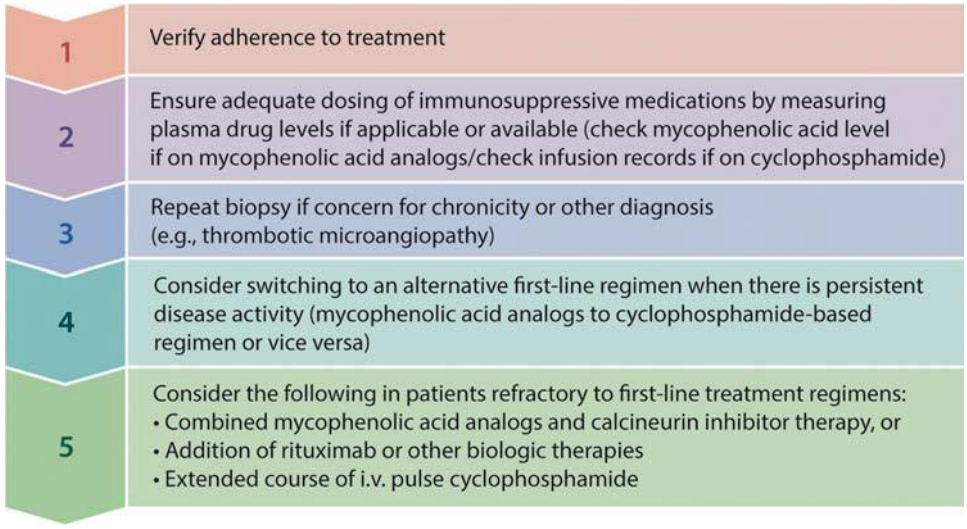


图96对活动性 LN 初始治疗反应不满意的患者的处理。i.v.，静脉内；LN，狼疮肾炎。

10.2.4.3 治疗 *LN* 复发

实践要点10.2.4.3.1：在达到完全或部分缓解后，应使用与达到最初缓解相同的初始治疗或替代推荐的一线治疗来治疗 *LN* 复发。

10.3 特殊情况

10.3.1 狼疮肾炎和血栓性微血管病

实践要点10.3.1.1：应根据 TMA 的基础病因管理 LN 和血栓性微血管病 (TMA) 患者，如图97[864]所示。

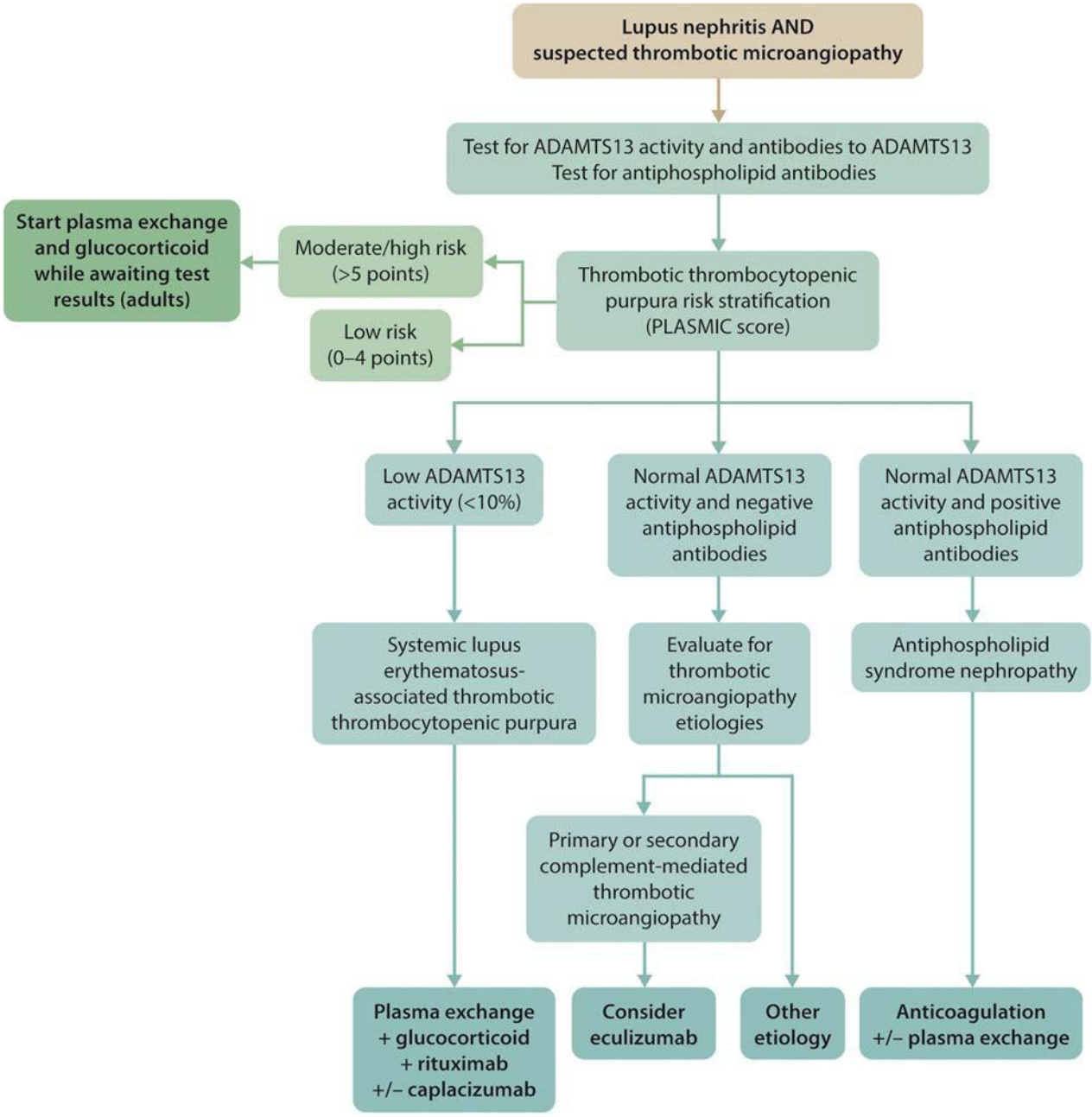


图 97 LN 和 TMA 患者的治疗Bendapudi PK,Hurwitz S,Fry A,et al.PLASMIC评分的推导和外部验证用于快速评估血栓性微血管病成人患者：一项队列研究。*Lancet Haematol.*2017;4:e157–e164.[864]ADAMTS13，一种具有血小板反应蛋白1型基序的去整合素和金属蛋白酶，成员13；PLASMIC，血小板计数，联合溶血可变，无活动性癌症，无干细胞或实体器官移植，MCV，INR，肌酐。

10.3.2 狼疮肾炎患者的妊娠

实践要点10.3.2.1：应建议活动性 *LN* 患者在疾病活动期间或正在接受潜在致畸药物治疗时以及 *LN* 变得不活动后‡6个月内避免妊娠。

实践要点10.3.2.2：为降低妊娠并发症的风险，应在妊娠期间继续使用羟氯喹，并在妊娠16周前开始使用低剂量阿司匹林。

实践要点10.3.2.3：只有糖皮质激素、羟氯喹、硫唑嘌呤和 *CNI* 被认为是妊娠期间安全的免疫抑制治疗。

10.3.3 治疗儿童狼疮肾炎

实践要点10.3.3.1：使用与成人相似的免疫抑制方案治疗儿童 *LN* 患者，但在设计治疗计划时考虑与该人群相关的问题，如剂量调整、生长、生育力和心理社会因素。

10.3.4 狼疮伴肾衰竭患者的管理

实践要点10.3.4.1：发生肾衰竭的 *LN* 患者可接受血液透析、腹膜透析或肾移植治疗；肾移植优于长期透析。

第11章：抗肾小球基底膜 (Anti-GBM) 抗体肾小球肾炎

11.1 诊断

实践要点11.1.1：所有疑似 *RPGN* 患者均应立即诊断抗肾小球基底膜 (*GBM*) 疾病（图98）。

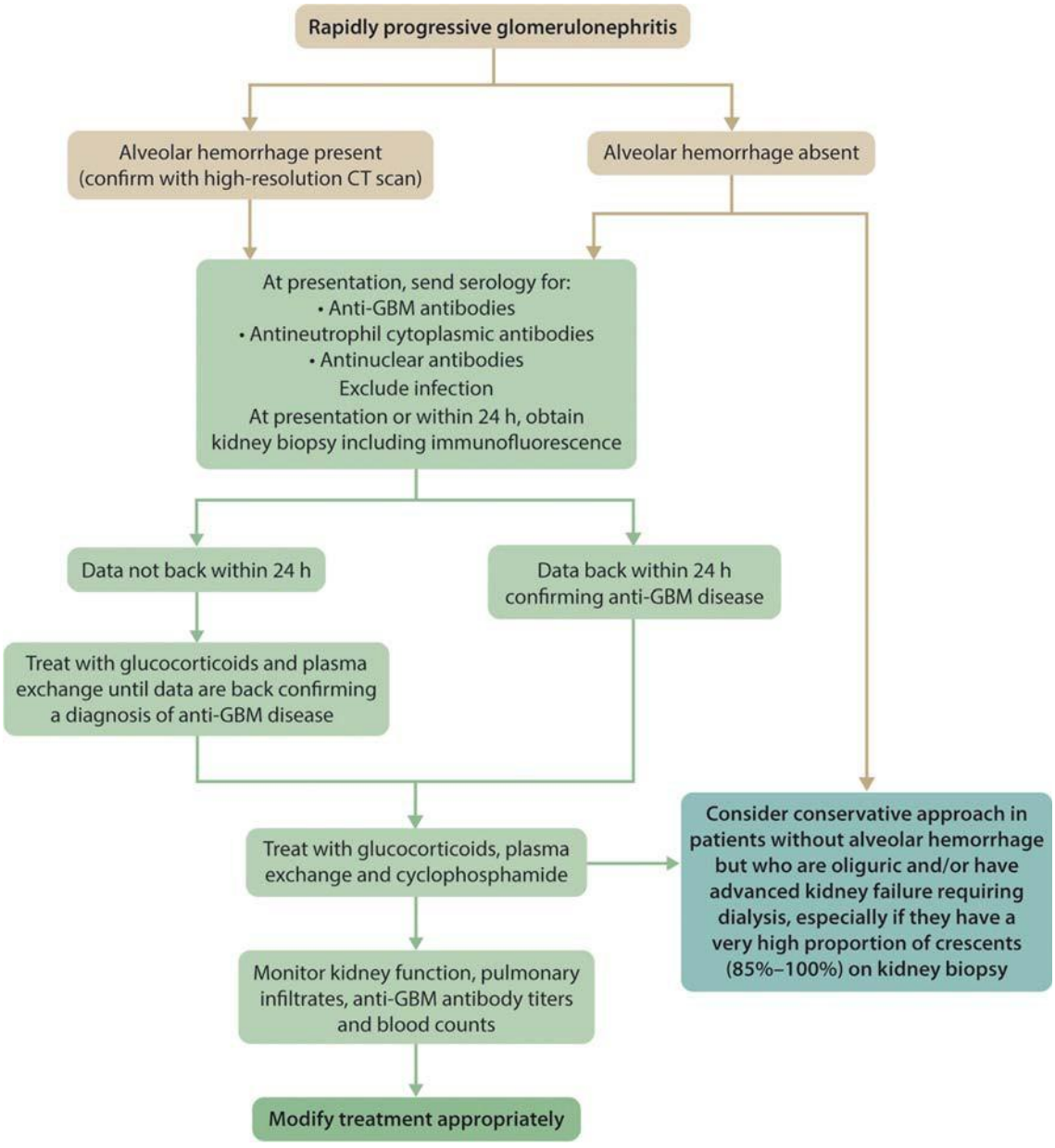


图98抗 GBM 疾病的诊断和治疗。CT，计算机断层扫描；GBM，肾小球基底膜。

11.2 治疗

建议11.2.1：我们建议所有抗 GBM GN 患者开始环磷酰胺和糖皮质激素免疫抑制治疗加血浆置换，以下患者除外： 在就诊时接受透析治疗，在充分的活检样本中有100%新月体或 > 50%整体肾小球硬化，并且没有肺出血 *(1C)*。	

实践要点11.2.1：如果怀疑抗 GBM 疾病，即使在确诊前，也应立即开始治疗。

实践要点11.2.2：应进行血浆置换，直至无法再检测到抗 GBM 滴度。

实践要点11.2.3：环磷酰胺应给药2–3个月，糖皮质激素应给药约6个月（图99[931、945、946]）。

Intervention	Dosing	Duration of treatment
Plasma exchange	• 40–50 ml/kg ideal body weight exchange daily against 5% albumin • Add fresh frozen plasma at the end of plasma exchange in patients with alveolar hemorrhage and/or after kidney biopsy	Until circulating anti-GBM antibodies can no longer be detected; usually 14 days
Cyclophosphamide	• 2–3 mg/kg orally (reduce to 2 mg/kg in patients >55 years); experience with pulse intravenous cyclophosphamide is limited and efficacy is uncertain • Cyclophosphamide dosing should be reduced (or treatment interrupted) in cases of leukopenia • In patients not tolerating (or not responding to) cyclophosphamide, rituximab or mycophenolate mofetil may be tried but experience is limited and efficacy uncertain	3 months
Glucocorticoids	• Pulse methylprednisolone may be given initially up to 1000 mg/d on 3 consecutive days • Prednisone 1 mg/kg orally • Reduce to 20 mg/d by 6 weeks	6 months

图99抗 GBM 疾病的治疗。摘自*Journal of the American Society of Nephrology*,volume 10,issue 11,Kluth DC,Rees AJ.Anti-glomerular basement membrane disease,pages 2446–2453,Copyright©1999,with permission from the American Society of Nephrology.[946]Adapted from *Clinical Journal of the American Society of Nephrology*,volume 12,issue 7,McAdoo SP,Pusey CD.抗肾小球基底膜疾病，第1162-1172页，版权©2017，经美国肾脏病学会许可。[931]摘自Kaplan AA,Appel GB,Pusey CE,et al.抗 GBM(Goodpasture) 疾病：治疗和预后。更新日期：循证临床决策支持。网址：www.uptodate.com.访问日期：2021年09月07日。[945]

实践要点11.2.4：无需抗 GBM 疾病的维持治疗。

实践要点11.2.5：抗 GBM 和 ANCA 阳性的 GN 患者应接受与 AAV 患者相同的维持治疗。

实践要点11.2.6：在难治性抗 GBM 疾病中，可试用利妥昔单抗。

实践要点11.2.7：因抗 GBM 疾病导致肾衰竭的患者应推迟肾移植，直至6个月无法检出抗 GBM 抗体‡。

第1章：肾小球疾病管理的一般原则

本章涉及的一般处理原则适用于大多数或所有组织学形式的肾小球疾病。我们对这些一般原则进行了广泛讨论，以尽量减少后续个体疾病特定指南中的重复。如果存在这些一般声明的具体申请或例外情况，则在每个疾病特定章节中给出这些变化和/或建议的扩展和依据。支持这些一般原则的证据多种多样，通常质量较低或中等，因为相关随机临床试验（RCT）不常见或仅在患有各种肾小球疾病（包括糖尿病肾病）和特定疾病的受试者中进行，如以下章节所述。因此，本节概述的一般原则通常不伴有基于具体证据的分级建议。

1.1 肾活检

当病因不明时，肾活检已被强制用于肾病综合征（NS）成人患者的诊断

从初步评价中可以明显看出，在大多数情况下，仍然如此。然而，在12岁以下儿童、类固醇敏感性NS（SSNS；第4章）和链球菌感染后肾小球肾炎（GN；第7章）中，临床表现通常与直接初始治疗（未进行活检）充分相关。在成人中，大多数无糖尿病的患者在治疗前通常需要对更广泛的可能基础肾小球疾病进行肾活检。近年来，当在临床表现和辅助实验室研究的背景下进行解释时，一些肾小球疾病的血清学检测的进展变得足够敏感和具体，即使在成人中也能做出推定诊断和指导治疗，而无需肾脏活检（例如膜性肾病；第3章）。[3] 尽管这种方法尚未针对所有疾病进行正式分析，但在存在禁忌症或患者反对活检的情况下，可以合理地免除在治疗前进行形态学诊断的要求。

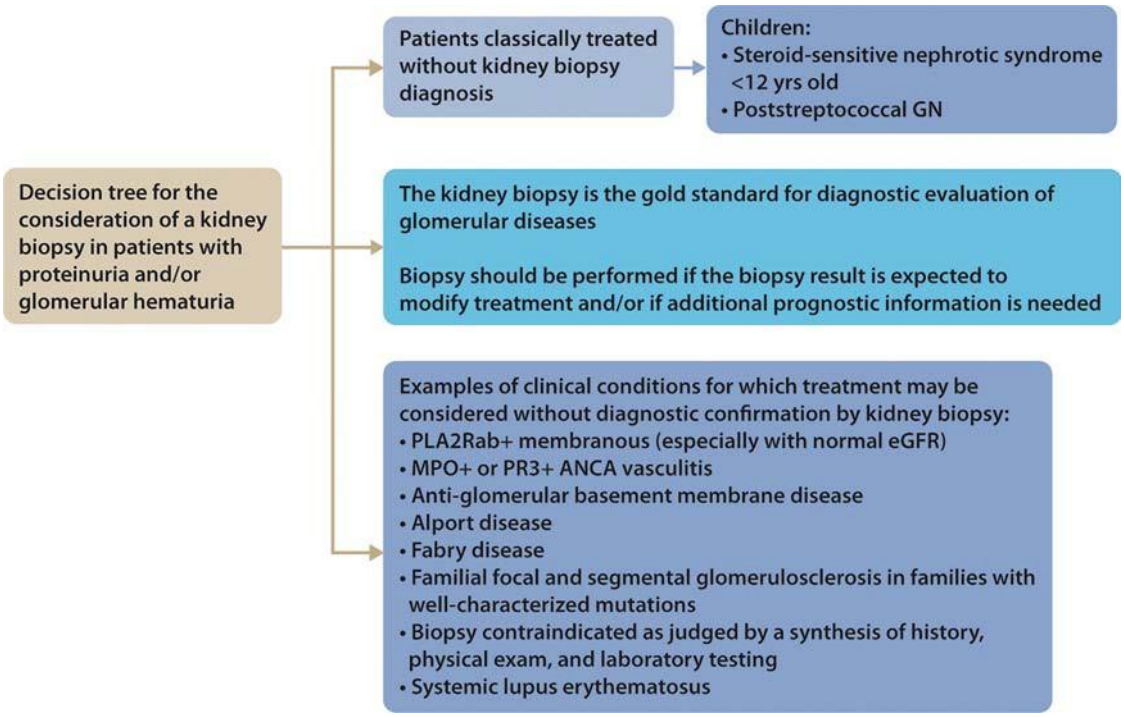


图2蛋白尿和/或肾小球性血尿患者肾活检的注意事项。ANCA，抗中性粒细胞胞浆抗体；eGFR，估计肾小球滤过率；GN，肾小球肾炎；MPO，髓过氧化物酶；PLA2Rab，M型磷脂酶 A2 受体抗体阳性；PR3，蛋白酶3。

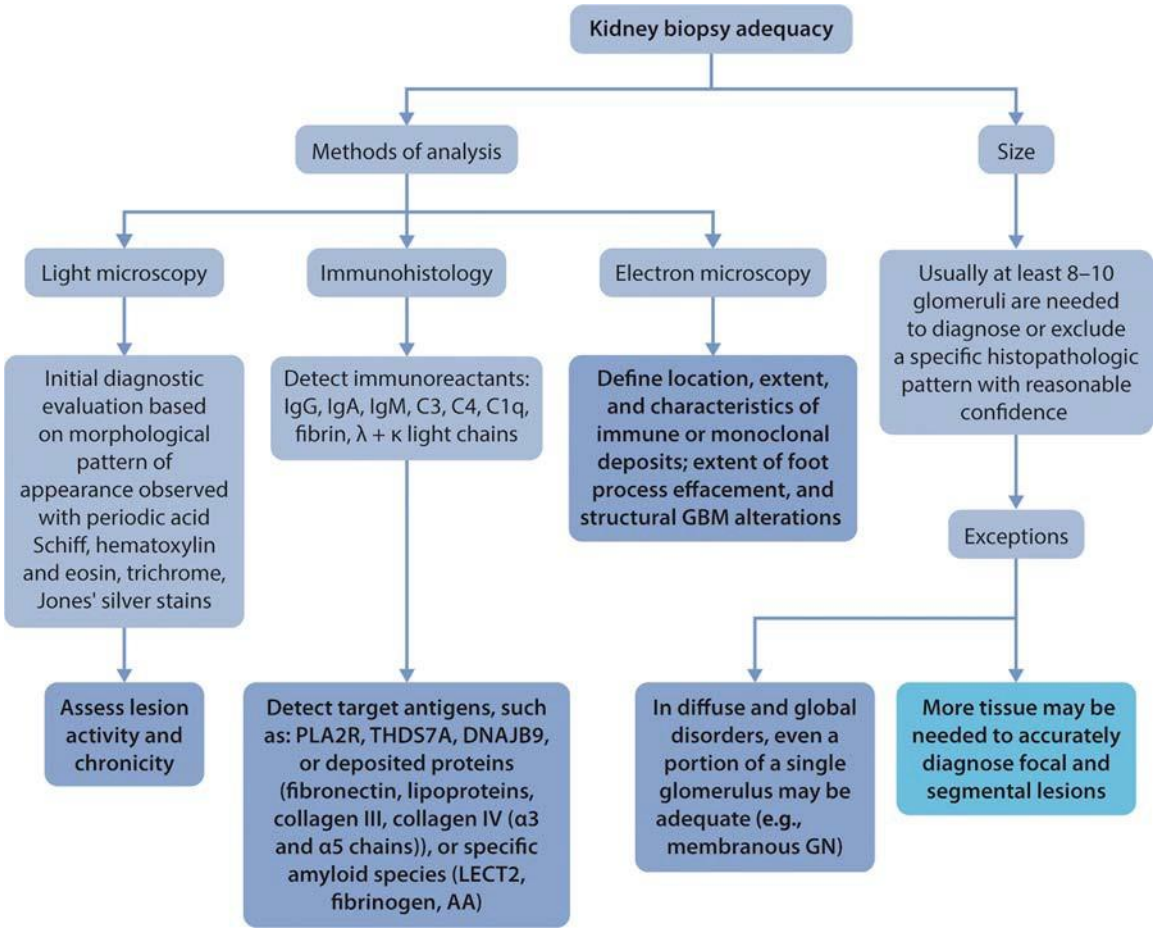


图3|肾组织评价。AA，淀粉样蛋白A；GBM，肾小球基底膜；DNAJB9，DnaJ同系物亚家族 B 成员9；GN，肾小球肾炎；IgA，免疫球蛋白A；IgG，免疫球蛋白g；IgM，免疫球蛋白M；LECT2，白细胞衍生趋化因子-2；PLA2R，M型磷脂酶 A2 受体；THDS7A，含 I 型血小板反应蛋白结构域的7A。

操作要点1.1.1：肾活检是肾小球疾病诊断评估的"金标准"。然而，在某些情况下，治疗可以在没有肾脏活检确诊的情况下进行（图2）。在未进行形态学分析的情况下进行治疗，可放弃从肾活检中获得的其他信息，包括活动性、慢性和其他非疑似肾小球、血管和/或肾小管间质疾病和损伤（如血栓性微血管病或间质性肾炎），这些疾病和损伤可能导致预后甚至治疗意义。

当从活检中获得的信息的价值超过所带来的风险时，应进行肾活检。患者（或父母）在开始治疗计划之前也可能对增加的诊断确定性和预后提出不同的意见，通常涉及具有显著副作用的药物与活检本身的潜在并发症。当地资源也可能决定目前的做法。

实践要点1.1.2：肾组织评价应符合活检充分性标准（图3）。

诊断或排除具有合理一致性的特定组织病理学模式所需的活检大小

（通过样本中存在的肾小球数量评估）通常至少有8–10个肾小球。[4,5]在一些疾病中，例如与抗中性粒细胞胞浆抗体 (ANCA) 相关的局灶性节段性肾小球硬化 (FSGS) 和坏死性GN，仅在一些肾小球的某些节段中观察到病变。在这些情况下，如果不遗漏病变，重要的是在几个水平通过光学显微镜检查活检。弥漫性和全身性疾病（如膜性肾病）可接受的肾小球较少，即使是单个肾小球的一部分也可能足够。

最佳情况下，应通过光学、免疫荧光和电子显微镜检查对样本进行研究，并由经验丰富的肾病学家进行评价。光学显微镜检查至少应根据用过碘酸雪夫染色、苏木精–伊红染色、三色染色和琼斯'银染色的组织切片上观察到的外观形态模式提供初步诊断评价。需要使用免疫荧光显微镜和/或免疫过氧化物酶分析检测免疫反应物免疫球蛋白G(IgG)、免疫球蛋白A(IgA)、免疫球蛋白M(IgM)、C3、C4、C1q、纤维蛋白以及 l 和 k 轻链。这些方法可进一步用于检测靶抗原，

例如 M 型磷脂酶 A2 受体 (PLA2R)、含血小板反应蛋白1型结构域的7A(THSD7A)、DnaJ同系物亚家族 B 成员 9（DNAJB9— 见于 brillary GN）、bronectin、脂蛋白、胶原蛋白III、胶原蛋白 IVa3 和 a5 链以及特定的淀粉样物质。抗原修复方法（如石蜡包埋组织的蛋白酶消化）可能有助于诊断。

理想情况下，所有肾活检应通过光学显微镜、免疫组织学和电子显微镜进行评估。由于成本和设备的限制，人们认识到电子显微镜可能并不适用于任何地方。电子显微镜检查确定了免疫或单克隆沉积物的位置、程度和具体特征，包括有组织的亚结构、足突消失的程度、肾小球基底膜 (GBM) 结构改变和糖蛋白或脂质沉积。一些诊断，包括微小病变 (MCD) 和免疫触须样沉积病，依赖于电子显微镜检查。在其他研究中，电子显微镜检查提供了关于足细胞和 GBM 的显著描述性和半定量信息，增加了诊断的确定性。在无法进行电子显微镜检查的中心，应考虑发展协商关系，以在这种情况下获得显微镜评估。

“活动性”病变为急性病变，可能对特异性治疗。“慢性”病变通常不可逆或不可治疗。肾小球瘢痕与下游肾小管萎缩和间质纤维化相关。根据间质纤维化和肾小管萎缩的程度最容易评估慢性不可逆损伤的程度。活检引起的慢性损伤评估必须始终与临床数据一起解释，以避免在从局灶性皮质瘢痕（偶然）进行活检时误解。在不同类型的肾小球疾病中，肾脏病理学的信息量差异很大；当具有特殊相关性时，在适当章节中专门讨论该问题。

临床医生在活检报告中应注意活动性或慢性组织病理学特征的内容和详细描述，而不仅仅是诊断。已经为一些实体开发了国际验证的评分系统（例如，MEST-C—系膜 (M) 和毛细血管内 (e) 细胞过多、节段性硬化 (S)；间质纤维化/肾小管萎缩 (T) 和新月体 (C)IgA 肾病评分 [IgAN；国际肾脏病学会和肾脏病理学会 [ISN/RPS] 类狼疮肾炎 [LN]），在讨论治疗时也应考虑到这一点。

实践要点1.1.3：如果信息可能改变治疗计划或有助于估计预后，应重复进行肾活检。

当初始活检不足以得出诊断时，可能需要重复肾活检。有时，治疗反应或肾病进展可能存在充分的不确定性，需要重复活检，即使是在确诊的患者中。

在有复发倾向或转化为其他组织病理学形式（如 MCD/FSGS）的疾病中，通常考虑重复进行肾活检。但是，没有证据表明在初始肾活检显示 MCD 或 FSGS 的 SSNS 中重复肾活检对管理有任何重大获益（第5章和第6章）。在下列情况下，可以考虑重复进行肾活检，即使最初的活检足以进行诊断：

- 当对肾功能非预期恶化的原因进行评价时，与已知的自然史不一致；
- 当对治疗的反应不满意时，尤其是当考虑改变治疗时；
- 评价提示同一诊断中损伤模式改变的临床或实验室参数变化（例如，膜性至弥漫性增生性 LN 的转化[6]）；
- 重新确定形态学诊断并重新评估疾病活动度和慢性的相对作用，以确定是否强化、维持、减少或以其他方式改变治疗；或
- 定义“无回报/治疗无效点”时。

考虑到手术的侵入性，当综合可用临床信息无法获得预期信息时，以及当结果可能改变治疗时，应重复进行肾活检。局部成本-将 t 分析应用于个体患者护理的临床决策可能是必要的。没有 RCT 支持何时或多久需要重复活检的建议。

研究建议

- 确定肾脏活检材料的蛋白质组学、质谱和/或 RNA 测序分析是否可以补充或替代仅基于形态学特征的治疗决策。

1.2 肾功能评估

肾小球疾病患者诊断、预后评估和管理决策的关键指标包括肾功能评估，尤其是蛋白尿和肾小球滤过率 (GFR) 的测量（或估计）。

蛋白尿

使用定时尿液采集评估尿总蛋白排泄率 (PER) 是肾小球疾病患者的首选方法，特别是当定性检测中存在明显的蛋白尿时。[7]它平均了昼夜节律、体力活动和姿势引起的蛋白尿变化，并避免了使用随机“点”蛋白-肌酐比 (PCR) 引入的误差。然而，24小时尿液采集也可能由于过度采集或采集不足而出错。在计划的12-24小时尿液采集的等分试样中同时测量尿肌酐和蛋白质是一个很好的折衷

Nephrotic syndrome	Nephrotic-range proteinuria	Non-nephrotic-range proteinuria
Proteinuria (adults)* • ≥3.5 g per 24 h • PCR ≥3000 mg/g (≥300 mg/mmol)	Proteinuria (adults) • ≥3.5 g per 24 h • PCR ≥3000 mg/g (≥300 mg/mmol)	Variable levels of proteinuria • 0.3–3.4 g per 24 h • PCR <300 mg/g (<30 mg/mmol)
Proteinuria (children)* • ≥40 mg/m²/h • ≥300 mg/dl • 3+ on urine dipstick • PCR ≥2000 mg/g (≥200 mg/mmol)	Proteinuria (children) • ≥40 mg/m²/h • ≥300 mg/dl • 3+ on urine dipstick • PCR ≥2000 mg/g (≥200 mg/mmol)	• Serum albumin normal • No clinical symptoms
• Hypoalbuminemia† • Edema‡ • Hyperlipidemia‡	• Serum albumin usually normal • Edema is usually absent or minor • Serum lipids usually normal or only mildly elevated	

图4|定义“肾病综合征”、“肾病范围蛋白尿”和“非肾病范围蛋白尿”*。
†实验室特定值：应通过溴甲酚紫（BCP；比色法）毛细管电泳 (CE) 或免疫散射比浊 (iMN) 法测定血清白蛋白。溴甲酚绿 (BCG) 方法可能给出错误的高结果 (Clase *et al.*[10])。BCG测得的血清白蛋白值比BCP、CE或 iMN 方法测得的值高约5.5 g/L，因此符合 NS 定义所需的低白蛋白血症程度的定义因用于定量血清白蛋白浓度的方法而异。
‡变量。

产生有用且合理一致的结果。也可以使用首次晨尿和 PCR 测定（实际上是过夜采集尿液），但由于夜间卧位的影响，倾向于低估24小时 PER 约20%。当存在明显（肾病范围）蛋白尿时，观察到该效应的程度较低。

白蛋白排泄率和白蛋白–肌酐比值 (ACR) 通常不用于非糖尿病形式的肾小球疾病，即使建议使用这些测量值对慢性肾病 (CKD) 进行分类并通过肾衰竭风险方程估计预后。[8]

可以使用预测公式根据 PER 或 PCR 值预测白蛋白排泄率或ACR，但在 PER 值较低（< 500 mg/日）时，这些预测并不可靠，可能是由于存在肾小管性蛋白尿，其中 PER 可能由非白蛋白低分子量蛋白组成。[9]平均而言，GN中白蛋白约占总尿蛋白的65%，但在某些疾病（如MCD）中可观察到较高的值。性别、饮食、人种和身体状况的变化可改变肌酐的生成，也可能导致定时尿液采集的 PCR/ACR 和 PER/ACR 值之间的差异。

使用24小时尿液采集同时测量尿钠有助于确定高钠摄入是否导致蛋白尿恶化。

肾病范围蛋白尿并不总是与“肾病综合征”相关，”因为可能不存在低白蛋白血症。这种形式的蛋白尿常见于继发性 FSGS 和 IgAN 患者。NS可存在于

一些患者的尿蛋白定量不完全符合肾病范围蛋白尿的传统定义，但其临床症状与典型症状匹配（图4[10]）。

实践要点1.2.1：在需要开始或强化免疫抑制治疗或临床状态发生变化的肾小球疾病患者中，采集24小时尿液，以测定总蛋白排泄。

蛋白尿定量是评估 GN 患者的重要指标，与本指南中讨论的几乎所有原发性和继发性肾小球疾病均相关。与 MCD 不同，GN的蛋白尿通常具有异质性，由白蛋白和其他蛋白组成。大多数 GN 临床试验包括24小时尿液采集，以评估治疗反应。

如果无法获得24小时尿液采集，则使用替代方法定量蛋白尿。最佳选择是在首次就诊或首次晨尿时尝试12–24小时尿液采集的等份试样上确定PCR。不建议进行随机“点”PCR评估来评估 GN 患者，除非在一天中的同一时间、在相似的体力活动条件下以及当患者病情稳定时采集尿液。

实践要点1.2.2：对于儿科，24小时尿液采集并不理想，因为其可能不准确，且采集繁琐。相反，应监测首次晨起蛋白–肌酐比值 (PCR)。

Direct measures of kidney function	Indirect measures of kidney function: estimating equations	Limitations
• Creatinine clearance - 24 h urine creatinine	• eGFR	• No estimate of kidney function has been specifically validated for glomerular diseases and/or nephrotic syndrome • Ethnicity is often a confounding influence • In creatinine-based formulas, hypoalbuminemia may lead to overestimation of true GFR due to increased tubular creatinine secretion[8] • Glucocorticoids may increase serum cystatin C, potentially underestimating eGFR[9] • Low muscle mass overestimates eGFR using creatinine-based formulae[10] • AKI confounds all estimates, which are valid only in steady-state
• Measured GFR* - Inulin clearance (gold standard) - Radioisotopic plasma clearance[1] • ^{125}Iothalamate; ^{99m}Tc-DTPA; ^{51}Cr-EDTA - Non-radioisotopic plasma clearance • Iohexol[2]	**Adults** • Cockcroft–Gault[3] (140-age) (wt [kg]) x 0.85, if female/serum creatinine (mg/dl) x 72 • Modification of diet in renal disease (MDRD) equations[4] (not valid for eGFR >60 ml/min/1.73 m^2) - CKD-EPI creatinine equation (preferred) • Valid with eGFR >60 ml/min/1.73 m^2 - CKD-EPI-cystatin C equations[5] (valid for eGFR >60 ml/min/1.73 m^2) - Full Age Spectrum (FAS) equation[7] • Valid even in eGFR >60 ml/min/1.73 m^2 **Children** • Schwartz equation and its modifications[6] • Full-age spectrum (FAS) formulae[7]	

图5肾小球疾病的肾功能评估。*以ml/min/1.73 m ^{2}表示。GFR估计方程中人种的校正系数存在争议，关于该主题的讨论正在进行中。[20]更多信息请参考 KDIGO CKD 指南。[18]Perrone 等人[13]，[2]Gaspari 等人[12],[3]Cockcroft和Gault.[11],[4]Stevens 等人[16]，[5]Stevens 等人[17],[6]Schwartz 等人[15],[7]Pottel 等人[14],
[8]Branten *et al.*[19],[9]Zhai *et al.*[21],[10]Levey *et al.*[22]AKI，急性肾损伤；CKD-EPI，慢性肾病流行病学协作组；^{51}Cr-EDTA，铬-51标记的乙二胺四乙酸；eGFR，估计的肾小球滤过率 (ml/min)/1.73 m^2；^{99m}Tc-DTPA，锝-二乙烯三胺五乙酸。

操作要点1.2.3：用于 PCR 的随机“点”尿液采集并不理想，因为蛋白和肌酐排泄均随时间发生变化。

实践要点1.2.4：首次晨尿采集可能低估了直立性蛋白尿中的24小时蛋白排泄。

规范点1.2.5：在可行的情况下，合理的建议是采集“预期”的24小时尿液样本，并测量等份采集物中的PCR。

实践要点1.2.6：无需在每次尿液采集时同时和常规定量钠排泄量，除非有理由怀疑未能遵守关于饮食钠限制的建议（图5以及实践要点1.4.2和1.5.9）。

实践要点1.2.7：定量肾小球疾病中的蛋白尿，因为其与疾病特异性预后和治疗决策相关。蛋白尿的定性评估在特定情况下可能有用。

关于用于对疾病进展风险和临床反应定义进行分类的蛋白尿（PER或PCR，如上文所述）水平和变化，参见后续肾小球疾病章节。这些参数并不一致，在肾小球疾病谱中甚至在个体肾小球疾病类型中也存在很大差异。

目前，尚无充分证据建议根据更详细的蛋白尿定性分析（如尿电泳 [儿童 MCD 之外] 或IgG、b-2微球蛋白、视黄醇结合蛋白或 a-1 微球蛋白的尿排泄分数测量）做出治疗决策，但在特定疾病（如膜性肾病 [MN] 和FSGS）中，后一种低分子量蛋白可能具有临床和预后效用。

估计 GFR

大多数关于 GN 治疗的现有证据是基于使用血清肌酐 (SCr) 或肌酐清除率 (CrCl) 估计排泄性肾功能，需要采集24小时尿液。很少有研究报告使用菊粉尿液清除率、放射性同位素碘酞酸盐或碘海醇、非放射性同位素碘酞酸盐、^{99m}Tc-DTPA或 ^{51}Cr-EDTA 技术的血浆消失进行 GFR 金标准测量。其他技术包括使用慢性肾病流行病学协作组 (CKD-EPI) 或其他公式根据年龄、体重和性别调整SCr，以及 SCr 的倒数或对数转换。血清胱抑素 C 作为 SCr 的替代方法，尚未在 GN 受试者中得到很好的验证。所有这些方法都有局限性，但在对每个受试者进行连续测量时具有参考价值。[11–17]GFR评估的详细信息可参见 *KDIGO CKD 评估和管理临床实践指南*（图5[11–22]）。[18]

使用基于 SCr 的 CKD-EPI 公式估计 GFR 获得了越来越多的认可，但尚未在 GN 患者中进行专门验证。它可能比早期方程更准确，尤其是在数值 > 60 mL/min/1.73 m ^{2}。种族、肌肉体积、肌肉减少症、
用于肌酐测量的方法可能会影响基于 SCr 估计的肾小球滤过率 (eGFR) 的准确性。当使用血清胱抑素 C 生物标志物估计 GFR 时，情况并非如此。在 NS 和低白蛋白血症中，肾小管肌酐处理发生改变，基于 CrCl-和 eGFR-肌酐的方程可能高估真实的 GFR 50% 或更多。[16,19]在急性肾损伤 (AKI) 发作期间，GFR估计值也不可靠，并且可能受到慢性糖皮质激素相关肌病患者肌酐生成改变的影响。

在儿童中，eGFR有其他经验证的公式，尤其是 Schwartz 或全年龄范围 (FAS) 公式。

实践要点1.2.8：在儿童中，定量蛋白尿，但疾病病因之间的治疗目标不应不同。任何肾小球疾病儿童的目标应是 24 小时尿液中 PCR < 200 mg/g(< 20 mg/mmol) 或 < 8 mg/m ^{2}/小时。接受较高的基线因此，只有当肾脏活检有肾脏瘢痕的证据时，才会出现。

实践要点1.2.9：慢性肾病流行病学协作组 (CKD-EPI) 估计的肾小球滤过率 (eGFR) 肌酐方程是成人肾小球疾病患者的首选方程，改良的 Schwartz 方程是儿童患者的首选方程。成人和儿童均可使用全年龄范围 (FAS) 公式（图5）。所有基于肌酐的 eGFR 方程倾向于高估 NS 和低白蛋白血症患者的真实GFR。eGFR、胱抑素 C 或eGFR、胱抑素 C 和肌酐的组合可用于特殊情况下的紊乱怀疑肌酐生成。

研究建议
- 评价“随机”与“定时”采集的尿液，以评价特定肾脏疾病中的蛋白尿
- 尿液蛋白质组学在特殊类型 GN 诊断和预后中的评价
- 用于检测和定量 GN 肾脏纤维化的尿液生物标志物评价
- 在显著蛋白尿患者中评价经验证的 GFR 估计方程是否可改善临床试验结局和患者管理

1.3 血尿评价

血尿是肾小球疾病的主要表现之一。血尿的初始检测通常是通过对随机尿液标本进行“试纸”分析来进行。试纸条法检测尿中血红蛋白（游离或红细胞相关）非常敏感，假阴性极少（服用大量维生素 C 的患者除外），但假

肌红蛋白尿或血红蛋白尿阳性。肉眼或肉眼血尿通常使排尿尿液呈红色或褐色“烟雾状”外观，具体取决于尿液 pH 值。在 GN 所致的可见血尿中，不发生血凝块。通常情况下，GN的血尿不伴有尿路症状。

应在低和高倍放大下，通过相差显微镜或明场光学显微镜对新鲜离心尿沉渣进行显微镜检查，确认血液试纸检查异常。尿沉渣 (Sternheimer-Malbin) 染色有助于细胞和有形成分的回收。流式辅助细胞分选技术可以极大地帮助血尿的自动化分析。在 GN 患者中，红细胞通常 (50%–80%) 畸形（异形）和小（小细胞）。存在含红细胞的管型或存在棘红细胞（> 占所有红细胞的 5%）通常提示炎症性肾小球疾病。应注意的是，在正常红细胞中观察到的少数红细胞中收集的尿液，均为肾小球（异形）型。

血尿持续存在和程度的预后意义可能对肾小球疾病的长期结局产生非常显著的影响。鉴于此，这些结果通常代表基础肾小球炎症过程的持续“低级”活性。血尿作为进展的“生物标志物”的这一方面，例如，在 IgAN 中，[23]现在受到的关注早该出现。我们认为，定期监测血尿的存在和程度应成为所有形式肾小球疾病护理过程的一部分。

实践要点1.3.1：在所有形式的肾小球疾病中，均应常规评价尿沉渣中的红细胞形态以及是否存在红细胞管型和/或棘红细胞。

实践要点1.3.2：监测血尿（程度和持续性）可能对多种形式的肾小球疾病具有预后价值。这尤其适用于免疫球蛋白 A 肾病 (IgAN) 和血管炎（IgAV；第2章）。

研究建议
- 持续性血尿对特殊形式肾小球疾病预后影响及其治疗意义的进一步前瞻性研究

1.4 肾小球疾病并发症的管理

肾小球疾病的许多并发症是临床表现的结果，而不是特定的组织病理学模式。应始终认为积极管理此类并发症对疾病的自然史有积极影响，并显著改善发病率甚至死亡率。包括控制水肿、减少蛋白尿、治疗体循环动脉血压 (BP) 升高、减缓疾病进展、

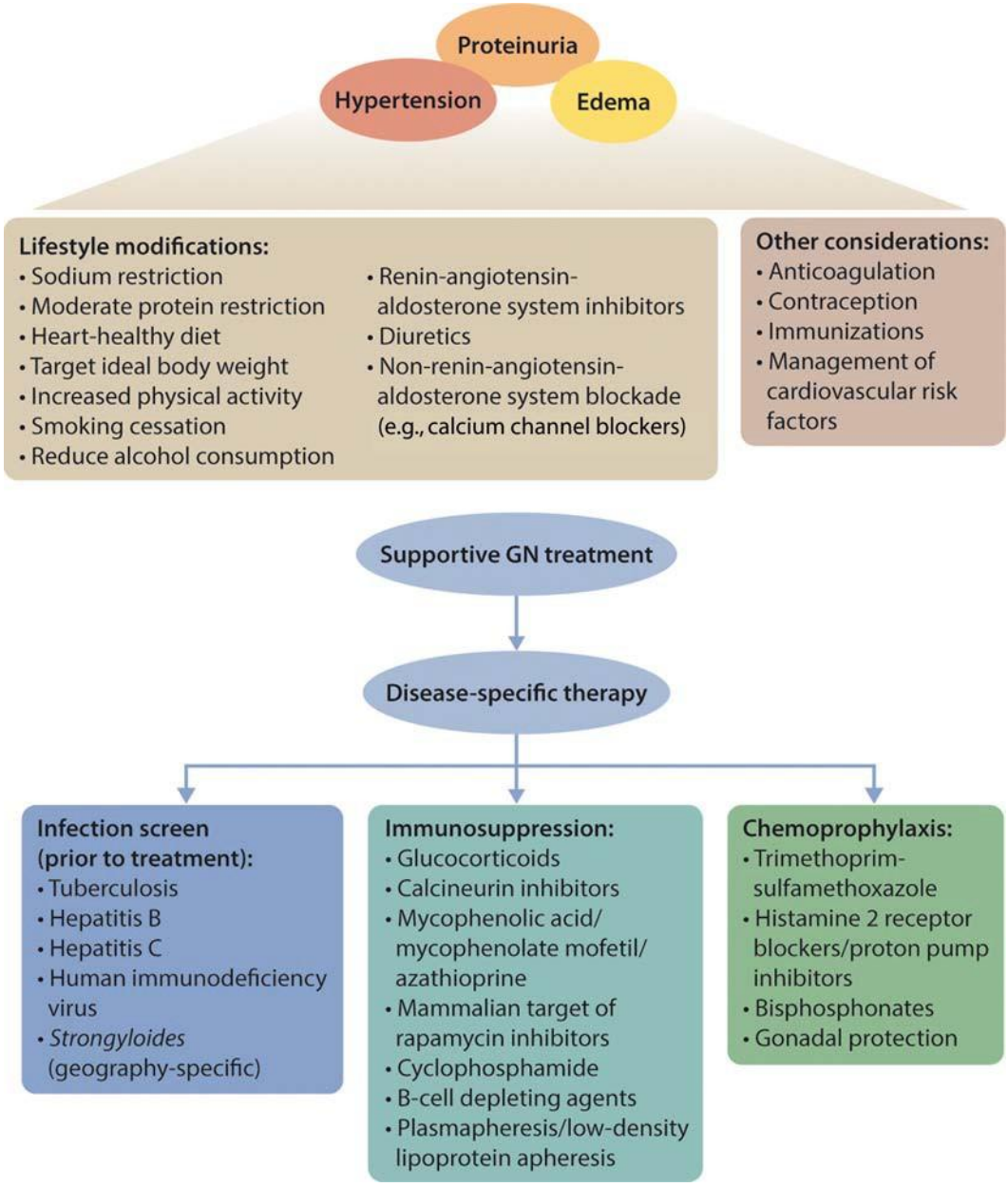


图6肾小球疾病支持性治疗总结。注：泼尼松和泼尼松龙等效，使用剂量相同，均已在 RCT 中使用，具体取决于原产国。本指导原则中的所有后续"泼尼松"均指泼尼松或泼尼松龙。除非另有说明，否则后面使用的所有"糖皮质激素"均指泼尼松或泼尼松龙。GN，肾小球肾炎；RCT，随机对照试验。

解决 *NS* 的其他代谢和易栓后果（图6）。这些相对无毒的治疗可能阻止或至少调节对免疫抑制药物的需求，这些药物具有潜在的不良反应。如此支持

在

类固醇敏感性 *MCD* 快速缓解、*GN*且仅有镜下血尿、*GFR*保留、无蛋白尿或高血压（常见于早期*IgAN*）的患者中，可能无需治疗。

Practice Point 1.4.1. Use loop diuretics as first-line therapy for treatment of edema in the nephrotic syndrome	• Twice daily dosing preferred over once daily dosing; daily dosing may be acceptable for reduced GFR • Increase dose of loop diuretic to cause clinically significant diuresis or until maximally effective dose has been reached • Switch to longer acting loop diuretic such as bumetanide or torsemide/torasemide if concerned about treatment failure with furosemide, or if concerned about oral drug bioavailability
Practice Point 1.4.2. Restrict dietary sodium intake	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d)
Practice Point 1.4.3. Use loop diuretics with other mechanistically different diuretics as synergistic treatment of resistant edema in the nephrotic syndrome	• All thiazide-like diuretics in high doses are equally effective. None is preferred. • Thiazide diuretics, administered with an oral or i.v. loop diuretic, will impair distal sodium reabsorption and improve diuretic response • Amiloride may provide improvement in edema/hypertension, and counter hypokalemia from loop or thiazide diuretics • Acetazolamide may be helpful for the metabolic alkalosis of diuresis • Spironolactone may provide improvement in edema/hypertension, and counter hypokalemia from loop or thiazide diuretics
Practice Point 1.4.4. Monitor for adverse effects of diuretics	• Hyponatremia with thiazide diuretics • Hypokalemia with thiazide and loop diuretics • Impaired GFR • Volume depletion, especially in pediatric/elderly patients • Hyperkalemia with spironolactone and eplerenone especially if combined with RAS blockade
Practice Point 1.4.5. Strategies for diuretic-resistant patient	• Amiloride • Acetazolamide • i.v. loop diuretics (bolus or infusion) alone • i.v. loop diuretics in combination with i.v. albumin • Ultrafiltration • Hemodialysis • Amiloride may reduce potassium loss and improve diuresis. Acetazolamide may help to treat metabolic alkalosis but is a weak diuretic

图7|NS中的水肿管理。GFR，肾小球滤过率；i.v.，静脉内；NS，肾病综合征；RAS，肾素-血管紧张素系统。

肾病性水肿

NS 常见显著水肿和体重增加。这种临床表现可使患者的症状和 BP 控制复杂化，可能是由肾脏的钠排泄内在缺陷介导的。[24]主要治疗方法是利尿剂，并伴有中度膳食钠限制（1.5–2 g/日或60–90 mmol/d钠；图7）。

肾病患者通常对利尿剂抵抗，即使 GFR 正常。袢利尿剂被认为是治疗肾病性水肿的一线药物，通常首选每日两次给药。通常需要更高剂量的袢利尿剂，因为药物递送至髓袢的量减少（分布容积更大伴低白蛋白血症），或滤过药物与滤过白蛋白结合。然而，重复给予呋塞米可诱导短期（制动现象、急性利尿剂抵抗）和长期（代偿性肾小管钠吸收、慢性利尿剂抵抗）适应，其机制尚不清楚。一些证据表明，与呋塞米相比，长效托拉塞米和布美他尼具有更有利的药代动力学特征和更一致的口服生物利用度（至少在心力衰竭研究中）。[25]

袢利尿剂与噻嗪类利尿剂（氢氯噻嗪、美托拉宗、氯噻酮）联合可

通

过阻断肾单位内多个部位的钠吸收，是克服利尿剂抵抗的有效口服方案。在高剂量下，噻嗪类利尿剂的疗效相似。建议在袢利尿剂输注前2 –5小时给予噻嗪类利尿剂达到药物峰浓度，并最大限度地阻断远端钠重吸收。

肾病尿液中的纤溶酶可激活上皮钠通道，可能导致利尿剂抵抗。阿米洛利可阻断上皮钠通道，可能是 NS 水肿/高血压和低钾血症管理的一种潜在有用的辅助治疗。[26]阿米洛利的使用尚未在 RCT 中得到验证。

乙酰唑胺是一种较弱的利尿剂，但作为碳酸酐酶抑制剂，如果存在严重的代谢性碱中毒可能有帮助。

如果患者最大剂量口服袢利尿剂治疗失败，则转换为静脉袢利尿剂是合理的，个人实践偏好静脉推注而不是连续输注。避免快速静脉“推注”给予袢利尿剂，因为可能发生毒性（听力丧失和/或耳鸣）。袢利尿剂连续输注给药可减轻毒性作用并提供持续的利尿剂排泄。

由于肠壁水肿，在重度 NS 患者中利尿剂的胃肠道吸收可能不确定，可能需要静脉内袢利尿剂（推注或输注）来引起有效的利尿。对静脉利尿剂的反应迟钝可能是由于血管内容量减少伴神经体液和肾素-血管紧张素系统 (RAS) 激活所致。对于静脉利尿剂抵抗的低白蛋白血症患者，可在静脉内利尿剂治疗的基础上加用静脉内白蛋白，以改善血管内容量、利尿和尿钠排泄。几项静脉（低盐）白蛋白与静脉呋塞米的研究显示，联合治疗具有一过性临床获益，但由于研究设计的差异，数据的比较存在差异。尚无大量研究表明白蛋白可有效减轻成人 NS 患者的水肿。白蛋白在儿童中的临床作用可能更有前景。对于最大剂量的静脉利尿剂单药或利尿剂联合治疗无效且血清白蛋白 < 2.0 g/dL(20 g/L) 的利尿剂耐药患者，考虑静脉输注白蛋白可能是合理的。白蛋白可以与袢利尿剂预混合给药，或者在静脉袢利尿剂给药前 30-60 min 给予 25-50 g 白蛋白溶液（血管内容量扩张的最大效应）。[27]然而，在肾病患者中，给予的大部分白蛋白将迅速经尿液排泄，对血浆白蛋白水平的任何影响充其量是短暂的。对于抵抗性水肿，有时需要机械超滤和/或血液透析，尤其是 GN 伴有 AKI 时。

保钾利尿剂（如螺内酯或阿米洛利）有助于将血钾水平维持在正常范围内，并且在利尿钠管理高血压或水肿方面可能与噻嗪类或环效利尿剂有叠加作用。[28]

NS 水肿的治疗通常不需要限水，因为患者通常血管内血容量不足，使用强化利尿剂更容易发生脱水。然而，发生低钠血症的患者可能需要限制饮水。

研究建议

- RCT：
  - 在重度 NS 的利尿剂耐药患者中评价静脉白蛋白 + 利尿剂与利尿剂单药治疗水肿的疗效[29]

  检测阿米洛利与其他利尿剂类别对肾病性水肿的疗效
  - 比较 NS 中袢利尿剂（呋塞米vs.布美他尼vs.托拉塞米）的疗效和最佳给药剂量
  - 在 NS 中比较口服与静脉推注与静脉持续输注利尿剂
  - 评价临床上何时最适合通过超滤或血液透析治疗利尿剂抵抗患者

1.5 肾小球疾病中高血压和蛋白尿减少的管理

与所有慢性肾病 (CKD) 一样，BP控制的目的是预防高血压（卒中、心力衰竭、冠状动脉疾病）的心血管 (CV) 风险并延缓 GFR 的进行性降低。生活方式改变（限盐、体重正常化、定期运动、减少酒精摄入和戒烟）应该是 BP 控制治疗的组成部分。并非所有肾小球疾病患者都需要降压治疗（即类固醇敏感性MCD；图8和图9）。

蛋白尿减少很重要，因为它反映了对原发性疾病的控制、肾小球高血压的降低以及足细胞损伤的减少（可能是肾小球瘢痕形成的主要因素）。大多数研究表明，如果蛋白尿可降至0.5 g/日以下，则可在很大程度上预防本指南中讨论的进展性组织学模式中的肾功能丧失，如果降至1 –1.5 g/日以下，则可减缓进展。例外情况是MCD 和SSNS，它们在病程中完全缓解。蛋白尿（或蛋白尿中存在的血浆因子）也可能对肾小管间质产生毒性。在 NS 中，蛋白尿减少至非肾病范围通常导致血清蛋白（尤其是白蛋白）升高至正常水平。血清白蛋白升高可降低血栓栓塞和感染风险，通常可缓解患者的许多症状和 NS 的代谢并发症，从而改善生活质量。

首选的抗蛋白尿药物是血管紧张素-转化酶抑制剂 (ACEi) 或血管紧张素 II 受体阻滞剂 (ARB)，可能以剂量依赖性方式将蛋白尿减少高达 40%-50%，特别是当患者遵守饮食中的盐限制时。几乎没有证据表明 ACEi 在这方面与 ARB 不同。尽管合并使用 ACEi 或 ARB 可能导致叠加性抗蛋白尿活性，但在涉及糖尿病受试者的 RCT 中，联合用药与 AKI 和高钾血症事件增加相关。[30,31]

尽管这尚未在大型研究中直接证实涉及非糖尿病患者的RCT，数据足以建议谨慎。即使作为单药治疗，ACEi和/或 ARB 也可降低GFR，通常观察到 SCr 升高10%–20%。除非肌酐继续升高，否则这种中度升高反映了其对肾脏血流动力学的影响，而不是内在肾脏疾病恶化，不应及时停药。但是，如果患者的 GFR 正在迅速变化，ACEi或 ARB 可能进一步导致肾功能不全，因此不应使用。如果抗蛋白尿药物给药受到具有临床意义的高钾血症的限制，则可通过使用钾消耗利尿剂、纠正代谢性酸中毒或口服钾结合剂来抵消。钠摄入量的自由化也可能在一定程度上有帮助。

或者，如果患者无法耐受 ACEi 或 ARB，一种直接肾素抑制剂 (DRI) 或盐皮质激素

Practice Point 1.5.1.	Use an ACEi or ARB to maximally tolerated or allowed dose as first-line therapy in treating patients with both hypertension and proteinuria	• Do not stop ACEi or ARB with modest and stable increase in serum creatinine (up to 30%) • Stop ACEi or ARB if kidney function continues to worsen, and/or refractory hyperkalemia • Combinations of ACEi and ARB may be used in young adults without diabetes or cardiovascular disease, but benefits and safety are uncertain Caveat: do not start ACEi/ARB in patients who present with abrupt onset of NS. These drugs can cause AKI especially in patients with MCD
Practice Point 1.5.2.	Target systolic blood pressure in most adult patients is <120 mm Hg using standardized office BP measurement. Target 24 h mean arterial pressure in children is ≤50th percentile for age, sex, and height by ambulatory blood pressure monitoring	• Refer to KDIGO BP Guideline (https://kdigo.org/guidelines/blood-pressure-in-ckd/) • Formally speaking, SBP <120 mm Hg has not been validated in GN. In practicality, we are able to achieve an SBP of 120–130 mm Hg in most patients with glomerular disease
Practice Point 1.5.3.	Uptitrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line therapy in treating patients with GN and proteinuria alone	• Indicated for persistent proteinuria despite treatment of primary GN with immunosuppression (where indicated) • Avoid use of an ACEi or ARB if kidney function is rapidly changing
Practice Point 1.5.4.	Proteinuria goal is variable depending on primary disease process; typically, <1 g/d	• It may be reasonable to delay initiation of ACEi or ARB for patients without hypertension with podocytopathy (MCD, SSNS, or primary FSGS) expected to be rapidly responsive to immunosuppression • Proteinuria goal is disease-specific in adults with GN
Practice Point 1.5.5.	Monitor labs frequently if on ACEi or ARB	• Titration of ACEi or ARB may cause acute kidney injury or hyperkalemia
Practice Point 1.5.6.	Counsel patients to hold ACEi or ARB and diuretics when at risk for volume depletion	• Increased risk for acute kidney injury and hyperkalemia • Counsel patients according to level of education in a culturally sensitive manner • Consider transiently stopping RASi during sick days
Practice Point 1.5.7.	Use potassium-wasting diuretics and/or potassium-binding agents to reduce serum potassium to normal, in order to use RAS blocking medications for BP control and proteinuria reduction Treat metabolic acidosis (serum bicarbonate <22 mmol/l)	• Loop diuretics • Thiazide diuretics • Patiromer • Sodium zirconium cyclosilicate (each 10 g of sodium zirconium cyclosilicate contains 800 mg of sodium) • Supplement with oral sodium bicarbonate
Practice Point 1.5.8.	Employ lifestyle modifications in all GN patients as synergistic means for improving control of hypertension and proteinuria	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d) • Normalize weight • Exercise regularly • Stop smoking
Practice Point 1.5.9.	Intensify dietary sodium restriction in those patients who fail to achieve proteinuria reductions, and who are on maximally tolerated medical therapy	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d). Consider using mineralocorticoid receptor antagonists in refractory cases (monitor for hyperkalemia)

图8肾小球疾病中高血压和蛋白尿的管理。ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；BP，血压；FSGS，局灶节段性肾小球硬化；GN，肾小球肾炎；KDIGO，肾病：改善全球预后；MCD，微小病变；NS，肾病综合征；RAS，肾素-血管紧张素系统；RASi，肾素-血管紧张素系统抑制剂；SBP，收缩压；SSNS，类固醇敏感性肾病综合征。

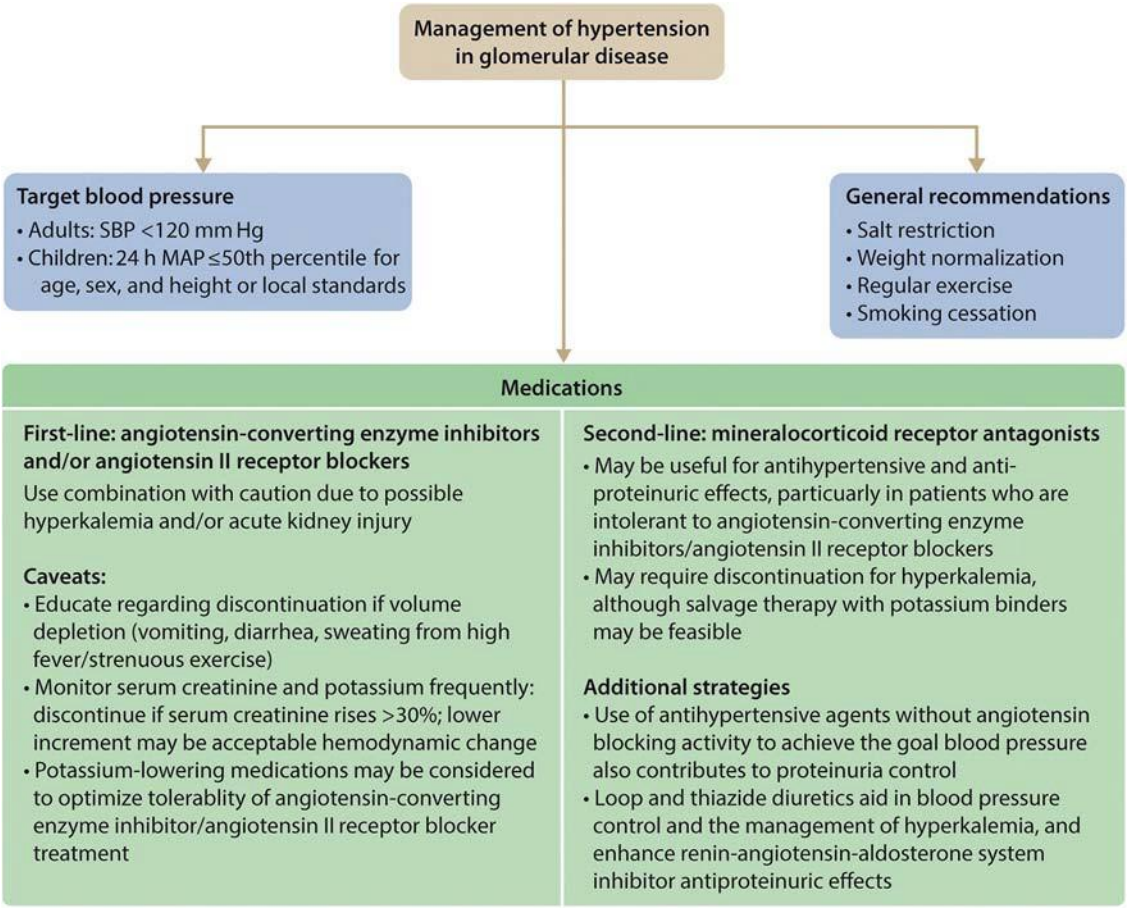


图9肾小球疾病中高血压的管理。MAP，平均动脉压；SBP，收缩压。

可以使用受体拮抗剂（MRA）。[32]与 ACEi/ARB 一样，高钾血症和 GFR 降低是这些药物的副作用，因此建议进行常规实验室监测。然而，由于高钾血症的风险增加，不建议 ACEi 或 ARB 与 DRI 联合使用，[33]至少如涉及糖尿病受试者的试验中所述。

一些患者甚至无法耐受低剂量ACEi、ARB、MRA或DRI。在这种情况下，建议使用替代抗高血压药物控制 BP 和改善尿蛋白排泄。非二氢吡啶类钙通道阻滞剂（CCB），如地尔硫卓和维拉帕米，可适度减少蛋白尿。β 受体阻滞剂、利尿剂和 α-1 受体阻滞剂也可减少蛋白尿，但程度较轻。二氢吡啶类CCB、甲基多巴和肼法辛对蛋白尿的影响很小，甚至可能增加蛋白尿。应建议尿蛋白未充分减少的患者（尽管控制了BP）进一步限制饮食中的钠，作为减少蛋白尿的非药物方法。

荟萃分析表明，白蛋白排泄率或总 PER 较基线持续下降30%可能是 SCr 最终加倍或肾衰竭的可接受替代结局，作为对 CKD 进展有利影响的硬结局标准。[34–36]

肾脏保护治疗的证据是 *KDIGO 慢性肾病评估和管理临床实践指南*[18]的主题。

研究建议

- RCT，确定在 RAS 抑制剂（RASi）单药治疗基础上加用 MRA 治疗非糖尿病蛋白尿性肾病的安全性和疗效
- RCT，旨在确定使用新型降钾药物最大限度地提高 RASi 治疗非糖尿病蛋白尿性肾病的安全性和有效性

1.6 肾小球疾病中高脂血症的管理

肾小球疾病患者的高血脂反映了饮食、患者的潜在遗传倾向、NS的存在和肾小球疾病治疗的并发症的影响，包括糖皮质激素、哺乳动物雷帕霉素靶蛋白（mTOR）抑制剂

（西罗莫司和依维莫司）和钙调磷酸酶抑制剂（CNI；环孢素 A 比他克莫司更常见）。[37,38]NS患者的高脂血症治疗可遵循适用于一般人群并使用相同脂质的指南。

降脂药，但在肾小球疾病或其治疗引起的高脂血症患者中缺乏 CV 事件减少或生活质量改善的证据（图10）。[39]风险因素包括家族史、肥胖、

Practice Point 1.6.1.	Treatment of hyperlipidemia may be considered in patients with the nephrotic syndrome, particularly for patients with other cardiovascular risk factors, including hypertension and diabetes	High quality data are lacking to guide treatment in these patients
Practice Point 1.6.2.	Use lifestyle modifications in all patients with persistent hyperlipidemia and glomerular disease: • Heart-healthy diet • Increased physical activity • Weight reduction • Smoking cessation	• Not well studied as primary means of reducing lipids in nephrotic syndrome • Can be used as primary therapy in low-risk individuals with mild to moderate hyperlipidemia • Additive to pharmacologic treatment of hyperlipidemia • Considered first-line treatment of hyperlipidemia in children • Consider a plant-based diet • Avoid red meat
Practice Point 1.6.3.	Consider starting a statin drug as first-line therapy for persistent hyperlipidemia in patients with glomerular disease: • Assess ASCVD risk based on LDL-C, Apo B, triglyceride and Lp (a) levels, age group, and ASCVD 'risk enhancers' • Align statin dosage intensity to ASCVD risk • Statins can be initiated in children aged > 8 years with concerning family history, extremely elevated LDL-C or Lp(a), in the context of informed shared decision-making and counselling with patient and family	• Reduced eGFR (<60 ml/min/1.73 m^2 not on dialysis) and albuminuria (ACR >30 mg/g) are independently associated with an elevated risk of ASCVD • ASCVD risk enhancers include chronic inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, history of preeclampsia, early menopause, South Asian ancestry, chronic kidney disease and human immunodeficiency virus/AIDS (accuracy of ASCVD risk estimators have not been well validated for adults with chronic inflammatory disorders or human immunodeficiency virus) • Adherence to changes in lifestyle and effects of LDL-C lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4–12 weeks after statin initiation/dose adjustment or inflammatory disease-modifying therapy/antiretroviral therapy, and every 3–12 months thereafter based on need to assess adherence or safety
Practice Point 1.6.4.	Consider initiation of non-statin therapy in those individuals who cannot tolerate a statin, or who are at high ASCVD risk and fail to achieve LDL-C or triglyceride goals despite maximally tolerated statin dose: • Bile acid sequestrants • Fibrates • Nicotinic acid • Ezetimibe • PCSK9 inhibitor • Lipid apheresis	• Bile acid sequestrants have a high rate of gastrointestinal side effects limiting their use • Bile acid sequestrants and fibrates have been shown in small studies to reduce serum cholesterol in nephrotic syndrome • Fibrates will increase serum creatinine level due to direct action on the kidney • Ezetimibe has limited vascular and clinical benefits, but is used in statin-intolerant patients as salvage therapy • Nicotinic acid and ezetimibe have not been studied in patients with nephrotic syndrome • PCSK9 inhibitors may be beneficial in nephrotic syndrome; trials ongoing

图10肾小球疾病中高脂血症的管理。ACR，白蛋白-肌酐比值；AIDS，获得性免疫缺陷综合征；Apo，载脂蛋白；ASCVD，动脉粥样硬化性心血管疾病；eGFR，估计的肾小球滤过率；LDL-C，低密度脂蛋白胆固醇；Lp，脂蛋白；PCSK9，前蛋白转化酶枯草溶菌素9。

糖尿病、伴随高血压、GFR受损、持续性白蛋白尿、既往心血管疾病和当前吸烟。高脂血症的管理与 GN 不能完全改善的患者最相关，当心血管疾病的其他危险因素共存时，最常见的是高血压和蛋白尿。高脂血症的持续存在可导致儿童和成人动脉粥样硬化的加速。

仅限制脂肪和胆固醇的饮食对肾小球疾病（尤其是 NS）中的高脂血症的影响不一致且极小，尚未在肾小球疾病中对生活方式改变（饮食、运动和体重减轻）进行完整研究。

他汀类药物耐受性良好，可有效纠正（至少部分纠正）NS中的异常血脂谱。他汀类药物治疗是否能预防 GFR 的下降尚未确定。一些数据表明，某些他汀类药物，特别是阿托伐他汀，可能会减少白蛋白尿。当他汀类药物与其他药物联合使用时需要谨慎；当他汀类药物与 CNI 联合使用时，肌痛/肌炎的风险增加。关于依折麦布或贝特类药物降低 NS 患者低密度脂蛋白 (LDL) 的疗效的数据非常有限。最近的一项荟萃分析得出结论，可用的有限信息不支持使用这些药物作为单药治疗。[39]

脂质单采，获批用于治疗家族性高脂血症，也被用于治疗激素耐药 NS(SRNS) 患者的高脂血症。在接受 NS 治疗的患者中，胆固醇和甘油三酯水平降低，在一些患者中，观察到 NS 缓解。在 NS 中使用 PCSK9 抑制剂的理由相当令人信服[38,40]，但迄今为止，仅有少数病例报告支持使用这些药物。在广泛推荐使用 PCSK9 抑制剂之前，需要更多关于 PCSK9 抑制剂在肾病性高脂血症中应用的数据。

研究建议

- 评估伴随肾病和非肾病肾小球疾病的高脂血症药物治疗的安全性和疗效的 RCT
- 生活方式改变对减少 NS 患者高脂血症影响的研究
- 他汀类药物对 NS 患者 CV 事件减少的影响；许多 RCT 显示接受他汀类药物治疗的一般人群中 CV 事件减少
- 高血脂治疗在老年 NS 患者（> 76岁）中的效用
- 药理学降低 NS 儿童高脂血症和治疗风险的 RCT
- 使用抗 PCSK9 单克隆抗体在 NS 中药理学减少高脂血症的 RCT
- 更好地了解他汀类药物治疗持续性 NS 患者的低密度脂蛋白胆固醇 (LDL-C) 目标的研究

1.7 高凝状态和血栓形成

NS 中儿童和成人的动脉或静脉血栓形成事件风险均高于一般人群，尤其是在诊断的前6个月内。血栓形成在成人中比儿童中更常见，更常见于静脉而不是动脉，并且根据基础组织病理学的不同，发生频率也不同。深静脉血栓形成 (DVT) 和肾静脉血栓形成 (RVT) 最为常见。肺栓塞 (PE) 也比较常见，可无症状发生。血栓事件最常见于MN，但可发生于其他病变，如 MCD 或补体相关肾小球病。组织学诊断、蛋白尿程度和血清白蛋白 < 2.5 g/dL（25 g/L；图4）仍然是血栓形成风险的最佳预测因素。低血清白蛋白水平（不考虑蛋白尿程度）可增加血栓形成事件的风险，这一结果是不可靠的。动脉血栓形成在成人和儿童中均不常见，但几乎在所有动脉血管床中均有报道，包括主动脉、肠系膜、腋窝、肺、髂、肾、股、腘、眼和脑循环。

其他风险因素包括既往血栓形成、血栓形成的地理倾向、抗磷脂抗体、不动、肥胖、恶性肿瘤、妊娠或手术。帮助计算 NS 患者出血风险与抗凝获益的在线工具见 https://www.med.unc.edu/gntools/bleedrisk.html.肝素或其衍生物和/或香豆素类药物（维生素 K 拮抗剂或华法林）是目前预防和/或治疗 NS 背景下发生的静脉或动脉血栓栓塞事件的首选药物。尚无比较低分子量肝素与华法林治疗 NS 的疗效和/或安全性的 RCT。与华法林存在许多药物相互作用，尤其是与免疫抑制剂（如CNI）的相互作用，因此当患者使用多种药物时，医生应谨慎。

尚未对直接口服抗凝剂 (DOAC) 进行系统-在肾病患者中进行血栓预防或治疗的初步研究。2018年8月，文献中仅包括4份病例报告和3份会议提案。41,42正在无dia-β的肾病患者中进行阿哌沙班的开放性药代动力学研究，主要结局为给药信息，而非临床结局（NCT02599532）。DOAC的药物相互作用可能少于华法林，但其在NS中治疗和预防静脉血栓栓塞（VTE）、动脉血栓栓塞（ATE）和PE的安全性和有效性需要额外研究。与华法林相比，在房颤中使用DOAC与出血和全因死亡率较低相关（CKD G1-G5D）。41,43

尚未确定 DOAC 在儿童患者中的疗效和安全性。儿童 VTE 并不常见；然而，其

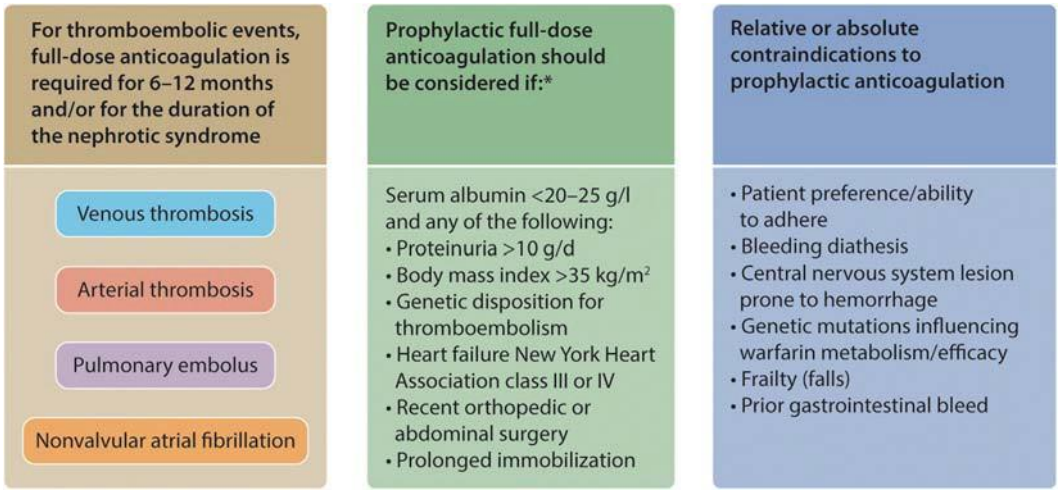


图11|NS中的抗凝治疗。*膜性 GN 发生血栓栓塞事件的风险特别高。NS，肾病综合征。

在过去20年中，发病率一直在增加。肝素和华法林传统上用于该人群，主要基于成人研究结果的外推。

操作要点1.7.1：完全抗凝适用于在肾病综合征背景下发生血栓栓塞事件的患者。当血栓栓塞风险超过抗凝药诱导的严重出血事件的估计患者特定风险时，肾病综合征患者应使用预防性抗凝治疗（图11）。

实践要点1.7.2：肾病综合征患者的抗凝剂给药考虑（图12和图13[44]）。

研究建议

- GN 肾病患者预防性抗凝治疗的RCT：这些 RCT 应检查肝素（低分子量或高分子量）、华法林、DOAC 与无抗凝治疗相比预防此类患者 VTE 或 ATE 的安全性和疗效。
- 经肾小球疾病类型、血清白蛋白、PCR、ACR、eGFR、年龄、合并症（例如，肥胖、遗传血栓形成倾向、制动、既往DVT/PE）校正的绝对血栓形成风险的稳健估计
- 比较 DOAC 与华法林预防和治疗 NS 的疗效和安全性的 RCT
- 确定 DOAC 的高蛋白结合率是否会导致尿丢失和药物疗效降低的研究
- 确定 NS 患者处方 DOAC 当前实践的观察性数据
- 比较未经治疗与接受抗凝治疗的肾病患者的动脉血栓形成率的观察性研究
- 进一步研究确定用于估计 VTE 风险的生化特征在成人和儿童之间是否存在差异
- 确定静脉或动脉血栓形成或 PE 患者最佳抗凝治疗持续时间的临床试验
- 一项在 NS 患者中确定下腔静脉滤器用于 PE 的有效性和安全性的临床试验

Prophylactic anticoagulation during transient high-risk events

- Low-dose anticoagulation (e.g., unfractionated heparin 5000 U subcutaneous twice per day)
- Low–molecular-weight heparin: dose reduction may be advised with creatinine clearance <30 ml/min (unadjusted for body surface area); avoid in kidney failure

Full warfarin anticoagulation for thromboembolic events

- Intravenous heparin followed by bridging to warfarin is preferred
- Higher than usual heparin dosing may be required in nephrotic syndrome due to antithrombin III urinary loss
- Long-term experience with warfarin makes it the anticoagulant of choice until pharmacokinetic studies are performed with newer agents
- International normalized ratio should be monitored frequently, since warfarin–protein binding may fluctuate with changing serum albumin
- Target international normalized ratio is 2–3
- These recommendations are not supported by randomized controlled trials
- Be watchful of interactions of warfarin with other medications

Factor Xa inhibitors (Xai): not systematically studied in patients with nephrotic syndrome

- Dosing in the general population is adjusted according to serum creatinine, creatinine clearance (estimated by Cockcroft–Gault equation), age, and weight. Urinary clearance of the Xa inhibitors varies:
  - Apixaban, 27%
  - Edoxaban, 50%
  - Rivaroxaban, 66%
- The effects of hypoalbuminemia on drug dosing have not been studied, and these drugs are heavily albumin-bound, which is likely to substantially affect their half-lives
- Protein binding:
  - Apixaban, 92%–94%
  - Edoxaban, 55%
  - Rivaroxaban, 92%–95%
- Despite a few favorable case reports, the pharmacokinetic properties of these drugs require additional study for both safety and efficacy before they can be generally recommended in nephrotic patients

Direct thrombin inhibitors (DTI): not systematically studied in patients with nephrotic syndrome

- Dosing in the general population is adjusted according to creatinine clearance for dabigatran. No adjustment is required for argatroban. The urinary clearance of the DTI varies:
  - Argatroban, 22% (6% metabolites; 16% unchanged drug)
  - Dabigatran etexilate, 7%
- The effects of hypoalbuminemia on drug dosing have not been studied, and these drugs are modestly albumin-bound, which is likely to affect their half-lives
- Protein binding:
  - Argatroban, 54%
  - Dabigatran etexilate, 35%
- Despite improved safety in the general population, the pharmacokinetic properties of these drugs require additional study for both safety and efficacy before they can be recommended in nephrotic patients

图 12 NS 患者的抗凝剂剂量考虑。NS，肾病综合征。

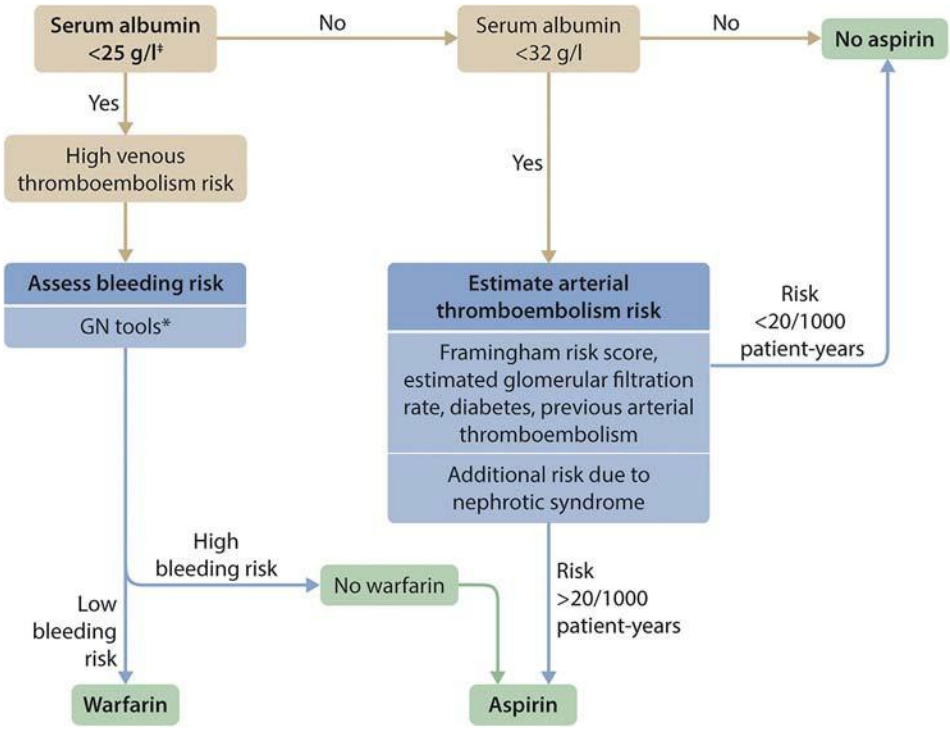


图13成人 GN/肾病综合征的预防性抗凝治疗。转载自*Kidney International*，第89卷，第5期，Hofstra JM，Wetzels JFM。阿司匹林是否应用于膜性肾病患者血栓事件的一级预防？第981-983页，版权a2016，经国际肾脏病学会许可。[44]注：该算法适用于膜性肾病患者。对于其他基础疾病所致的肾病综合征 (NS) 患者，其价值尚不清楚。在肾小球肾炎 (GN) 儿童患者中，考虑正式血液学会诊，以评价静脉血栓栓塞 (VTE) 和出血风险。Framingham风险评分不适用于儿科患者。‡使用溴甲酚绿 (BCG) 测得白蛋白值为 25 g/L 或32 g/L（2.5 g/dL或3.2 g/dL）。当使用溴甲酚紫 (BCP) 或用于血清白蛋白水平的免疫测定时，应使用 20 g/L 或30 g/L（2 g/dL或3 g/dL）的值。*请转至 https://www.med.unc.edu/gntools/bleedrisk.html.

1.8 感染风险

流行病学

临床高度警惕细菌感染对肾小球疾病患者至关重要，包括肾病患者。这在伴有腹水的肾病患儿中尤为重要，在这些患儿中，应在显微镜下检查液体并进行培养，以确定是否存在自发性细菌性腹膜炎。即使临床体征局限于腹部，也可能发生菌血症。红细胞沉降率无帮助，但 C 反应蛋白水平升高可能提供信息。

一旦采集培养物，应开始肠外抗生素治疗。如果反复感染，应测定血清免疫球蛋白。如果血清 IgG <600 mg/dL(6 g/L)，有限的证据表明每月静脉注射免疫球蛋白 400 mg/kg 以保持血清 IgG >600 mg/dL(>6 g/L) 可降低感染风险。接受免疫抑制剂的肾小球疾病患者发生多种感染的风险增加，包括社区获得性肺炎、败血症和其他感染性疾病。

未被识别的潜在感染性疾病的筛查未被识别的未治疗的潜在疾病可能是在开始免疫抑制治疗肾小球疾病时。

在开始治疗前或治疗的同时进行诊断性评估以发现和治疗这些情况可降低发病率和死亡率。适当的筛查显然取决于特定地理区域和/或职业中可能独特的暴露。虽然我们不能详尽地涵盖这些问题，但提出了一些警告。

- 梅毒、HIV、乙型肝炎 (HBV) 和丙型肝炎 (HCV) 的血清学检测通常被认为是肾小球疾病的潜在非主要原因（第7章）。如果确定与诊断的肾小球疾病相关或不相关，应根据免疫抑制时间的紧迫性，考虑在免疫抑制治疗之前或伴随免疫抑制治疗。免疫抑制治疗（糖皮质激素和/或细胞毒性/免疫调节剂、利妥昔单抗）可诱导 HBV 复制严重恶化，从而加重肝病（第7章）。
- 潜伏性结核病 (TB)，常见于许多人群，如适用，应通过 QuantiFERON 检测和/或纯化蛋白衍生物皮肤试验进行筛查，并与免疫抑制伴随治疗。最近的一项研究表明，利福平治疗4个月不劣于异烟肼和吡哆醇治疗9个月。

潜伏性TB。[45]在为接受糖皮质激素治疗的患者处方利福平时应谨慎，因为利福平可能会降低糖皮质激素的生物利用度。

- 在开始免疫抑制（尤其是糖皮质激素）前，应对高危个体进行蠕虫*粪类圆线虫*感染筛查和治疗。最近对*类圆线虫*引起的高度感染的诊断、治疗和预防进行了综述。[46]嗜酸性粒细胞增多症和高血清 IgE 水平可能会引起来自流行区的无症状个体的怀疑。*类圆线虫*可通过仅暴露于数天糖皮质激素治疗，从无症状感染转化为潜在致死性全身性疾病（过度感染综合征）。对于存在无症状*类圆线虫*风险且计划接受糖皮质激素治疗的患者，建议进行筛查。最便宜的类型是粪便检查虫卵和寄生虫。在高危患者筛查不可用或延迟的情况下，如果伊维菌素禁忌或不可用，一些人主张用伊维菌素或二线药物进行经验性治疗。

疫苗接种和预防

成人和儿童 GN 和 NS 患者（以及一般 CKD 患者）发生侵袭性肺炎球菌感染的风险增加，他们及其家庭接触者应接种七价结合疫苗 (7vPCV) 和23价多糖疫苗 (23vPPV) 的肺炎球菌疫苗以及每年一次的流感疫苗。联合糖皮质激素治疗似乎不会损害应答。在使用免疫抑制剂或细胞毒性药物期间禁止接种活疫苗（餐后、腮腺炎、风疹、水痘、轮状病毒、黄热病），应推迟至泼尼松剂量 < 20 mg/日和/或免疫抑制剂已停用至少1-3个月。在治疗首次 SSNS 发作后，未免疫儿童应尽快接种活疫苗，尤其是水痘带状疱疹病毒。

接受补体拮抗剂的患者应同时接种脑膜炎球菌结合疫苗 (MenACWY) 和血清群 B 脑膜炎球菌疫苗 (MenB)。由于这些疫苗接种可能仅部分预防脑膜炎球菌感染，疾病控制中心建议考虑同时进行脑膜炎球菌抗生素预防 (https://www.cdc.gov/meningococcal/clinical/eculizumab.html) .

接触水痘可危及生命，尤其是儿童。如果确实发生暴露，应给予带状疱疹免疫球蛋白治疗，并在首次出现水痘病变体征时开始阿昔洛韦或伐昔洛韦抗病毒治疗（儿童管理的更多详细信息见第4章，SSNS）。建议预防带状疱疹。减毒活 Zostavax

疫苗禁用于免疫抑制和免疫缺陷患者。较新的重组 Shingrix 疫苗是安全的，但免疫抑制可能会降低其有效性。

对健康的家庭接触者接种活疫苗，以最大限度地降低向免疫抑制儿童传播感染的风险，但在接种后3-6周内避免儿童直接暴露于接种接触者的胃肠道、尿液或呼吸道分泌物。

如下所述，应在高剂量泼尼松治疗期间预防性给予甲氧苄啶–磺胺甲恶唑 (TMP-SMX)，以预防*肺囊虫*感染。该策略也可能适用于其他免疫抑制剂，如利妥昔单抗。

实践要点1.8.1：肾小球疾病和肾病综合征患者以及慢性肾病 (CKD) 患者接种肺炎球菌疫苗。患者和家庭接触者应接种流感疫苗。患者应接种带状疱疹疫苗 (Shingrix)。

实践要点1.8.2：在临床适当患者中筛查结核病 (TB)、乙型肝炎病毒 (HBV)、丙型肝炎病毒 (HCV)、人类免疫缺陷病毒 (HIV) 和梅毒（第7章）。

实践要点1.8.3：对于曾居住在地方性热带环境中并有嗜酸性粒细胞增多和血清免疫球蛋白 E(IgE) 水平升高的接受免疫抑制治疗的患者，应考虑类圆线虫二重感染。

实践要点1.8.4：在接受高剂量泼尼松或其他免疫抑制剂（利妥昔单抗、环磷酰胺）的患者中，应考虑预防性甲氧苄啶–磺胺甲恶唑 (TMP-SMX)。

对磺胺过敏可用阿托伐醌或喷他脒代替。这一建议主要是基于对无肾小球疾病的免疫抑制患者的研究。

研究建议

- 关于预防和治疗接受免疫抑制剂的肾小球疾病患者发生感染的进一步研究
- 旨在更好地了解免疫抑制诱导的低丙球蛋白血症管理的其他研究

1.9 结局指标

缓解、肾衰竭、死亡率

GN 治疗有效性的明确评估要求证明已预防或显著延迟肾衰竭、降低死亡率或改善生活质量。肾脏病学标准化结局

(SONG) 倡议从患者和提供者的角度关注这些问题。[47] 安全性也是评估治疗效果的重要组成部分。在肾小球疾病中开展的研究中，很少有研究的持续时间足够长，也很少有研究分析足够数量的患者来准确评估这些结局。这并不奇怪，因为本指南中许多肾小球疾病组织学变体的自然病程缓慢。其中许多疾病的另一个公认结局指标是完全缓解，通过异常蛋白尿完全消失（< 300 mg/24小时）进行评估。然而，大多数研究依赖于其他替代品作为临床结局的预测因素。这些替代结局指标包括蛋白尿变化（例如，蛋白尿部分缓解）、肾功能变化、"无回报点"、生活质量和健康质量。

蛋白尿的变化

在大多数研究中显示了蛋白尿（或白蛋白尿）的定量变化。通常将其归类为完全缓解，通常定义为蛋白尿<0.3 g/24小时 (PCR <300 mg/g[<30 mg/mmol]) 或部分缓解，定义为蛋白尿>0.3 g但<3.5 g/24小时或蛋白尿较初始值减少$50%且<3.5 g/24小时。然而，定义各不相同，即使在特定 GN 模式下也不能一致使用。这些定义的变化将在每个疾病特定章节中讨论。蛋白尿或白蛋白尿的下降百分比>30%也可预测预防进展为肾衰竭，具有中等可靠性。[35,48]

肾功能变化

肾功能变化通常通过SCr、eGFR或内源性 CrCl 的变化进行测量。这些指标需要足以提示真实的疾病进展（例如，SCr加倍或 CrCl 或 eGFR 减半）。这是因为大多数 GN 患者的肾功能逐渐变化，除肾病进展外，还有许多因素可能改变 SCr 值（见上文 *GFR 评价*）。在最近的研究中，已报告 eGFR 随时间的变化可预测更难的结局指标，如肾衰竭。在2-3年期间，eGFR较基线下降$40%被认为是临床试验中确定的肾衰竭替代结局指标。其在各种形式肾小球疾病患者一般管理中的实用性需要进一步检测。在没有肾衰竭作为已确定不良结局的情况下，eGFR随时间的斜率也可能是肾功能变化的充分和可靠的标志物，前提是连续时间点的充分数据可用，斜率具有充分的线性，且用于治疗 GN 的药物无急性作用。[49,50]

G

FR 变化通常定性描述为肾功能"恶化"或"迅速恶化"。这些术语没有精确的定义，但它们是常用术语，尤其是在某些组织学类别中，如血管炎和LN。这些是描述性术语，只有当与具有相似临床和组织学特征的另一组治疗进行比较时，并且在 RCT 的背景下，才能正确评价特定治疗的价值。如可用，这些信息将在每一章中列出。

"无回报点"

该概念没有明确定义，但描述了慢性肾小球疾病自然史中的一种情况，即重度肾功能丧失 (eGFR < 20–30 mL/min/1.73 m^2) 伴有广泛且不可逆的肾损伤（主要是间质纤维化和肾小管萎缩，和/或双侧肾萎缩），因此无法合理改变肾功能进行性恶化的自然史（治疗无效）。假设此类患者应被排除在临床试验之外，因为预计他们是"无应答者"，"因此可能会稀释任何治疗效果，并对研究的效力产生不利影响。此外，这些肾功能降低的受试者发生试验治疗的不良反应的风险可能更高。在缺乏对"无回报点"的精确定义的情况下，在大多数已发表的试验中，不可能知道纳入或排除此类患者是否掩盖了任何治疗获益。即使在特定干预可能无效的患者中，继续进行旨在避免非肾脏并发症（如冠状动脉疾病、卒中和充血性心力衰竭）的治疗也是非常合适的。

生活质量和健康质量

患者对其生活质量和健康质量的认知以及其偏好是治疗评估中极其重要的要素，但在本指南审查的许多临床试验的评价中，它们往往是一个未被重视和/或不可测量的参数。在考虑干预措施的风险-风险比分析时，这些因素尤其相关，可能包括免疫抑制治疗的短期和长期风险，但它们通常不能从患者的角度考虑对其生活质量的实际或感知影响。这些未评估的要素有可能导致结果显著模糊（例如，对接受糖皮质激素治疗的年轻女性/女孩身体形象的担忧可能影响治疗依从性）。最近引入的患者相关结局（患者报告结局测量信息系统 [PROMIS]）允许更快速的评估，有可能提供更统一的结果

生活质量测定是所有慢性疾病的标准（见 SONG-GN 倡议[47]）。

缺乏此类数据是肾小球疾病管理相关研究评价中的实质性证据缺口。

实践要点1.9.1：治疗后蛋白尿减少的目标因肾小球疾病的各种特定原因而异。

实践点1.9.2：‡建议将2-3年期间 eGFR 较基线降低40%作为肾衰竭的替代结局指标。

该阈值主要在临床试验背景下进行检查，需要更好地了解其在非临床试验环境中的实用性。

研究建议

- 在特定形式的肾小球疾病中进一步分析疾病特异性替代结局指标，如 GFR 斜率
- 关于治疗对肾小球疾病生活质量影响的其他数据

1.10 年龄、性别、种族和遗传背景的影响

与已发表研究相比，GN治疗的 RCT 很少导致无法确定普遍性（即，如果患者接受来自不同种族和/或不同年龄或性别的治疗，是否仍会出现任何治疗的已证实获益 [或缺乏疗效]）。这个问题的例子是：将治疗推荐从儿童外推到成人 MCD 是否合理，反之亦然；在白种人中证实的 LN 治疗方案的有效性预期是否可以适当扩展到其他种族；在年轻人中使用免疫抑制疗程观察到的安全性是否同样适用于老年人。

此外，很少有现有 RCT 具有统计学把握度检查治疗中不太常见的不良反应。目前尚不清楚对这些和其他问题的新见解是否会从更好地理解可显著改变免疫抑制剂和其他药物的药代动力学和/或药效学的药物遗传学变异中出现，例如在选择接受硫唑嘌呤的受试者中进行硫嘌呤转移酶活性评估或评估影响华法林抗凝特性的地磁变异。尽管早期的证据表明这些遗传性状可能改变临床结果，但这种药物遗传学检测的成本也需要考虑，而且，目前几乎没有强有力的证据表明这些因素应该改变肾小球疾病的治疗。

研究建议

- 关于种族和血统对 GN 治疗和结局影响的其他研究

1.11 基因组学、转录组学、蛋白质组学、代谢组学

对“个性化”或“精准”医学的关注不断发展，使基因组学、转录组学、蛋白质组学和代谢组学的不同领域成为肾小球疾病管理领域的中心。到目前为止，这些开发是初步的，处于“概念验证”阶段。然而，对管理和治疗决策产生重要影响的证据正在出现，在质量和数量上都在迅速增长。在一些肾小球疾病中，如 FSGS 病变，靶向全基因组或全外显子测序可能对评估类固醇耐药型 FSGS 的表型有价值（第6章）。[51]肾小球病理学表型的转录组模式可能揭示新疗法的新的有前景的靶标。[52]血清或尿液的蛋白质组学和代谢组学模式也可能为人类肾小球疾病的预后和治疗变异提供重要见解。这些研究的实例是最近观察到的血清可溶性尿激酶型纤溶酶原激活物受体 (suPAR) 水平和尿蛋白质组模式可预测 CKD 的结局。[53,54]

研究建议

- 继续研究特异性肾小球病变的遗传起源（尤其是在 FSGS 中）
- 继续寻找可预测预后和间质性肺病病变的血清和/或尿液生物标志物
- 通过转录组学继续研究可能改变的肾小球损伤的新途径

1.12 使用糖皮质激素和免疫抑制治疗

理想情况下，医生寻求一种治疗方案，以避免原发疾病过程的即刻发病（例如，达到 NS 缓解）并防止疾病进展，同时将免疫抑制的有害副作用降至最低。但是，医生也必须认识到，为了预防/延缓 CKD 进展或发生肾衰竭，可能需要长期免疫抑制治疗。慢性肾小球疾病管理的重点已从治愈转向控制，蛋白尿减少的短期和长期益处已得到公认。该范例已转化为使用更扩展（或重复）的治疗方案，其推论是毒性药物暴露随时间增加。

推荐的免疫抑制剂的特定不良反应和常规预防措施的需求超出了本指南的范围，但在临床实践中很熟悉，并且已经过审查。[55]可能需要长期暴露于这些免疫抑制剂的速度方案在以下章节中确定。

不良反应

在开始治疗前，必须始终与患者和家属讨论免疫抑制治疗的潜在不良反应；这一部分的处理不能过分强调。应告知患者个体药物的特定风险，以及感染和某些癌症的总体风险增加。许多药物的治疗风险显著，并且可能具有明显的潜伏期（例如环磷酰胺）。有时很难调和其他临床状况良好患者的免疫抑制直接风险与进展为晚期 CKD 和肾衰竭的可能性，两者均与预期寿命显著缩短相关（即使是透析或移植）。医生应意识到这一难题；如果治疗证据很弱（但可能会改变生命），伤害风险很强，则必须充分披露。

个体患者对以下药物的可接受性的看法

不良反应可能强烈影响决策（例如，

年

轻女性对环孢素治疗多毛症的耐受性可能低于老年男性）。医生认为可接受的权衡可能不会被患者视为相似，导致治疗依从性问题。

使用更强化的免疫抑制方案时，可能需要预防治疗，以尽量减少可能的不良反应（图14[62]）。具体建议超出了本指南的范围，并且没有专门针对肾小球疾病治疗的证据基础。根据肾移植数据，考虑长期免疫抑制治疗肾小球疾病的潜在并发症是合理的。

免疫抑制的其他长期副作用包括感染风险以及骨髓抑制。某些免疫抑制会增加患癌症的风险。在性腺毒剂环磷酰胺和苯丁酸氮芥治疗前，应向患者提供保存精子或卵子的机会（如可用）。为防止性腺毒性，为

Assessment	Measures
Peptic ulcer disease	H_2 blockers Proton pump inhibitors
Bone health and protection	Individual fracture risk assessment/bone mineral density Calcium and vitamin D supplementation Bisphosphonates Growth hormone (pediatric population)
Infection risk	Assess medical history of herpes zoster infection Screening for hepatitis B virus, hepatitis C virus, human immunodeficiency virus Hepatitis B virus vaccination Zoster vaccination Screening for tuberculosis Screening for strongyloides Pneumocystis prophylaxis Influenza and pneumococcal vaccination* Meningococcal vaccination (if C5 antagonists are used) Monitor gammaglobulin levels and white blood cells levels (rituximab, cyclophosphamide)
Ultraviolet light protection	Limit ultraviolet exposure Broad-spectrum sunscreen
Fertility protection	Gonadotropin receptor hormone agonists (i.e., leuprolide) in cyclophosphamide Sperm/oocyte cryopreservation in cyclophosphamide
Effective contraception	Individual evaluation (preference, thrombosis risk, age)
Cancer screening	Evaluate individual risk factors for malignancy Age-specific malignancy screening Annual dermatology exam Bladder cancer (cyclophosphamide cumulative dose >36 g)

图14|所有接受免疫抑制治疗的肾小球疾病患者的筛选/预防。*由于抗体应答降低，不建议在接受中度至高度免疫抑制（例如，泼尼松 10 mg/日）治疗时使用 (Salemi and d'Amelio [62])。

例如，在环磷酰胺治疗期间，女性可接受促性腺激素释放激素类似物（亮丙瑞林）预防治疗，男性可接受睾酮治疗。[56]上文讨论了在开始某些形式的免疫抑制前筛查潜伏性感染。

糖皮质激素

长期使用高剂量和低剂量糖皮质激素与身体变化（体重增加、水牛背、痤疮、皮肤变薄、紫癜、肌肉萎缩、生长迟缓）和代谢并发症（高血糖症或发生显性糖尿病、高血压、高脂血症、骨丢失、胃溃疡）相关。常见的长期糖皮质激素预防包括使用抗菌药以减少机会性感染，以及使用 H2 受体拮抗剂或质子泵抑制剂 (PPI) 预防消化性溃疡。然而，由于最近的回顾性数据表明在不明原因的 CKD 中长期使用PPI，以及 PPI 使用与 AKI 和间质性肾炎相关的病例报告，可能需要重新考虑使用 PPI 作为一线消化性溃疡预防。[55,57,58]使用双膦酸盐类药物（存在肾衰竭的情况除外），以尽量减少糖皮质激素长期治疗期间的骨密度损失。请参阅 *KDIGO 慢性肾脏疾病的诊断、评估、预防和治疗临床实践指南—矿物质和骨异常*。[59]

钙调磷酸酶抑制剂

CNI 具有潜在肾毒性，但用于 MCD 和其他肾小球疾病的血清谷水平较低，这种副作用并不常见。[60]儿童期 MCD 中管样间质病变的风险因素包括环孢素治疗期间使用环孢素 > 24个月和 > 30天出现大量蛋白尿。[61]肾功能受损患者对 CNI 肾毒性的易感性也增加。钙调磷酸酶药物也通常与代谢副作用相关，包括高血压（环孢素 [CSA] > 他克莫司 [TAC]）、高脂血症 (CSA > TAC) 和糖尿病 (TAC > CSA）。此外，CNI副作用特征包括毛发生长 (CSA)、牙龈增生 (CSA) 和震颤 (TAC > CSA)。

环磷酰胺

在eGFR < 30 mL/min/1.73 m ^{2}的患者中，环磷酰胺的剂量应减少（减少$30%），在透析患者中减少50%，并密切监测其骨髓抑制作用。为减少膀胱毒性，环磷酰胺治疗的持续时间不应超过6个月，在接受口服环磷酰胺治疗的患者中，应在早晨服药，并指导患者大量摄入液体。如果认为环磷酰胺的剂量较高，可酌情处方2-巯基乙烷磺酸钠（美司钠）。

如果患者一生中环磷酰胺的总累积剂量超过36 g（成人中约500 mg/kg），则膀胱癌（和其他癌症）的风险更高。应严格避免高于该阈值的剂量。建议对高危个体进行每年一次的泌尿外科筛查。

利妥昔单抗（抗 CD20 药物）

利妥昔单抗与输液反应相关，有时可能为重度反应，包括过敏反应。长期使用利妥昔单抗可能与低丙球蛋白血症相关，尤其是在老年和既存低丙球蛋白血症患者中。重度 (< 200–400 mg/dL) 低丙种球蛋白血症可增加细菌感染的风险。可能需要给予多克隆静脉注射免疫球蛋白（无蔗糖），但 RCT 未证实有效性。在利妥昔单抗治疗患者中可观察到迟发型白细胞减少或全血细胞减少。粒细胞集落刺激因子 (G-CSF) 可能适用于感染风险高的患者。

1.13 免疫抑制的药理学方面治疗指数较窄的免疫抑制剂包括CNI、环孢素和他克莫司，以及 mTOR 抑制剂西罗莫司和依维莫司。不幸的是，没有 RCT 比较肾小球疾病治疗的反应和这些免疫抑制剂不同达到的血液水平。剂量和目标血液水平是基于肾移植的既定实践。血液水平监测的主要目标是避免由于高药物水平导致的毒性，同时保持有效性。治疗药物监测也可用于评估依从性。治疗反应通常可以通过蛋白尿减少来评估，有时可以通过 CNI 的血液谷水平达到，这被认为是实体器官移植的亚治疗。

尽管在大多数患者中没有必要测量麦考酚酸 (MPA) 的暴露量，但测量 MPA 谷水平或其浓度-时间曲线下面积可能为选定患者提供有用的信息，例如 LN 和反复发作的患者，或尽管接受常规麦考酚酸剂量治疗但仍发生药物相关并发症的患者。这是评估依从性的良好工具，应更频繁地使用（图15）。

研究建议

- 确定最适合 GN 缓解的特定目标药物水平
- 制定 GN 患者短期使用高剂量糖皮质激素的骨丢失筛查/预防指南
- 利妥昔单抗治疗低丙种球蛋白血症受试者预防性静脉注射免疫球蛋白 (i.v. Ig) 的 RCT

Practice Point 1.13.1.	Choose a glomerulonephritis treatment regimen that averts the immediate morbidity of the primary disease process	• Intensity of induction therapy is predicated on the severity of presenting symptoms and type of glomerulonephritis • The level of GFR needs to be taken into account for determining safe dosage
Practice Point 1.13.2.	Choose a glomerulonephritis treatment regimen that prevents disease progression	• Complete clinical remission may not be possible in all forms of chronic glomerulonephritis • Prolonged immunosuppression or multiple rounds of immunosuppression may be required to prevent or delay chronic kidney disease progression or the development of kidney failure • Proteinuria reduction is a surrogate endpoint in the treatment of glomerulonephritis
Practice Point 1.13.3.	Choose a glomerulonephritis treatment regimen that minimizes harmful side effects from immunosuppression	• Disclose individual drug side effects (both short- and long-term) • Consider the patient's point of view in shared decision-making • Screen for latent infections, where appropriate, prior to initiation of certain immunosuppression protocols • Monitor therapeutic drug levels where clinically indicated • Prescribe prophylaxis for specific immunosuppressive drug side effects • Review vaccination status and update as required • Offer fertility preservation, where indicated • Monitor for development of cancers or infections • Prolonged immunosuppression or multiple rounds of immunosuppression is associated with more toxic drug exposure over time

图15|免疫抑制相关不良反应的最小化。GFR，肾小球滤过率。

1.14 肾小球疾病的饮食管理

如上所述，饮食中限制钠 < 2 g/日 (< 90 mmol/d) 是控制 BP 和水肿（尤其是肾病患者）以及改善尿蛋白排泄量 (UPE) 的主要原则，也是减少蛋白尿药物的主要原则（图16）。

确保蛋白尿患者摄入足够的膳食蛋白质（每日0.8–1.0 g/kg），并摄入高碳水化合物（35 kcal/kg理想体重，除非肥胖），以最大限度地利用该蛋白质。在 MDRD 研究中，将高达 5 g 的膳食蛋白质添加回处方中 (g/g)，以部分补偿肾病患者的重度蛋白尿。建议在 NS 中谨慎使用高–蛋白饮食，因为这可能会加重蛋白尿。在GFR < 60 mL/min/1.73 m ^{2}的患者中，进一步限制蛋白质摄入可对肾功能和代谢性酸中毒产生积极影响。但是，由于营养不良风险增加，应避免极低蛋白饮食。植物

应尽可能鼓励

（植物）来源的蛋白质。

建议 GFR 降低和体重指数 (BMI) 高于理想值的患者限制卡路里摄入，以促进体重减轻并预防 CV 和肾脏并发症（即，CKD和肾衰竭的进展速度更快）。GFR < 60 mL/min/1.73 m ^{2} 的患者应消耗 30–35 kcal/kg/d。有 CV 并发症风险的血清胆固醇升高患者应遵循心脏健康饮食。此外，脂肪应限制在总热量的 < 30%，饱和脂肪应 < 10%。

研究建议

- 进一步研究饮食对肾小球疾病进展和生活质量的有益作用
- 在肾小球疾病患者中开展的植物性低蛋白饮食 RCT

Practice Point 1.14.1.	Restrict dietary sodium to reduce edema, control blood pressure, and control proteinuria	• Dietary sodium <2.0 g/d (<90 mmol/d)
Practice Point 1.14.2.	Restrict dietary protein based on degree of proteinuria	• Nephrotic-range proteinuria: 0.8–1 g/kg/d protein intake* • Add 1 g per g of protein losses (up to 5 g/d) • The safety of protein restriction in GN has not been established in children • Plant-based diets may be preferred
Practice Point 1.14.3.	Restrict dietary protein based on kidney function	• Estimated glomerular filtration rate <60 ml/min/1.73 m^2 with nephrotic-range proteinuria • Limit or target intake to 0.8 g/kg/d • Avoid <0.6 g/kg/d due to safety concerns and risk of malnutrition • Emphasis on vegetable (plant) sources of protein is appropriate
Practice Point 1.14.4.	Restrict caloric intake to achieve normal body mass index and limit central adiposity in order to reduce chronic kidney disease progression, development of kidney failure, cardiovascular events, and mortality	• Target caloric intake 35 kcal/kg/d • Estimated glomerular filtration rate <60 ml/min/1.73 m^2: 30–35 kcal/kg/d
Practice Point 1.14.5.	Restrict dietary fats in patients with elevated serum cholesterol to prevent cardiovascular complications	• Heart-healthy diet • Dietary fat <30% of total calories • Mono- or polyunsaturated fat 7%–10% of total calories

图16肾小球疾病的饮食建议。*理想体重。GN，肾小球肾炎。

1.15 肾小球疾病妇女的妊娠和生殖健康

在有生育能力的女性中，必须考虑妊娠对患者、胎儿和基础肾病的风险。妊娠合并 GN 患者的护理需要与妇产科医生 (OB-GYN) 和母亲胎儿医学进行协调和规划，详见图17。[63,64]对诊断为 GN 的女性进行的审查显示，许多患者在妊娠期间出现并发症，这可能是医疗保健提供者在疾病早期发挥作用的机会。[65]

避孕也是一个重要的考虑因素。已知 RASi 和许多 GN 治疗为 X 类（潜在致畸或胚胎毒性）药物。此外，免疫抑制，如环磷酰胺，可对长期生育能力有影响。停用麦考酚酯后应继续避孕至少6周。在接受麦考酚酯治疗的男性中，建议在与可能怀孕的女性性交时使用避孕套，这种做法应在停用麦考酚酯后持续至少90天。必须考虑这些问题以及这些治疗对患者的心理影响。下文提供了肾小球疾病与避孕亚型考虑的总结（图18[64,66]和图19[64]）。

妊娠期间出现肾小球疾病的频率因具体疾病而异。IgAN是最常报告的GN，FSGS、MCD和 MN 的数量较少。其中许多患者的数量

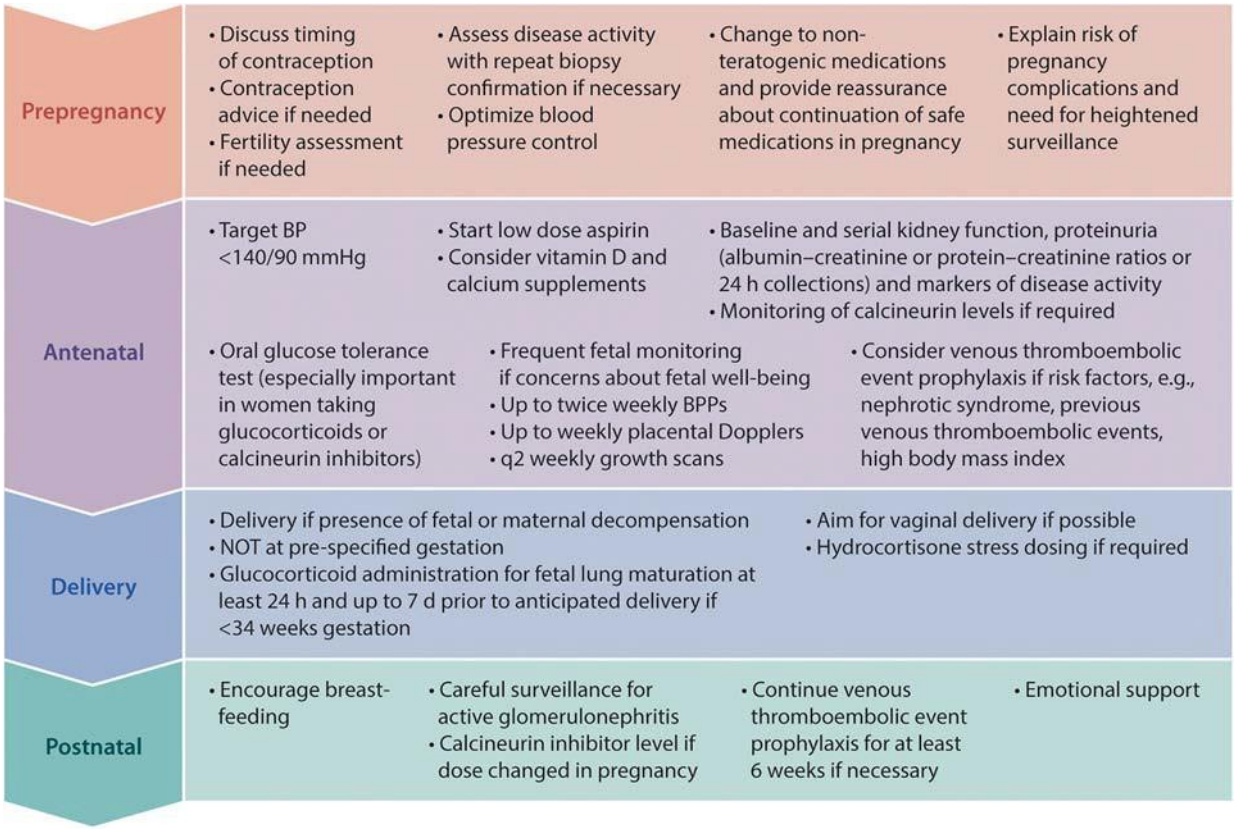


图17肾小球疾病妊娠患者的协调护理。经Blom K,Odutayo A,Bramham K,et al.许可改编妊娠和肾小球疾病：文献与管理指南的系统综述。*Clin JAm Soc Nephrol.* 2017;12:1862–1872.[63]Copyright[a]2017 by the American Society of Nephrology.BP，血压；BPP，生物物理特征；q2，每2次。

审查研究规模较小。[63]建议在计划妊娠前控制肾小球疾病和BP。妊娠结局的主要预测因素是受孕时[67-69]和妊娠中期的GFR。[70]

由于提示肾小球疾病患者发生先兆子痫的风险较高，因此应在孕早期后考虑使用低剂量阿司匹林（60–150 mg），以降低风险和重要不良围产期健康结局的发生，但尚未进行大型试验。[71]

妊娠期间对母亲和胎儿的风险可能因肾小球疾病类型而异。最近的一篇综述表明，IgAN无母体进展风险，但不良妊娠相关结局和不良胎儿结局。

已证明系统性红斑狼疮（SLE）和抗磷脂综合征的风险较高，但确切风险尚不清楚。[72]在SLE患者中，荟萃回归分析显示早产率与活动性肾炎呈正相关，在活动性肾炎或有肾炎病史的受试者中，高血压和先兆子痫的发生率增加。[73]抗磷脂抗体与高血压、早产和人工流产率增加相关。疾病稳定似乎预示着最佳结局。[74,75]所有这些信息的关键信息

Contraceptive method	Unintended pregnancy rate within 1st year of use (%)†		Contraindications in glomerular disease	Other considerations
	Perfect use	Typical use		
Estrogen-containing methods (pill, patch, ring)	0.3	9	• Lupus • Venous thromboembolism • Vascular disease	• Breast cancer risk • Cervical cancer risk with immunosuppression • Venous thromboembolism risk in nephrotic syndrome
Progesterone-only pill	0.3	9	• None	• Longest re-dosing interval with desogestrel (may improve typical use) • Possible breast cancer risk, especially >40 yr
Progesterone intrauterine device (Mirena)	0.2	0.2	• None	• Possible breast cancer risk, especially >40 yr • Effective with immuno-suppression, no evidence of increased infection
Progesterone implant (Nexplanon)	0.05	0.05	• None	• Possible breast cancer risk, especially >40 yr
Copper intrauterine device	0.6	0.8	• None	• No associated hormonal risk
Male condom	2	18	• Ineffective for long-term use	• Protects against human immunodeficiency virus and sexually transmitted infection
Female condom	5	21		
None	85	85		

图18肾小球疾病妇女的避孕。转载自*Kidney International Reports*,volume 3,issue 2,Wiles K,Lightstone L. Glomerular disease in women,pages 270–258,https://www.kireports.org/article/S2468-0249(18)30017-2/fulltext,Copyright[a]2018,International Society of Nephrology.[64]这是一篇根据CC BY NC-ND 许可的开放获取文章 ([a])。http://creativecommons.org/licenses/by-nc-nd/4.0/）。†Trussell.[66]

研究强烈建议患有活动性疾病的女性在狼疮得到控制之前不要怀孕。[76–79]GN男性不建议使用睾酮。

实践要点1.15.1：妊娠合并肾小球疾病患者的护理需要肾内科之间的协调和产科，理想情况下，应在妊娠前考虑此类计划。

研究建议

- 关于每种肾小球疾病对母体和胎儿结局的特异性影响的进一步研究

Aspect of health	Glomerular etiology	Impact	Details
Disease prevalence	All	Increased opportunities for diagnosis in women	Higher use of primary care by women, with opportunities for urine and blood pressure screening
	SLE	Female preponderance	Hypothesized modulation of immune system by sex steroids
	Preeclampsia	Affects 3%–5% of women	Estimated to be the most common glomerular disease worldwide. Prevalence underestimated by histological data as biopsy is rare
Fertility	All	Reduced	Effects of CKD on reproductive hormone profile. Voluntary childlessness may contribute
	SLE	Reduced	Active disease, anti-corpus luteum antibodies, endometriosis, reduced ovarian reserve
	SLE, vasculitis, rapidly progressive GN	Reduced	Dose- and age-dependent premature ovarian failure secondary to cyclophosphamide. Consider fertility preservation in premenopausal women
	All	Need for artificial reproductive techniques	Risk of VTE and ovarian hyperstimulation. Single-embryo transfer in CKD
Contraception	All	Required with teratogenic medication	Includes mycophenolate, cyclophosphamide, methotrexate. Progesterone-only preparations are safe and effective in SLE and CKD
Pregnancy	All	Remove teratogens in advance of pregnancy	Advise 3 months for washout and to ensure disease stability. CNI, AZA, HCQ, glucocorticoids are considered safe for pregnancy
	All	Adverse pregnancy outcomes	Increased risk with CKD, hypertension, and proteinuria
	All	Preeclampsia	Prophylaxis with low-dose aspirin (75–150 mg). No diagnostic criteria for superimposed preeclampsia. Clinical overlap with GN signs and symptoms. Surveillance by an expert clinical team. Future use of anti/angiogenic biomarkers predicted
	All	VTE risk in pregnancy increased if proteinuria	Threshold for LMWH prophylaxis unknown
	All	BP	Aim <140/90 mm Hg
	All	Vitamin D deficiency	Replacement if 25-hydroxyvitamin D is <20 ng/ml (50 nmol/l). Continue activated vitamin D analogs as pre-pregnancy
	All	Anemia	Increased erythropoietin requirement. May need synthetic replacement
	All relapsing-remitting GN	Disease activity associated with adverse pregnancy outcome	Aim remission for 6 months before conception. HCQ for all women with lupus nephritis
	SLE	Risk of flare	Risk of ~15% during pregnancy and ~15% in 1-year postpartum
	SLE	Placental transfer of maternal antibodies	Risk of neonatal cutaneous lupus and congenital heart block with anti-SSA (Ro)/SSB (La). Thromboprophylaxis in antiphospholipid syndrome.
	Membranous	Anti-PLA2R	Role in maternal diagnosis/prognosis and fetal effects unknown
Long-term outcomes	Membranous and FSGS	Slower rate of decline in kidney function	Lower levels of BP and proteinuria in women contribute. Additional protective effect also measured in women
	All with a history of preeclampsia	Increased future vascular and kidney disease risk	Causality versus association not determined
	IgA	Kidney disease progression	Not affected by pregnancy if kidney function preserved

图19女性肾小球疾病的影响概述。摘自*Kidney International Reports*,volume 3,issue 2,Wiles K,Lightstone L. Glomerular disease in women,pages 258–270,https://www.kireports.org/article/S2468-0249(18)30017-2/fulltext,Copyright ª2018,International Society of Nephrology.[64]这是一篇根据CC BY NC-ND 许可的开放获取文章 (http creativecomons.org/licenses/by-nc-nd/4.0/)。AZA，硫唑嘌呤；BP，血压；CKD，慢性肾病；CNI，钙调磷酸酶抑制剂；FSGS，局灶节段性肾小球硬化；GN，肾小球肾炎；HCQ，羟氯喹；LMWH，低分子量肝素；PLA2R，M型磷脂酶 A2 受体；SLE，系统性红斑狼疮；SSA/SSB，Sjögren综合征抗体；VTE，静脉血栓栓塞。

1.16 治疗费用及相关问题

制定这些指南的目的是为肾小球疾病提供循证治疗建议，可供世界各地的医生使用。在世界许多地区，推荐的大多数药物都是低成本的。包括泼尼松、硫唑嘌呤、环磷酰胺片等。监测（例如，通过定期检查血细胞计数）也是廉价且广泛可用的。

一些药物（例如，*CNI*、麦考酚酯、利妥昔单抗、*Acthar* 凝胶和*eculizumab*）的成本仍然很高，但仿制药和生物类似药的开发和上市现在正在迅速降低成本。但是，必须注意确保这些较便宜的仿制药的生物利用度变化不会损害有效性或安全性。

世界一些地区仍然无法获得血浆置换，这不仅与置换液（包括人白蛋白和新鲜冷冻血浆）的高成本和有限可用性有关，还与设备和工作人员成本有关。

本指南中建议作为潜在"补救"治疗的一些治疗（例如利妥昔单抗）在世界大多数地区仍然非常昂贵，因此，是迫切需要开发试验的另一个迹象，将提供这些治疗疗效的稳健证据。如果有全面的国家或国际登记系统收集关于此类高成本药物使用的全面观察性数据，则此类高成本药物价值的不确定性也会得到缓解；不幸的是，不存在此类登记系统。该主题领域的研究已经开始，但数据仍然很少。

实践要点*1.16.1*：应向肾小球疾病患者提供参加疾病登记研究和临床试验的机会（如可用）。

研究建议

- 进一步分析治疗药物（包括生物类似药）治疗肾小球疾病的成本效益

1.17 肾小球疾病治疗的目标

肾小球疾病治疗的总体目标是：

1. 确保肾小球疾病临床表现的持续缓解。完全缓解更可取，但在许多情况下部分缓解可能就足够了。对于那些有复发倾向的疾病，目标是最大限度地减少复发的频率和严重程度。治疗选择应考虑肾衰竭和肾外并发症的风险，并估计可能的疗效和无效性。
2. 确保上述获益，避免或尽量减少治疗相关不良事件的发生，尤其是可能危及生命或可能对患者的生活质量产生不利影响的不良事件。
3. 以最大限度提高患者舒适度和生活质量的方式进行治疗。

1.18 移植后 GN

几乎本指南中讨论的所有组织学变体（*MCD*可能除外）在移植后均可能复发。复发性疾病被公认为是肾移植失败的第二或第三大常见原因。应尝试在移植前评估疾病复发的风险，因为这可能会影响供体的选择和移植后管理。少数情况下，由于复发疾病的风险极高，可能需要避免活体移植（见具体疾病章节）。目前，尚无已证实的预防肾移植受者肾小球疾病复发的策略。尽管疾病的复发率很高，但在大多数情况下，移植物的长期存活率仍然非常好，移植仍然是继发于肾小球疾病的肾衰竭患者的最佳治疗选择。如果存在与移植前管理相关的特定肾小球疾病变体的特定建议，则在每个相关章节中讨论。

第2章：免疫球蛋白 A 肾病 (IgAN)/免疫球蛋白 A 血管炎 (IgAV)

免疫球蛋白 A 肾病

IgA 肾病 (IgAN) 是全球最常见的原发性肾小球疾病模式，仍然是 CKD 和肾衰竭的主要原因。最常见的是，IgAN无症状，呈缓慢进展的病程，任何队列中约25%-30%在就诊20-25年内发生肾衰竭。与本指南中纳入的大多数肾小球疾病不同，IgAN的管理侧重于基于非免疫抑制剂的策略，即所谓的支持治疗，以减缓疾病的进展速度。这包括严格的血压控制、RAS的最佳抑制和生活方式调整，包括减轻体重、运动、戒烟和限制饮食中的钠（第1章）。

虽然 IgAN 的特征是单一的组织病理学肾活检显示主要或共显性 IgA 沉积的标准，目前公认该“疾病”在其临床和病理学特征方面表现出明显的异质性。有充分的证据表明，IgAN的流行病学、临床表现、疾病进展和长期结局在世界各地不同种族人群中存在差异。IgAN在东亚血统人群中发病率最高，更易引起肾衰竭，其次是白种人，在非洲人后裔个体中相对罕见。尚不清楚这些观察结果是否是由于发病机制的差异和/或不同遗传和环境影响的作用。

本章对IgAN 成人，并为如何将这些建议应用于1-18岁儿童提供了实践点。在可能的情况下，我们强调了特定治疗方案可能的人种差异。

IgA 血管炎（过敏性紫癜）将在本章后面讨论。

2.1 诊断

操作要点2.1.1：诊断免疫球蛋白 A 肾病 (IgAN) 的注意事项：

- IgAN 只能通过肾活检确诊。
- 根据修订后的 Oxford 分类确定 MEST-C 评分（系膜 [M] 和毛细血管内 [E] 细胞过多、节段性硬化 [S]、间质纤维化/肾小管萎缩 [T] 和新月体 [C]）。[80]
- 没有经验证的*诊断*血清或尿液 IgAN 生物标志物。
- 评估所有 IgAN 患者的次要原因。

2.2 预后

已经开发了几种预后评分来帮助预测 IgAN 的肾脏结局。早期的评分系统包括统一人种和地理来源队列中的各种病理分类模式。[80–85]最近，修订版牛津分类中定义的标准化 MEST-C 评分已被纳入预后评分系统的开发[86]和用于选择预测变量的机器学习。[87]迄今为止最大的研究在多国和多人种队列中开发了预后评分，包括大量的培训和验证人群，包括超过4000名受试者。[88]肾功能减半或肾衰竭预测评分的5年风险包括 MEST-C 组织学评分和肾活检时测量的临床变量。该工具可作为在线计算器，帮助与患者讨论结局。需要进一步的工作来确定从活检开始更远程测量的临床数据是否可以以类似的方式使用。此外，不能使用该工具对治疗做出推断。然而，人们可以设想未来使用该工具进行临床试验设计和分析。该预测算法中的变量见图20。

实践要点2.2.1：原发性 IgAN 预后的考虑因素：

- 活检时的临床和组织学数据可用于对患者进行风险分层。
- 国际 IgAN 预测工具是量化进展风险和告知与患者共同决策的宝贵资源。
  - 通过 QxMD 计算
- 国际 IgAN 预测工具结合了活检时的临床信息，不能用于确定任何特定治疗方案的可能影响。
- 除 eGFR 和蛋白尿外，没有经验证的 IgAN *预后*血清或尿液生物标志物。

2.3 治疗

实践要点2.3.1：治疗所有无变体形式原发性 IgAN 的 IgAN 患者的注意事项：

- 管理的主要重点应是优化支持治疗。

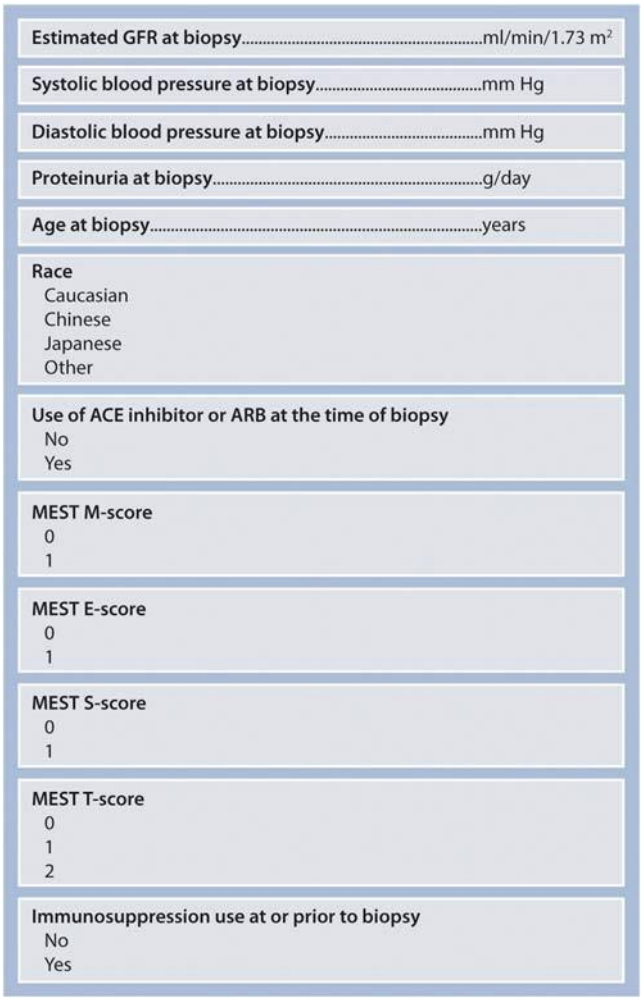


图20|国际 IgAN 预测工具中包含的数据要素。使用活检时的临床和组织学数据，用户可以在选定的时间间隔确定 eGFR 下降50%或肾衰竭。该工具未被确认可与活检时远程获得的数据一起使用。ACE，血管紧张素转换酶；ARB，血管紧张素 II 受体阻滞剂；GFR，肾小球滤过率；MEST，系膜 (M) 和毛细血管内 (E) 细胞过多、节段性硬化 (S) 和间质纤维化/肾小管萎缩 (T)。

- 评估心血管风险，并在必要时开始适当的干预。
- 提供生活方式建议，包括饮食限钠、戒烟、控制体重和适当运动的信息。
- 除饮食限钠外，无特定饮食干预显示可改变 *IgAN* 结局。
- *IgAN* 的变异型：*IgA*沉积伴微小病变 (*MCD*)、*IgAN* 伴急性肾损伤 (*AKI*) 和 *IgAN* 伴急进性肾小球肾炎 (*RPGN*) 可能需要特定的立即治疗。

实践要点2.3.2：*IgAN*患者的初始评估和管理算法（图21）

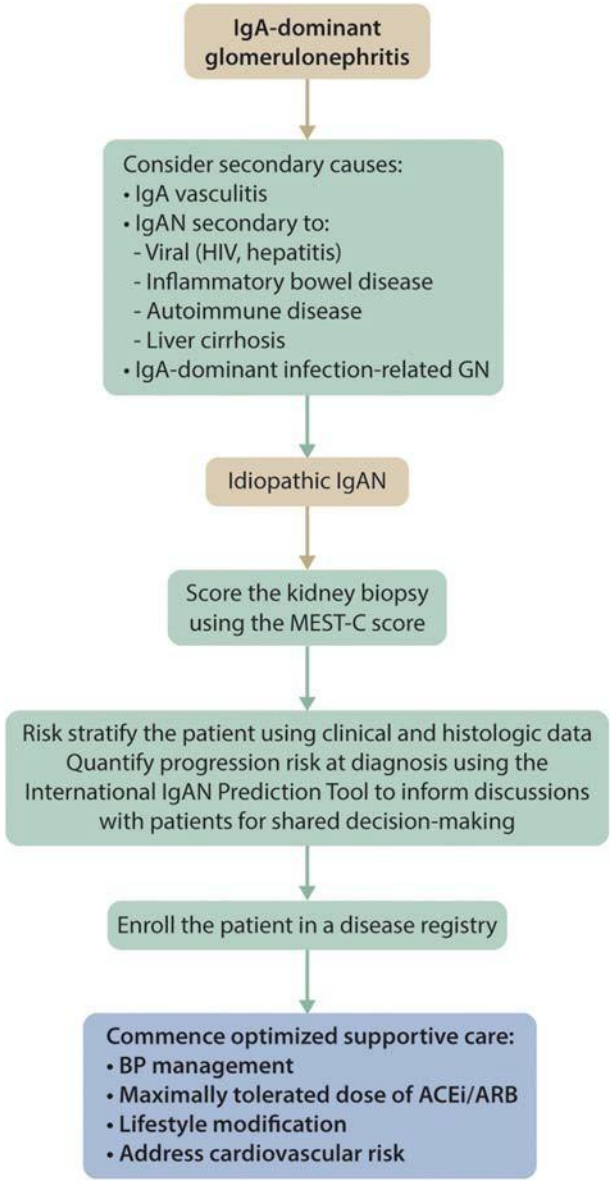


图21|IgAN患者的初步评估和管理。ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；BP，血压；GN，肾小球肾炎；HIV，人类免疫缺陷病毒；IgAN，免疫球蛋白 A 肾病；MEST-C，系膜 (M) 和毛细血管内 (E) 细胞过多、节段性硬化 (S)、间质纤维化/肾小管萎缩 (T) 和新月体 (C)。

建议2.3.1：我们建议对所有患者的血压进行管理，如第1章所述。如果患者出现蛋白尿 > 0.5 g/日，我们建议使用血管紧张素转换酶抑制剂进行初始治疗 (ACEi) 或血管紧张素 II 受体阻滞剂 (ARB)*(1B)*。

该建议是基于大量证据，表明高血压和蛋白尿是 CKD 进展的主要风险因素，治疗高血压和减少蛋白尿可降低进展为肾脏的风险

失败。IgAN中的特定数据虽然不广泛，但与这些观察结果一致。尚无研究显示 ACEi 和 ARB 双重阻断在 IgAN 中优于单一阻断。STOP-IgAN试验的事后分析表明，双重阻断没有额外的获益。[89]*在根据工作组的判断，强烈建议是必要的，因为在各种肾脏疾病中观察到的高血压和蛋白尿治疗获益一致，高血压和抗蛋白尿治疗的危害风险通常较低，并且缺乏专门针对 IgAN 的不同建议的依据。*

关键信息

平衡危害。在一般 CKD 人群中，控制 BP 和减少蛋白尿可减缓 CKD 进展并降低 CV 风险。[90,91]治疗获益低于潜在危害（例如，体位性低血压和药物不良反应）。没有证据表明 IgAN 引起的 CKD 患者的获益和危害不同，也有证据表明二者相似。

*证据质量。*高质量的数据支持 BP 控制和蛋白尿减少对减缓所有 CKD 人群的肾病进展有益。[92]IgAN的特定数据有限，但没有*先验*理由怀疑大量证据不能推广到 IgAN 患者。

由于依赖于一般 CKD 研究的间接证据，IgAN人群的证据质量为中等。此外，在 IgAN 患者中检查抗高血压药物的 RCT 数量较少，很少报告关键和重要结局，如全因死亡率、肾衰竭或完全缓解，并且由于研究限制（缺乏同种异体药物隐藏，或参与者和结局评估者设盲不充分）或不精确（仅一项研究或很少事件；补充表S4[93-95, 104]和补充表S5[93,95–99]）。

*价值和偏好。*工作组认为，与治疗相关的潜在危害相比，大多数患者对高血压和抗蛋白尿治疗的潜在获益的评价更高。

*资源使用和成本。*根据全球健康观察数据库（世界卫生组织 [WHO]），ACEi（和CCB）在高 IgAN 流行率地区广泛但并非统一可用。在不同地区和国家内，解决生活方式改变的整体计划的可用性存在更广泛的差异，包括戒烟、减轻体重/改变饮食和控制高血压的运动计划。

*实施考虑。*BP控制包括持续性高血压患者初始生活方式调整后用药（第1章）。应向患者提供减重、饮食调整和运动计划，如适用，作为控制 BP 整体方法的一部分。IgAN中 BP 控制目标与第1章所述目标无差异。特别是，没有证据表明 BP 目标在男性和女性之间或不同人种的人群之间应该是不同的。

依据

与其他肾小球疾病（可能与不同的疾病复发、NS发作或 AKI 相关）相比，IgAN通常是一种缓慢进展的疾病。在 IgAN 中，除了尝试使用免疫抑制剂改变基础疾病发病机制外，目前认为控制 BP 和尽量减少蛋白尿的策略至关重要。[100]

北美、亚洲和欧洲大型 IgAN 队列的流行病学研究一致确定未控制的高血压和蛋白尿为 IgAN 进展的独立风险因素。[94,101,102]在Le et al.的研究中，包括1155例患者的结局，与 > 1 g/日相比，持续蛋白尿为0.5–1 g/日的患者的10年肾脏存活率显著改善，10年无透析存活率为94%(95%CI:90%–98%)，20年无透析存活率89%(95%CI：82%-96%)。[101]在一项49例 IgAN 患者的 RCT 中，平均 BP 达到129/70 mmHg，GFR 在3年内稳定，而平均 BP 达到 136/76 mmHg 的患者在3年内的 GFR 平均下降13 mL/min。[103]大型登记研究的回顾性数据显示，与未接受 ACEi 或 ARB 治疗的类似患者相比，接受 ACEi 治疗以控制 BP 的 IgAN 患者的肾功能年下降率较低。[102]一项44例 IgAN 患者的 RCT 显示，ACEi（依那普利）对进展性肾病（肾脏存活率较好，蛋白尿减少）的获益大于其他降压药（硝苯地平、氨氯地平、阿替洛尔、利尿剂、和多沙唑嗪）。[96]一项109例亚洲 IgAN 患者的 RCT 显示，与安慰剂相比，ARB（缬沙坦）可更大程度地减少蛋白尿并减缓肾脏恶化速度。[104]

尚无关于在 IgAN 患者中使用 ACEi 和 ARB 双重阻断的疗效或安全性的 RCT 数据。STOP-IgAN试验的*事后*分析表明，双重阻断没有额外的获益。[89]

建议2.3.2：我们建议所有蛋白尿 > 0.5 g/日的患者（无论是否患有高血压）均接受以下治疗 ACEi 或ARB *(1B)*。

该建议是基于所有类型蛋白尿性肾小球疾病（包括 IgAN）的广泛证据，即较高水平的蛋白尿与较差的肾脏结局相关，且蛋白尿减少，

与 BP 控制变化无关，与肾脏结局改善相关。尚无研究表明，在 IgAN 中，ACEi或 ARB 双重阻断优于单一阻断。STOP-IgAN试验的事后分析表明，双重阻断没有额外的获益。[89]*在根据工作组的判断，强烈建议是必要的，因为在肾脏疾病谱中观察到的蛋白尿治疗获益一致，抗蛋白尿治疗的危害风险通常较低，并且缺乏对 IgAN 特殊推荐不同的依据。*

关键信息

*平衡危害。*减少蛋白尿可减缓 CKD 进展并降低 CV 风险。[91,105]对于其他肾脏疾病，治疗获益远远超过潜在危害（例如，体位性低血压和药物不良反应）。没有证据表明 IgAN 的益处和危害在特定方面是不同的，也有一些证据表明它们是相似的。在血压正常的个体中，应谨慎开始 RAS 阻断，我们在*实施考虑*章节中概述了一种潜在方法。

*证据质量。*肾脏保护作用的证据在血压正常的情况下蛋白尿减少的质量低于支持高血压治疗的证据。然而，Inker et al进行的个体患者水平荟萃分析。包括具有一系列 BP 目标并达到 BP 的研究，在所有这些研究中，蛋白尿减少与临床结局改善相关，与 BP 变化无关。[106]随后根据 TESTING 和 STOP-IgAN 试验的结果更新了该分析，并证实了 Inkeret al 的初步观察结果。荟萃分析。[36]

个体患者水平荟萃分析的证据是间接的，因为在无高血压和蛋白尿 > 0.5 g/g的 IgAN 患者中比较 RASi 与常规治疗的研究数量有限。然而，纳入该人群的3项研究报告了中等质量的蛋白尿和 CrCl 证据（研究局限性包括缺乏分配隐藏，或参与者和结局评估者设盲不充分）和低质量的 SCr 加倍证据（由于非常严重的不精密度；补充表S5 [93,95–99]）。

*价值和偏好。*工作组认为，与治疗相关的潜在危害相比，大多数患者对抗蛋白尿治疗的潜在获益具有较高价值。然而，由于存在直立性低血压风险，较年轻的低/正常 BP 患者可能对 RAS 阻断的潜在获益评估较低。

*资源使用和成本。*根据全球健康观察数据库 (WHO)，ACEi在高 IgAN 患病率地区广泛但并非统一可用。[107]然而，重要的是要注意，在一些国家，在血压正常但蛋白尿患者中使用 RAS 阻断被广泛实施，但并不总是得到医疗保险的支持。

*实施考虑。*在血压正常的患者中开始 RAS 阻断治疗时，患者必须首先接受低剂量治疗，并控制剂量递增，以便患者接受最大耐受剂量的 ACEi 或 ARB 治疗，从而最大限度地减少蛋白尿，同时最大限度地减少副作用，尤其是直立性低血压。最大耐受剂量通常低于该区域的推荐最大剂量。

依据

北美、欧洲和亚洲的研究一致表明，蛋白尿的严重程度是 IgAN 进展的独立风险因素。[94,101,102]Le et al.的研究纳入了1155例患者的结局，与 > 1 g/日相比，持续蛋白尿为0.5–1 g/日的患者的10年肾脏存活率显著改善，10年无透析存活率为94%(95%CI:90%–98%)，20年无透析存活率89%(95%CI：82%-96%)。[101]一项包含866例患者的8项试验的荟萃分析评价了 ARB 在血压正常伴蛋白尿患者中的抗蛋白尿作用。与对照组相比，使用 ARB 可显著降低糖尿病患者的尿蛋白排泄量，中度增加白蛋白尿患者以及无糖尿病的肾病患者的尿蛋白排泄量。在西方和亚洲人群中均一致观察到该效应。[108]该荟萃分析中纳入的是一项在 IgAN 中进行的小型研究，纳入了32例血压正常的18-54岁蛋白尿（1-3 g/日）和肾功能正常 (CrCl > 80 mL/min) 患者，将其随机分为4个治疗组（维拉帕米 120 mg/日；群多普利 2 mg/日；坎地沙坦酯 8 mg/日；和安慰剂）。[93]群多普利组和坎地沙坦酯组的抗蛋白尿反应相似 (–38%vs.–40%)，且显著高于维拉帕米组 (P < 0.01)。对来自11项 RCT 的830例患者的数据进行个体参与者水平的荟萃分析，发现蛋白尿减少与 IgAN 中 SCr 水平加倍、ESKD或死亡风险降低相关，且各研究结果一致。[106]该效应与是否存在高血压无关。尚无关于在 IgAN 患者中使用 ACEi 和 ARB 双重阻断的疗效或安全性的 RCT 数据。STOP-IgAN试验的*事后*分析表明，双重阻断没有额外获益。[89]

然而，RAS阻断是否会导致在伴有中度白蛋白尿增加（30-300 mg/日）和正常 BP 的 IgAN 患者中，由于缺乏解决该问题的RCT，结局更好。

2.3.1 尽管接受了最大程度的支持治疗，但仍存在进展性 CKD 高风险的 IgAN 患者

这些患者定义为持续UPE > 1 g/d 尽管以最大耐受剂量或允许的每日 RAS 阻断剂量治疗至少3个月，并达到第

1至少3个月。变异型 IgAN 可能需要立即进行特异性治疗。

实践要点2.3.1.1：尽管进行了最大限度的支持治疗，但仍有进展性 CKD 高风险的 IgAN 患者的治疗考虑。

- IgAN 进展的高风险目前定义为蛋白尿 > 0.75–1 g/日，尽管‡进行了90天优化支持治疗。
- 免疫抑制药物应仅考虑用于尽管接受了最大程度的支持治疗但仍处于进展性 CKD 高风险的 IgAN 患者（入组唯一一项提示免疫抑制获益的大型随机对照试验 [RCT] 的患者的平均蛋白尿为2.4 g/日）。
- 鉴于现有免疫抑制治疗选择的安全性和有效性目前尚不确定，所有尽管接受了最大程度的支持治疗但仍处于进展性 CKD 高风险的患者均应有机会参加临床试验。
- 所有正在接受免疫抑制治疗的患者
  考虑到，应与患者详细讨论每种药物的风险和获益，认识到eGFR < 50 mL/min/1.73 m ^{2}的患者更可能发生不良治疗作用。
- 没有足够的证据支持使用 Ox-
  确定 IgAN 是否应开始免疫抑制时的分类 MEST-C 评分。
- 没有足够的证据根据肾活检中新月体的存在和数量来做出治疗决策。
- 国际 IgAN 预测工具不能用于确定任何特定治疗方案的可能影响。
- 应动态评估患者风险随时间的变化，因为免疫抑制相关决定可能会发生变化。

多项观察性登记研究表明，持续蛋白尿是长期肾脏结局的最有力预测因素。无论干预的性质如何，观察性研究中蛋白尿的减少也与肾脏结局的改善独立相关。近期对 RCT 数据进行的试验级分析证实了蛋白尿的治疗效果和肾脏生存的治疗效果（至 SCr 加倍、ESKD或死亡时间的复合终点）之间的相关性[36]，从而确定蛋白尿减少是 IgAN 结局改善的有效替代标志物。本分析中纳入的临床试验通常针对 < 1 g/日的蛋白尿减少。因此，将蛋白尿降至 < 1 g/日是 IgAN 住院患者的合理干预目标，这些患者尽管接受了最大程度的支持治疗，但仍存在进展性 CKD 的高风险。

实践要点2.3.1.2：蛋白尿降至 1 g/日以下是 IgAN 肾脏结局改善的替代标志物，降至 1 g/日以下是合理的治疗目标。

建议2.3.1.1：我们建议，尽管接受了最大程度的支持治疗，但仍处于进展性 CKD 高风险的患者应考虑接受以下治疗：
6个月疗程的糖皮质激素治疗。必须与患者讨论治疗期间毒性的重要风险，尤其是以下患者
eGFR < 50 mL/min/1.73 m ^{2}(2B)。

在没有快速进展性肾功能丧失的情况下，支持疗法是IgAN 成人患者的主要治疗方法。支持性治疗优化6个月后，大量蛋白尿 > 1 g/日的患者不再符合入组临床试验的条件
由于蛋白尿减少而进行随机化。[100]对于活检诊断前已接受 RAS 阻断的患者，可考虑缩短3个月的治疗期。

现有最大的糖皮质激素 RCT 是 TESTING 研究；由于糖皮质激素治疗组的安全性问题，研究者提前停止入组。[109]尽管进行了强化保守治疗，但该研究中患者的平均蛋白尿水平为2.4 g/日；该水平明显高于 STOP-IgAN 研究中入组的患者，后者的蛋白尿水平为1.6–1.8 g/天。早期分析提示了糖皮质激素的疗效，这是考虑在 IgAN 中使用该药物的建议基础。但是，发生了严重不良事件，包括2例与感染并发症相关的死亡。与临床医生讨论后，患者可因风险而选择不接受糖皮质激素治疗。

关键信息

*平衡危害。*由于治疗的显著毒性风险，这是一个较弱的推荐。糖皮质激素治疗的注意事项必须包括与该药物相关的治疗后出现的毒性风险的讨论和个体化风险评估。尚不清楚相似人群中较低剂量糖皮质激素的疗效和毒性，是正在进行的研究 (NCT01560052) 的主题。*证据质量。*该建议是基于中等质量的证据。由于研究局限性或不精确性（很少事件），比较糖皮质激素治疗与支持治疗的4项 RCT 的关键和重要结局（全因死亡率、肾衰竭、感染、SCr加倍和每年 GFR 降低）的证据质量为中等。然而，由于研究的局限性和不一致性，完全缓解的证据质量较低（I ^{2}¼60%；补充表S6 [100,109–112]）。

*价值和偏好。*工作组认为，大多数患者对长期肾功能的保护价值较高。然而，在 2 g/日以下肾功能相对保留和无症状蛋白尿的患者中，对副作用和不良事件的耐受性也可能有限。因此，临床医生必须全面讨论糖皮质激素的风险和获益，以及

考虑可能使其处于较高毒性风险中的个体患者特征（实践要点2.3.3）。

资源使用和成本。糖皮质激素被纳入 WHO 基本药物示范目录（2017年），通常容易获得且价格低廉。[107] 然而，用于监测治疗中出现的毒性风险的资源（例如，筛查潜伏性感染、骨密度扫描）并不统一。

实施考虑。执业医师应对患者的疾病进展风险和治疗中出现的毒性风险进行个体化评估。可使用国际 IgAN 预测工具估计发生肾功能降低和肾衰竭的风险，以指导与患者的讨论。执业医师可考虑不为具有特定临床特征的患者提供糖皮质激素，使其发生治疗后出现的毒性的风险更高（实践要点2.3.2）。

依据

工作组承认蛋白尿减少和 eGFR 短期损失作为长期预防 CKD 和肾衰竭的替代标志物的重要性。[36]最初的一系列小型 RCT 支持与单独支持治疗相比蛋白尿减少更多，无论是否统一使用 RAS 阻断。[110,111,113]然而，由于样本量较小，这些研究的疗效和毒性估计值的一致性较低。

STOP-IgAN RCT 纳入了162例受试者，以评估在支持治疗的基础上加用免疫抑制治疗对分层系列主要结局（包括蛋白尿和 GFR 目标）的影响。[100]3年时，接受免疫抑制治疗的患者蛋白尿缓解率更高 (17%vs. 5%，$P < 0.01$)。这与3年时 GFR 终点的差异无关。随机化时的蛋白尿相对较低（1.6 g/日和1.8 g/日），在3年内，支持治疗组患者的肾功能仅下降4.2 mL/min/1.73 m^2，证实了严格支持治疗对 IgAN 的影响。但该结果也意味着免疫抑制组患者的 eGFR 降低基线率较低，因此不太可能出现终点

在

相对较短的3年随访期内。1例患者发生1例免疫抑制相关死亡。中位随访7年后 STOP-IgAN 队列的长期结局数据显示，48%的队列达到终点，即 eGFR 降低40%、ESKD或死亡，25%的试验参与者发生ESKD。[114]在标准治疗的基础上加用免疫抑制未改变长期结局。

现有最大的针对疾病进展高风险患者的RCT（TESTING试验）在计划750例受试者中的262例随机化后停止入组，因为糖皮质激素组严重不良事件的风险高11%(95%CI：4.8%-18.2%)。[109]这包括2例与感染并发症相关的死亡。在分析时，糖皮质激素组中主要肾脏结局（eGFR降低40%、肾衰竭、肾病导致的死亡）的发生频率显著较低 (HR：0.37；95%CI：0.17–0.85)，表明有效。未观察到 ESKD 发生率存在差异，尽管是在因安全性问题提前停止研究的背景下。TESTING研究中的患者与 STOP-IgAN 试验中的患者存在差异，这可能解释了观察到的糖皮质激素毒性和疗效的一些差异。患者几乎全部为亚裔，中位蛋白尿排泄量较高（基线时2.5 g/日），安慰剂组受试者的肾功能年下降率为–6.95 mL/min/1.73 m^2。

TESTING 研究纳入了 eGFR 低至 20 mL/min/1.73 m^2。然而，只有26例随机化患者的eGFR < 30 mL/min/1.73 m^2，亚组分析受到试验提前终止的限制。因此，在 eGFR 极低的患者中疗效证据较低，免疫抑制的毒性可能更大。TESTING研究继续采用剂量调整方案进行入组，原计划的主要结局分析待定。在这些数据可用之前，只能使用提示疾病进展风险高且毒性风险显著的患者中糖皮质激素疗效早期迹象的可用数据。

最近3项 RCT 中使用的糖皮质激素治疗方案详见图22[109-111]。

Study	Medication	Start dose	Duration high dose	Taper	Total exposure
TESTING[1]	Methylprednisolone	0.6–0.8 mg/kg/d (per investigator), rounded to nearest 4 mg. Max 48 mg/d	2 months	8 mg/month	6–8 months
Manno[2]	Prednisone	1 mg/kg/d, max 75 mg/d	2 months	0.2 mg/kg/ month	6 months
Lv[3]	Prednisone	0.8–1 mg/kg/d	8 weeks	5–10 mg/d every 2 weeks	8 months

图22|统一使用肾素-血管紧张素系统 (RAS) 抑制的 IgAN 临床试验中使用的糖皮质激素方案。[1]类固醇治疗 IgA 肾病的全球治疗评价（试验）[109]：试验低剂量研究正在进行中 [NCT01560052]，[2]Manno 等人[111]，[3]Lv 等人[110]

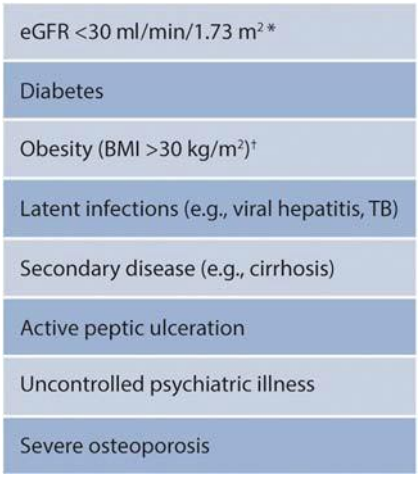


图23应避免使用糖皮质激素或慎用糖皮质激素的情况。*全球 IgA 肾病类固醇治疗评价 (TESTING)[109] 研究纳入 eGFR 为20-30 mL/min/1.73 m²的患者，但总计仅26例患者具有该范围的肾功能。预先设定的亚组
疗效和毒性信号的分析效力不足，无法区分eGFR < 30 mL/min/1.73 m ²的患者。†TESTING研究中的高 BMI 未被特别视为排除标准，但平均BMI < 24 kg/m ²。BMI，体重指数；eGFR，估计肾小球滤过率；TB，结核病。

实践要点2.3.1.3：IgAN中糖皮质激素的使用：

- 尚未确定糖皮质激素治疗 IgAN 的临床获益，应极其谨慎给药或在图23[109]中列出的情况下完全避免使用。
- 没有足够的证据支持使用牛津分类 MEST-C 评分来确定何时应开始任何糖皮质激素治疗。
- 没有数据支持隔日糖皮质激素方案或剂量降低方案的疗效或毒性降低。
- 根据当地指南，在适当情况下，糖皮质激素（泼尼松等效剂量±0.5 mg/kg/d）治疗应包括预防*肺囊虫*肺炎以及胃保护和骨保护。

实践要点2.3.1.4：最大程度支持治疗后仍处于进展高风险的 IgAN 患者的管理（图24[109]）

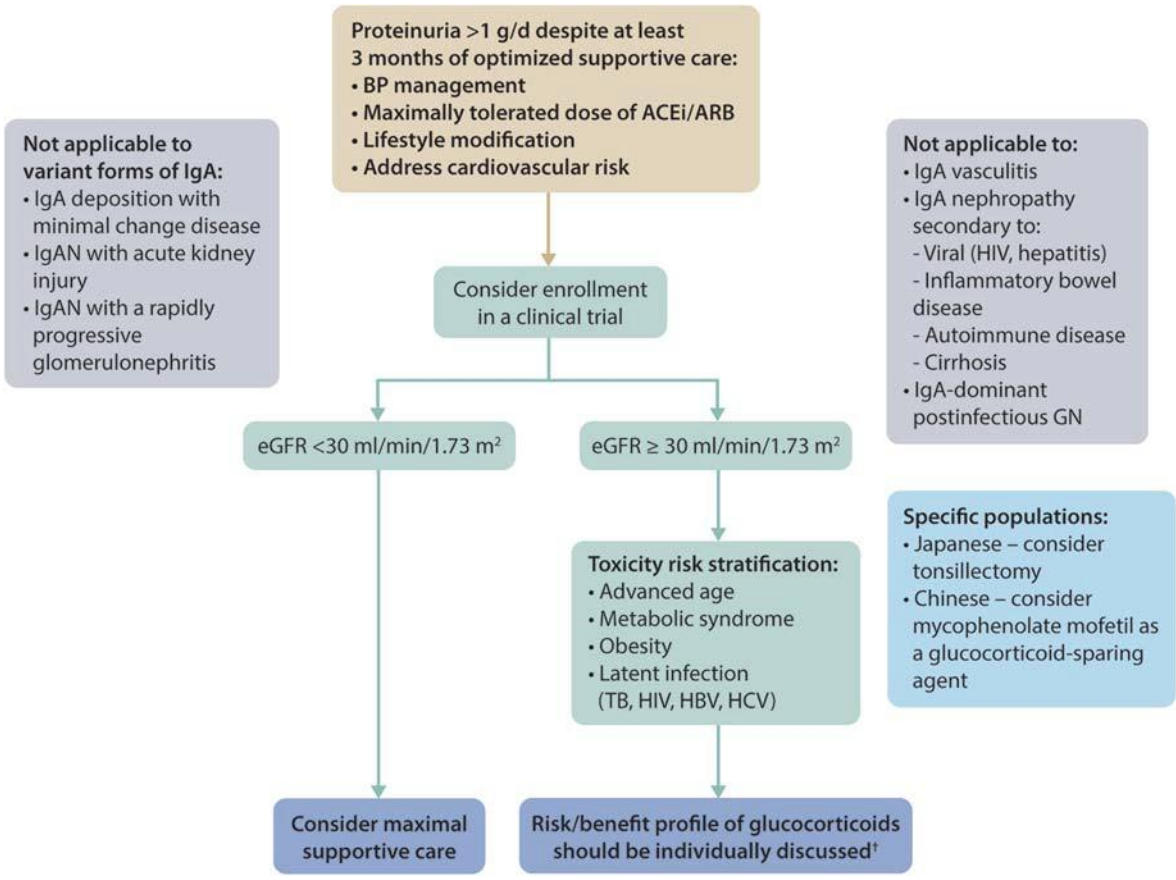


图24最大限度支持治疗后仍处于进展高风险的 IgAN 患者的管理。*IgAN伴急进性肾小球肾炎见操作要点2.4.3。†TESTING研究[109]显示了显著蛋白尿（平均2.4 g/日）患者疗效的早期证据，以牺牲治疗相关发病率和死亡率为代价。ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；BP，血压；eGFR，估计肾小球滤过率；GN，肾小球肾炎；HBV，乙型肝炎病毒；HCV，丙型肝炎病毒；HIV，人类免疫缺陷病毒；IgAN，免疫球蛋白 A 肾病；TB，结核病。

实践要点2.3.1.5：IgAN中评价的其他药物治疗（图25[115-120]）

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No documented evidence of efficacy
Rituximab	Not recommended	No documented evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	In a single RCT conducted in China, MMF with low-dose glucocorticoids was noninferior to standard-dose glucocorticoids for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d. There were significantly fewer glucocorticoid-related side effects in the combination-therapy arm.[1, 5]
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy.[2–5]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[6]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

图25|IgAN中评价的其他药物治疗。[1]Hou *et al.*[115],[2]Hogg *et al.*[116],[3]Frisch *et al.*[117],[4]Maes *et al.*[118],[5]Vecchio *et al.*[119],[6]Liu *et al.*[120]ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；IgAN，免疫球蛋白 A 肾病；MMF，吗替麦考酚酯；RCT，随机对照试验。

	Japanese IgAN	Chinese IgAN	Caucasian IgAN
Clinical practice	Performed routinely (often with pulsed glucocorticoids)	Not routinely performed	Not performed
Remarks	Multiple cohort studies,[1–5] including a large retrospective study with propensity matching,[5] report improved kidney survival following tonsillectomy. A single RCT failed to show a difference in eGFR at 1 year comparing tonsillectomy vs. tonsillectomy and pulsed glucocorticoids, and no longer term data are available from this study.[6]	Inconsistent data from small retrospective cohort studies and a small single-center RCT	Very few data available in this population. Available data do not support the efficacy of tonsillectomy as a treatment for IgAN in Caucasian patients

图26局部使用扁桃体切除术治疗IgAN。[1]Yang *et al.*[124],[2]Kawasaki *et al.*[123],[3]Hotta *et al.*[121],[4]Reid 等人[95]，[5]Hirano 等人[125]，[6]Kawamura *et al.*[122]eGFR，估计肾小球滤过率；IgAN，免疫球蛋白 A 肾病；RCT，随机对照试验。

实践要点2.3.1.6：IgAN中的扁桃体切除术：

- 在高加索患者中，不应进行扁桃体切除术治疗IgAN。
- 一些国家 IgAN 患者复发性扁桃体炎治疗指南建议行扁桃体切除术。
- 来自日本的多项研究报告了单独扁桃体切除术或联合脉冲式糖皮质激素治疗后肾脏存活率改善以及血尿和蛋白尿的部分或完全缓解（图26[95,121–125]；补充表S7[95,121–124]）。

2.4 特殊情况

实践要点2.4.1：IgAN伴肾病综合征：

- 罕见情况下，IgAN患者表现为肾病综合征（包括水肿以及低白蛋白血症和肾病范围蛋白尿 > 3.5 g/日）。
- 在这些情况下，系膜 IgA 沉积可能与与光学和电子显微镜特征相反，与类似 MCD 的足细胞病一致。
- 目前尚不清楚这是 IgAN 的特异性足细胞病变变体还是 IgAN 患者存在MCD。
- 肾活检显示系膜 IgA 沉积以及光学和电子显微镜检查与 MCD 一致的患者应按照 MCD 指南进行治疗（第5章）。
- 对于肾活检同时具有系膜增生性肾小球肾炎 (MPGN) 特征的肾病综合征患者，尽管采取了最大程度的支持治疗，但仍应采用与 CKD 进展高风险患者相同的方式进行治疗。
- 在 IgAN 中也可能观察到不伴肾病综合征的肾病范围蛋白尿，这通常反映了共存的继发性局灶节段性肾小球硬化 (FSGS)（例如，肥胖、不受控制的高血压）或发生广泛肾小球硬化和肾小管间质纤维化。

实

践要点2.4.2：IgAN伴AKI：

- IgAN 患者可在重度可见血尿的背景下发生AKI，通常与上呼吸道感染相关。对于血尿停止后2周内肾功能未改善的患者，应考虑重复进行肾活检。伴有可见血尿的 AKI 的即刻治疗应侧重于 AKI 的支持治疗。
- 由于 RPGN 伴广泛新月体形成（通常无可见血尿），IgAN也可能出现*新发* AKI 或在其自然病程中出现AKI。在无可见血尿且排除 RPGN 的其他原因（例如，抗中性粒细胞胞浆抗体 [ANCA] 相关血管炎 [AAV]、抗肾小球基底膜 [GBM] 疾病）和可逆性原因（例如，药物毒性、并发肾前和肾后原因）的情况下，应尽快进行肾活检。

练习点2.4.3：IgAN与RPGN：

- 快速进展的 IgAN 定义为±eGFR在≤3个月内下降50%，其中排除了 RPGN 的其他原因（例如AAV、抗 GBM 疾病）和可逆性原因（例如药物毒性、常见的肾前和肾后原因）。
- 在这些病例中，肾脏活检至关重要，通常会显示系膜和毛细血管内细胞过多，以及高比例的肾小球受到新月体影响并伴有局灶性坏死区域。
- 在血清肌酐 (SCr) 未伴随变化的情况下，肾活检中存在新月体并不构成快速进展的IgAN；然而，这些患者需要密切随访，以确保及时发现 GFR 的任何下降。如果发生这种情况，可考虑进行第二次肾活检。

- 应根据 AAV 指南（第9章）为快速进展的 IgAN 患者提供环磷酰胺和糖皮质激素治疗。
- 在第1章中讨论了应伴随免疫抑制的预防措施。
- 没有足够的证据支持使用利妥昔单抗治疗急进性 IgAN。

实践要点2.4.4：IgAN和妊娠计划：

- IgAN 是一种以青壮年为主的疾病，所有有生育能力的妇女均应酌情提供孕前咨询。
- 孕前咨询应包括停止肾素-血管紧张素系统 (RAS) 阻断的讨论。受孕前应使用其他天然抗高血压药物优化血压控制。
- 在最大程度支持治疗后仍有进展性 CKD 高风险的女性患者中（建议2.3.1.1），在受孕前进行优化免疫活性和减少蛋白尿的免疫抑制试验可能优于妊娠期间紧急启动免疫抑制。

操作要点2.4.5：儿童IgAN：

一般注意事项

- 出于本实践点的目的，将儿童定义为年龄 < 18岁的儿童。众所周知，青春期后儿童在某些方面的治疗过程和反应可能与 IgAN 成人相似，但目前尚无充分的数据
  建议将其作为 IgAN 成人患者进行管理。
- 可见血尿在儿童中比成人中更常见，这可能解释了儿童早期诊断的原因。[126]
- 诊断时，儿童的 eGFR 通常高于成人，尿蛋白排泄量低于成人，血尿多于成人。[127]

儿童肾活检

- 通常在出现症状（血尿、蛋白尿、正常C3）时进行肾活检，以确诊（并排除其他诊断）并评估炎症/坏死的程度。
- 在儿童 IgAN 的肾活检中，炎症、系膜和毛细血管内细胞过多往往比成人更常见[128–131]。

治疗

- 有强有力的证据表明 RAS 阻断对儿童有益。[132]所有 IgAN 儿童和

  蛋

  白尿 > 200 mg/日或PCR > 200 mg/g(> 20 mg/mmol) 应接受 ACEi 或 ARB 阻断治疗，建议低钠饮食，并采取最佳生活方式和血压控制（收缩压 [SBP] < 年龄、性别和身高的第90百分位数）。
- 众所周知，成人和儿童使用免疫抑制治疗 IgAN 不同，在儿童中，免疫抑制剂的使用更广泛，尤其是糖皮质激素的使用。但是，缺乏 RCT 和专家共识驱动的适应症。
- 主要来自回顾性研究的证据表明，糖皮质激素治疗（加二线免疫抑制）可改善肾脏存活率。[126,133]
- 蛋白尿 > 1 g/日或PCR > 1 g/g（100 mg/mmol）和/或系膜细胞过多，大多数儿科肾病学家从诊断时开始除 RAS 阻断外还将接受糖皮质激素治疗。尚未确定治疗持续时间，但通常采用4周 1–2 mg/kg/d 口服泼尼松龙（或等效药物），随后在4–6个月内隔日逐渐减量。还使用了包括静脉注射甲泼尼龙的方案。[127,128,130,134]
- 除糖皮质激素外使用非糖皮质激素免疫抑制剂的证据很少，但在更严重的病例中可考虑这种方法。
- 对于成人，可能会发现伴有 MCD 的IgAN，应将其视为类固醇敏感性肾病综合征（SSNS；第4章）。
- 与成人一样，快速进展型 IgAN 儿童的结局较差，尽管证据有限，但仍应对该亚组提供糖皮质激素（通常为甲泼尼龙冲击）和环磷酰胺治疗。[128,130,135]

随访

- 针对蛋白尿£200 mg/日 (£400 mg/1.73 m^2/d) 或PCR£200 mg/g(£0.2 g/g[£20 mg/mmol])。
- 目标是使年龄、性别和身高的SBP < 第90百分位数。
- 即使在完全缓解后，也应继续随访患者，因为患者在多年后仍可能复发。[136]

研究建议

以下领域是未来改善 IgAN 患者治疗和结局研究的重中之重：

- 风险分层：这对患者评估和临床试验设计都很重要。
- 国际 IgAN 预测工具应为：
  - 在未纳入原始队列的其他人种人群中进行了验证

- 进一步开发，以便在肾活检后和随访期间连续预测进展风险
- 评价与特定治疗反应的关系

- 评价尽量减少或避免全身性糖皮质激素暴露的治疗策略：
  - 需要新获得的数据来阐明新型疗法在非免疫抑制性综合支持治疗中的作用。3期PROTECTstudy(NCT03762850)正在评估sparsentan在IgAN中的抗蛋白尿和肾脏保护作用，IgAN是一种新型的双效血管紧张素II和内皮素a型受体拮抗剂。还正在进行试验，以评价钠-葡萄糖协同转运蛋白-2抑制剂(SGLT2i)对非糖尿病肾病患者肾脏和CV结局的影响(NCT03036150、NCT03594110)。[137,138]在所有这些研究完成之前，不建议在无糖尿病的情况下使用SGLT2i治疗IgAN。
  - 我们需要更好地理解MMF和羟氯喹在不同人种IgAN管理中的应用，以及临床疾病严重程度。
  - 在一项IIb期研究中，在150例IgAN患者中评估了布地奈德的靶向释放制剂(TRF)（一种在回肠末端局部释放并发挥作用的糖皮质激素）[139]。据报告，这种方法可显著减少蛋白尿，并且与全身作用的糖皮质激素相比具有优势，治疗中出现的不良事件更少。目前正在一项III期研究中评估TRF-布地奈德的安全性和疗效。
  - 正在评估的其他治疗策略包括抑制补体系统（凝集素[MASP-2]、替代[因子B]和最终共同[C5]途径）以及抑制B细胞活化和存活（通过阻断TNF家族的B细胞活化因子[BAFF]和增殖诱导配体[APRIL]向B细胞的信号转导）。
- 血清、血浆、尿液和/或尿液的鉴别和验证或肾脏生物标志物，以告知：
  预后、
  - 治疗选择，
  - 监测治疗反应，
  - 基础生物学：继续进行跨大陆综合研究，以确定影响不同人种疾病表型的遗传和环境因素。

免疫球蛋白A血管炎

IgA血管炎(IgAV)，以前称为Henoch–Schönlein紫癜，是一种以受累组织血管内IgA沉积为特征的血管炎。IgAV通常影响皮肤、关节、肠和肾脏的小血管。罕见情况下，可影响肺和中枢神经系统。是小儿最常见的一种血管炎。当IgAV发生于<16岁的儿童时，通常具有自限性。成人可能患有更严重和复发性疾病。IgAV累及肾脏的组织病理学

与肾脏限制性疾病IgAN中观察到的结果无法区分。本章概述了成人IgAV相关肾炎(IgAVN)的管理指导，并为1-18岁儿童提供了实践点。必须承认，IgAVN的证据基础极其有限，因此严重依赖将数据从IgAN外推至IgAVN，尽管我们对这2种疾病如何相关仍无明确了解。我们对如何治疗肾外器官受累，尤其是胃肠道血管炎和肺出血未提出具体建议，这些疾病可能危及生命，无论是否累及肾脏，均需要免疫抑制治疗。

2.5 诊断

操作要点2.5.1：诊断免疫球蛋白A血管炎(IgAV)的注意事项：

- 与儿童不同，国际上尚无一致的成人IgAV诊断标准，但通常根据儿童标准进行IgAV的临床诊断。[140,141]
- 对于具有IgAV典型血管炎性皮疹的成人，应在符合持续性和/或显著肾炎、RPGN、蛋白尿>1 g/日和/或肾功能受损特征的情况下进行肾活检。
- 评估所有IgAV成人患者的次要原因。
- 通过适合年龄和性别的筛查试验，评估所有IgAV成人患者的恶性肿瘤。

2.6 预后

实践要点2.6.1：IgAV预测的考虑因素：

- 来自有限数量的小型登记研究的回顾性数据已确定，不受控制的高血压和就诊时的蛋白尿量以及随访期间的高血压和平均蛋白尿是IgAV成人肾脏结局不良的预测因素[142–144]。
- 牛津分类尚未针对IgAV进行验证。
- 国际IgAN预测工具不适用于IgAV的预测。

2.7 治疗

2.7.1 IgAV中肾炎的预防

建议2.7.1.1：我们建议在孤立性肾外IgAV(1B)患者中不要使用糖皮质激素预防肾炎。

该建议高度重视证明使用糖皮质激素存在风险的中等质量证据，在IgAV中预防肾炎没有额外获益。

关键信息

平衡危害。由于缺乏获益和糖皮质激素相关的明确风险，工作组无法支持其用于预防 IgAV 肾炎。

证据质量。该建议基于 RCT 的中等质量证据。在 IgAV 患者中比较泼尼松与安慰剂或支持治疗的 RCT 尚未报告关键和重要结局，如全因死亡率、肾衰竭和完全缓解。有中等质量的证据表明肾病的发生和持续，但由于研究限制（分配隐藏不充分）和不精确（事件非常少）而存在问题（补充表S8 [145–150]）。

价值和偏好。工作组认为大多数患者对该药物的潜在毒性评价较高，且缺乏任何明确获益。

资源使用和成本。无

实施考虑。无

依据

目前尚无关于预防 IgAV 成人发生 IgAVN 策略有效性的 RCT 数据。然而，在儿童中有大量证据表明，在肾外 IgAV 中预防性使用糖皮质激素不会降低肾脏受累的发生率。在一项352例 IgAV 患儿的 RCT 中，疾病发作后12个月，早期泼尼松龙治疗并未降低蛋白尿的患病率。[145]在171例儿童中重复了这一发现，表明早期使用泼尼松龙并不能预防肾炎的发生。[150]对5项 RCT 进行了荟萃分析，其中在介绍后6个月和12个月检查了789例儿童使用短期糖皮质激素（2–4周）预防持续性肾炎的作用，得出的结论是，在入院前使用糖皮质激素进行此类治疗对持续性肾炎的发生没有预防作用。[146]

实践要点2.7.1.1：治疗所有无 RPGN 的 IgAV 相关肾炎 (IgAVN) 患者的注意事项：

- 评估心血管风险，并在必要时开始适当的干预。
- 酌情提供生活方式建议，包括戒烟、控制体重和锻炼相关信息。
- 未显示特定饮食干预可改变 IgAVN 的结局。
- 治疗达到国家商定的血压目标。KDIGO建议治疗至 SBP 目标值 < 120 mmHg（使用标准化常规血压测量值测量）（图8）。
- 如果蛋白尿 > 0.5 g/日，则使用最大耐受剂量的 ACEi 或 ARB 进行治疗。
- 提供参与临床试验的机会（如果有）。

2.7.2 尽管接受了最大程度的支持治疗，但仍存在进展性 CKD 高风险的 IgAVN 患者

这些患者被定义为持续性 UPE 患者 > 1 g/日，尽管接受最大耐受剂量 RAS 阻断治疗至少3个月，且已达到第1章中描述的推荐 BP 目标至少3个月。

实践要点2.7.2.1：尽管进行了最大程度的支持治疗，但仍存在进展性 CKD 高风险的 IgAVN 患者的治疗考虑因素：

- 没有足够的证据支持使用牛津分类 MEST-C 评分来确定 IgAVN 患者是否应开始免疫抑制治疗。
- 肾活检中新月体的存在本身并不是免疫抑制开始的自动指征。
- 在考虑免疫抑制的所有患者中，应与患者详细讨论每种药物的风险和获益，并认识到不良治疗作用更多还原可能发生在eGFR < 50 mL/min/1.73 m ^{2}的患者中。
- 在那些希望尝试免疫抑制治疗的患者中，糖皮质激素的治疗如上所述用于IgAN。

2.8 特殊情况

操作要点2.8.1：IgAV和RPGN：

- 应在个体患者水平评价免疫抑制的潜在风险和获益，并与患者进行讨论。
- 同意治疗的患者应按照 AAV 指南进行治疗（第9章）。
- IgAV 伴 RPGN 以及其他 IgAVN 可能与显著的肾外受累（肺、胃肠道和皮肤）相关，这可能需要其他免疫抑制策略。
- 现有数据不足以确定 IgAVN 与 RPGN 血浆置换的疗效。然而，非对照病例系列描述了在糖皮质激素治疗的基础上加用血浆置换对 IgAV 危及生命或器官的肾外并发症患者加速康复的潜在作用。[151]临床医生参考了美国单采血浆学会关于 IgAV 血浆置换建议的指南。[152]

2.8.1 儿童 IgAV 相关肾炎

练习点2.8.1.1：出于该练习点的目的，将儿童定义为 < 18岁的儿童。众所周知，青春期后儿童在某些方面可能具有与 IgAN 成人，但目前尚无充分数据建议将其作为 IgAN 成人进行管理。

欧洲联盟倡议的结果，最近公布了儿童 IgAVN 的管理适应症。[140]简报：

- 没有数据支持在 IgAV 儿童中使用糖皮质激素预防肾炎，但有轻度或无肾脏受累证据。[153,154]
- > 10岁儿童更常表现为非肾病范围的蛋白尿和肾功能受损，它们可能遭受更多的慢性组织学病变，导致活检延迟和治疗延迟超过30天。[155]
- 大多数将发生肾炎的儿童将在就诊后3个月内发生肾炎。‡6个月和最佳12个月（从首次出现全身性疾病起）需要进行尿液监测。
- IgAVN 伴持续性蛋白尿 > 3的儿童
  应使用 ACEi 或 ARB 治疗数月。应咨询儿科肾病学家。
- 对以下儿童应进行肾活检

  肾病范围蛋白尿、GFR受损或持续性中度（> 1 g/日）蛋白尿。
- 轻度或中度 IgAVN 患儿应口服泼尼松/泼尼松龙或静脉冲击甲泼尼龙。
  利
- 伴有肾病综合征和/或肾功能快速恶化的 IgAVN 儿童的治疗方法与伴有快速进展的 IgAN 儿童相同。

研究建议

- 应在 IgAVN 中验证牛津分类 MEST-C 评分和国家间 IgAN 预测工具。
- 与 IgAN 不同，目前 IgAVN 新型疗法的临床试验很少。BIOVAS试验（治疗非 ANCA 血管炎的生物制剂）可能是规模最大的，将在140例难治性血管炎（包括IgAV）患者（儿童和成人）中考察3种不同的生物制剂（英夫利西单抗、托珠单抗和利妥昔单抗），这些患者来自英国和爱尔兰的15家血管炎中心。
- 根据初步观察性数据，[156,157] 示
  提
  妥昔单抗的潜在获益，我们建议开展利妥昔单抗治疗 IgAV 的专门前瞻性RCT。
- 建议目前正在 IgAN 中评价的药物也应在成人和儿童 IgAVN 中进行安全性和有效性检测。

第三章：膜性肾病

本章对 > 18岁膜性肾病 (MN) 成人患者提出管理建议。来自儿科人群的数据极为有限，但在实践点3.4.4中提供了 MN 儿童管理的方法。

3.1 诊断

实践要点3.1.1：在肾病综合征和抗 PLA2R 抗体检测阳性的患者中，确认膜性肾病 (MN) 的诊断不需要肾活检。

在临床表现相符的患者中确诊 MN 对于指导治疗和治疗决策至关重要。肾脏活检通常被认为是诊断肾小球疾病的金标准；然而，对于MN，抗 PLA2R 抗体是一种生物标志物，可高准确度地确诊MN，且无活检相关风险，包括组织不足以进行结论性诊断、疼痛和出血。因此，肾活检应用于确定抗 PLA2R 抗体阳性患者的 MN 诊断之外的其他目的。有

目前支持使用抗 THSD7A 抗体代替活检作为 MN 诊断生物标志物的数据不足。在一项包括710例 MN 患者和1502例对照患者的9项研究的荟萃分析中，抗 PLA2R 抗体检测阳性诊断 MN 的灵敏度为0.78，特异性为0.99。[158]最近的一项单中心研究证实了该方法的高精度，灵敏度为64%，特异性为99%。[159]特异性的95%置信区间 (CI) 为0.96-1.0，与肾活检的诊断性能相当。在97例抗 PLA2R 抗体检测呈阳性、无继发性 MN 证据但接受了自体肾活检的患者中研究了肾活检诊断 MN 的附加价值[160]。所有活检的主要诊断均为 MN。在基线eGFR > 60 mL/min/1.73 m ^{2}的60例患者中，活检显示仅2例患者发生叠加糖尿病肾病或 FSGS，这些结果不影响患者护理或治疗。在37例 eGFR < 60 mL/min/1.73 m ^{2}的患者中，5例患者报告了其他结果，包括急性间质性肾炎 (n¼1)、糖尿病肾病 (n¼1)。急性肾小管坏死 (n¼1) 和FSGS(n¼2)伴细胞性新月体 (n¼1)。尽管未报告，但该信息可能影响治疗决策。最近

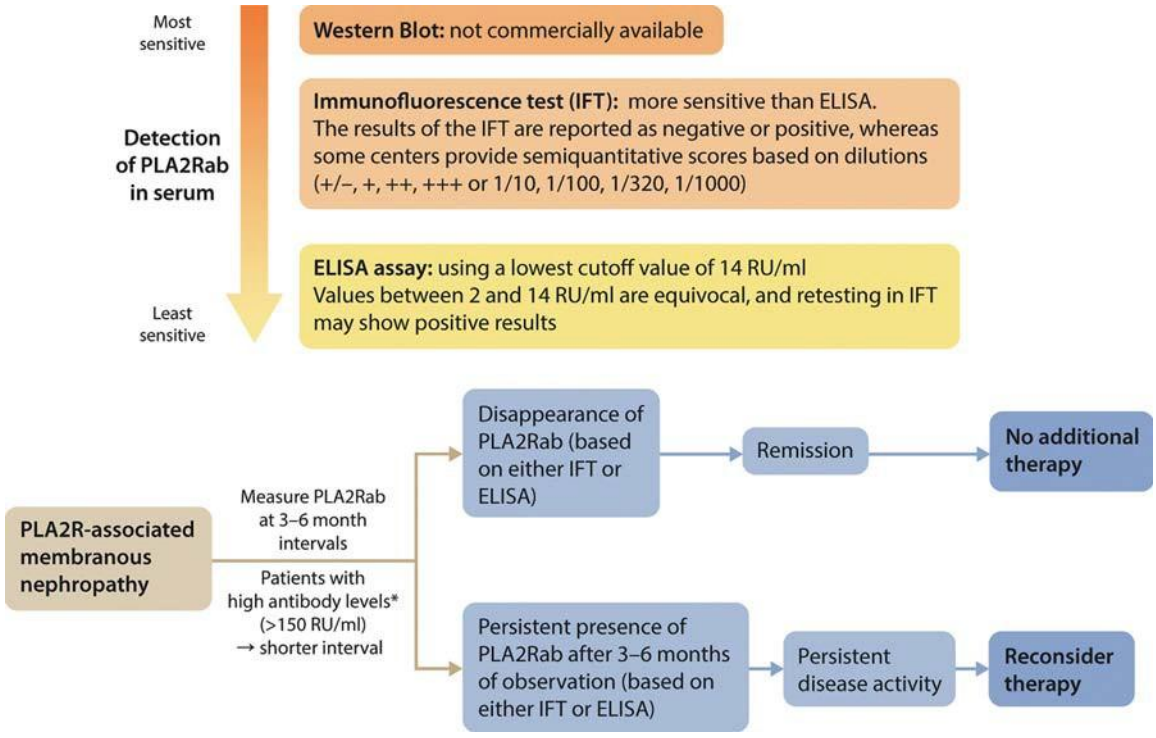


图27|抗 PLA2R 抗体检测在已知抗 PLA2R 相关 MN 患者中的使用和解释指南。*高滴度 (ELISA) 与自发缓解的可能性较低和对低剂量利妥昔单抗无应答的可能性较高相关。ELISA，酶联免疫吸附试验；PLA2Rab，抗 M 型磷脂酶 A2 受体的抗体。

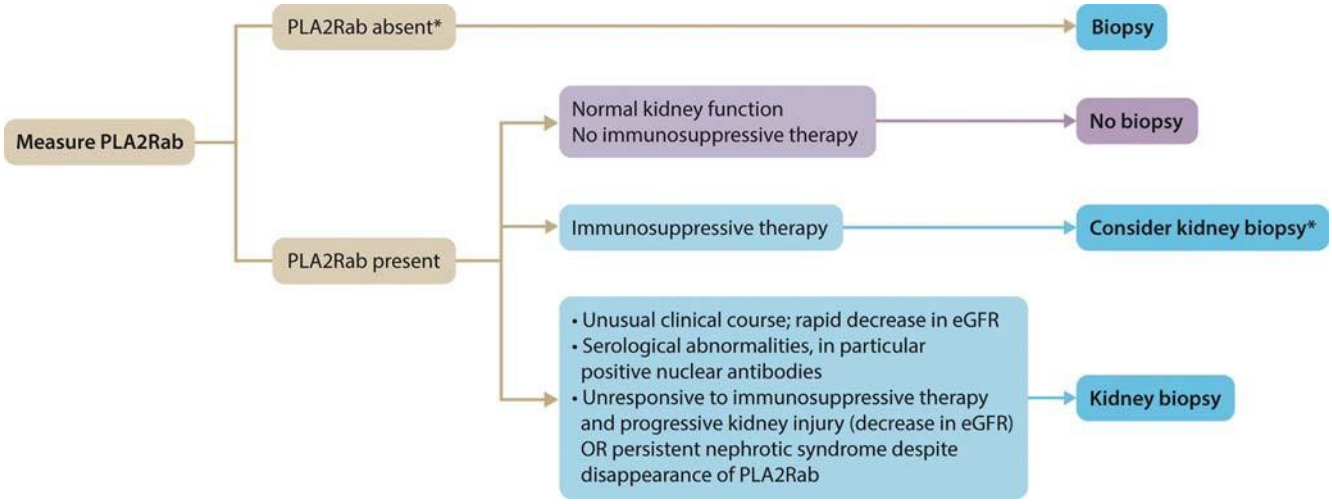


图28抗 PLA2R 抗体阳性的患者何时考虑肾活检。*在决定进行肾脏活检时，必须考虑活检的风险。该决定基于患者和医生的偏好。随着分子诊断的发展，这种进行肾脏活检的决定可以在不久的将来进行修订，这可以允许更好地预测结果，以便更个性化的医疗。eGFR，估算肾小球滤过率；PLA2Rab，抗 M 型磷脂酶 A2 受体抗体。

研究进一步证实了以下结论：在 *eGFR* 正常的抗 *PLA2R* 抗体–阳性患者中，肾活检不会改变原发性 *MN* 的诊断。[161]

关于抗 *PLA2R* 抗体检测的更多详细信息（图27）以及抗 *PLA2R* 抗体阳性患者何时考虑肾活检（图28）如下所示。在抗 *PLA2R* 抗体阴性的患者中，应进行肾活检和 *PLA2R* 抗原染色，这可能揭示抗 *PLA2R* 抗体相关的*MN*。这可能发生在血清酶–例如，由于低滴度，连接免疫吸附试验 (*ELISA*) 和免疫反应试验为假阴性。此外，有人认为 *MN* 早期可能不存在抗体，在肾脏中被捕获，并在长期随访后可检测到。

实践要点3.1.2：应对 *MN* 患者进行相关疾病评价，无论是否存在抗 *PLA2R* 抗体和/或抗 *THSD7A* 抗体（图29）。

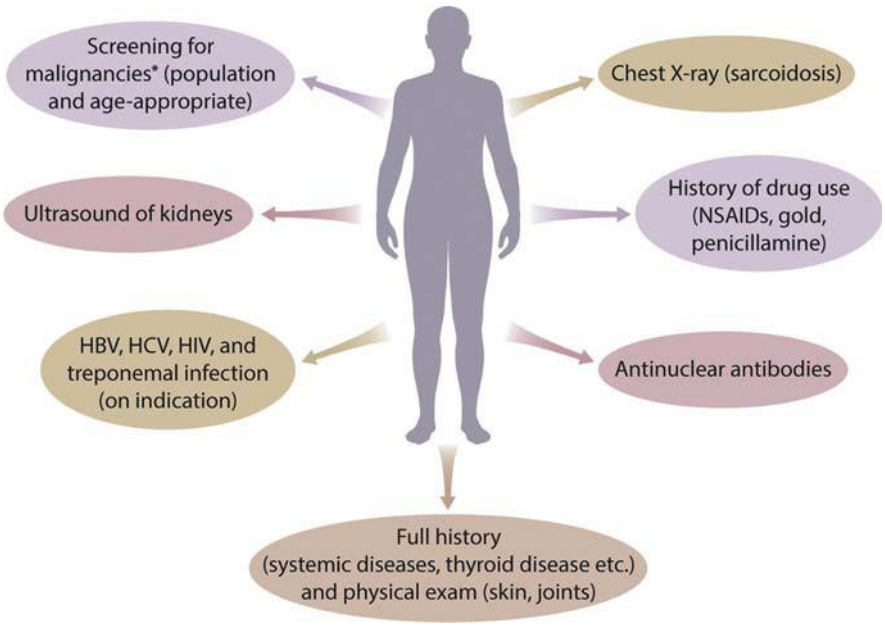


图29|MN患者相关疾病的评价。应评价 MN 患者的相关疾病，无论是否存在抗 PLA2R 抗体或抗 THSD7A 抗体。*每个国家各不相同；癌症筛查的诊断率不是很高，尤其是在年轻患者中。许多中心将进行胸部 X 线或计算机断层扫描 (CT)，寻找铁缺乏，并要求患者参加国家乳腺癌和结肠癌筛查项目；在 > 50-60岁的成年男性中进行前列腺特异性抗原 (PSA) 检测。HBV，乙型肝炎病毒；HCV，丙型肝炎病毒；HIV，人类免疫缺陷病毒；NSAID，
非甾体类抗炎药。

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and serum albumin >30 g/l OR • Normal eGFR, proteinuria <3.5 g/d or a decrease >50% after 6 months of conservative therapy with ACEi/ARB	• Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND • Not fulfilling high-risk criteria	• eGFR <60 ml/min/1.73 m^{2*} and/or proteinuria >8 g/d for >6 months OR • Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND at least one of the following: • Serum albumin <25 g/l† • PLA2Rab >50 RU/ml‡ • Urinary α_1-microglobulin >40 μg/min • Urinary IgG >1 μg/min • Urinary β_2-microglobulin >250 mg/d • Selectivity index >0.20§	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

图30评估进展性肾功能丧失风险的临床标准。eGFR和 PCR 用于常规临床护理。其他生物标志物可能并非在所有中心均可用；本表提供了有用生物标志物的概述。*大多数研究使用血清肌酐 (SCr) 值来指导管理，SCr值 > 1.5 mg/dL(133 mmol/l) 通常用于定义肾功能不全。eGFR值为60 mL/min/1.73 m^2（年轻成人的肾功能不全）。重要的是要认识到 eGFR 随年龄增长而降低，1.5 mg/dL(133 mmol/l) 的 SCr 值反映了60岁男性患者的 eGFR 为50 mL/min/1.73 m^2，60岁女性患者为37 mL/min/1.73 m^2。因此，当使用 eGFR 进行风险估计时，应考虑年龄。†应通过 BCP 或
免疫测定法。‡临界值未经验证。应每隔3-6个月测量一次抗 PLA2R 抗体，在基线时抗 PLA2R 抗体水平较高的患者中进行较短的间隔。随访期间抗 PLA2R 抗体水平的变化可能增加风险估计。抗 PLA2R 抗体的消失先于临床缓解，应导致避免额外的治疗。缺乏详细的数据。§选择性指数计算为 IgG 清除率/白蛋白清除率。ACEi，血管紧张素转换酶抑制剂；ARB，血管紧张素 II 受体阻滞剂；BCP，溴甲酚紫；eGFR，估计肾小球滤过率；IgG，免疫球蛋白G；PLA2Rab，抗 M 型磷脂酶 A2 受体抗体。

3.2 预后

实践要点3.2.1：在 MN 患者中，使用临床和实验室标准评估进行性肾功能丧失的风险（图30）。

由于自发性缓解在 MN 中相对常见，并且免疫抑制治疗具有不良反应，因此在决定是否以及何时实施免疫抑制治疗之前，评估肾功能进行性丧失的风险非常重要。图30显示了可用于将患者分为低、中、高和极高肾功能进行性丧失风险类别的临床标准。

MN 风险评估存在注意事项。在大多数患者中，在使用最大抗蛋白尿治疗的同时，等待6个月自发缓解是合理的。高水平蛋白尿、抗 PLA2R 抗体或低分子量蛋白尿应导致在6个月内重新评价。肾功能恶化或重度无反应 NS 的患者可考虑立即进行免疫抑制治疗，因为在任何不到24个月的时间内记录到 eGFR 降低20%的患者进展[的可能]性为84%。162文献调查显示，保守治疗6个月后蛋白尿 > 4 g/日的患者自发缓解的几率为45%，蛋白尿患者自发缓解的几率为34%。[163] > 8 g/日，持续6个月以上，[164]a 25%–30%

尽管低分子量蛋白的尿排泄量较高，但仍有的几率，[165]在抗 PLA2R 抗体水平上三分位数的患者中有17%的几率，[166]在抗 PLA2R 抗体水平 > > 275 RU/ml [167]（A. Rousseau，定期沟通，2019年01月15日）。目前还没有一个模型综合了所有这些临床考虑，但我们建议在临床实践中，将风险作为因素的组合来考虑是有用的（例如，低抗体滴度患者的高蛋白尿可能与高抗体滴度患者的高蛋白尿判断不同）。更重要的是疾病轨迹；因此，应考虑上述任何参数的变化。

3.3 治疗

实践要点3.3.1：原发性 MN 患者的治疗考虑：

- 所有原发性 MN 伴蛋白尿的患者均应接受最佳支持治疗。
- 免疫抑制治疗应仅限于被认为有进展性肾损伤风险的患者（图31）。

实践要点3.3.2：MN、蛋白尿<3.5 g/日、血清白蛋白>30 g/L（溴甲酚紫 [BCP] 或免疫测定法）和 eGFR >60 mL/min/1.73 m^2的患者无需免疫抑制治疗。

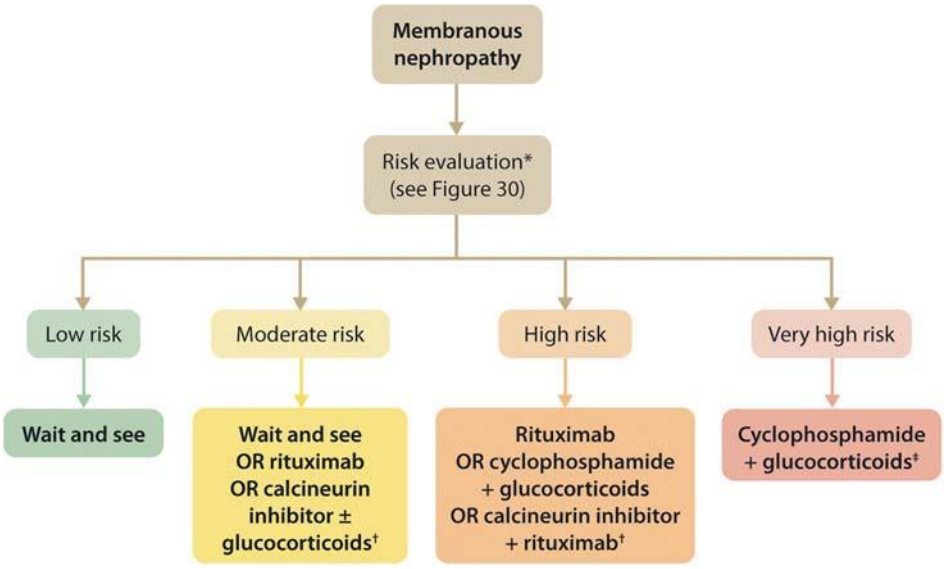


图31|基于风险的 MN 治疗。*风险评估的详细描述参见规范点3.2.1和图30。†钙调磷酸酶抑制剂 (CNI) 单药治疗被认为疗效较差。CNI治疗6-12个月，快速停药与高复发率相关。然而，可考虑在 eGFR 正常和中度进展风险的患者中使用，因为其中许多患者将发生自发缓解。使用 CNI 将缩短蛋白尿期。在进展风险高的患者中，建议在 CNI 治疗6个月后加用利妥昔单抗，CNI治疗后抗 PLA2R 抗体消失的患者可能除外。‡没有充分的证据表明使用标准剂量的利妥昔单抗可预防肾衰竭的发生。如果 eGFR 低于50 mL/min/1.73 m^2，环磷酰胺的剂量应减半。在不耐受或不能再使用环磷酰胺的患者中，可提供利妥昔单抗。建议咨询专家中心。eGFR，估计肾小球滤过率；MN，膜性肾病；PLA2R，M型磷脂酶 A2 受体。

MN、*eGFR*正常和非肾病蛋白尿患者通常具有良好的结局（见下文）。这些患者发生血栓栓塞并发症的风险也很低，症状负担也很低（如水肿）。可采用保守疗法治疗（第1章）。*MN*、*eGFR*正常和非肾病性蛋白尿患者的血清白蛋白水平通常 > 30 g/L。在*MN*、*eGFR*正常、非肾病性蛋白尿和低血清白蛋白水平的患者中，应排除低白蛋白血症的其他原因。

尚无 *RCT* 比较接受和未接受免疫抑制治疗的 *MN* 和非肾病性蛋白尿患者的结局。然而，临床经验和队列研究的数据显示，尽管未接受免疫抑制治疗，但持续非肾病 *MN* 患者的肾脏结局良好。因此，免疫抑制治疗增加了风险，而无潜在获益。

可通过发生 *NS* 或 *eGFR* 降低来识别疾病进展，这在随访期间很容易发现。基线时高水平抗 *PLA2R* 抗体的存在与发生 *NS* 的风险较高相关。

实践要点3.3.3：*MN*、肾病综合征和 *eGFR* 正常的患者不需要免疫抑制治疗，除非至少存在一个疾病进展的风险因素或已发生肾病综合征的严重并发症（例如，*AKI*、感染、血栓栓塞事件）。

许多原发性 *MN* 和 *NS* 患者会出现自发缓解。没有比较 *MN* 患者结局的*RCT*，也没有 *MN* 风险因素伴和不伴免疫抑制治疗的进展。然而，纳入 *MN* 患者甚至至少有一个风险因素的 *RCT* 和队列研究的数据支持此类患者的有利结局。这些研究显示了许多 *MN* 患者的有利结局，在高达*40%*或更多患者中发生了自发缓解。如果不存在风险因素且无明显 *NS* 并发症，则使用免疫抑制治疗会增加风险，几乎无获益（如果有）。将患者分类为低、中、高或极高的进行性肾功能丧失风险（实践要点3.2.1），将允许更好地选择更可能出现自发缓解的患者。

建议3.3.1：对于具有至少一种疾病进展风险因素的 MN 患者，我们建议使用利妥昔单抗或环磷酰胺和隔月糖皮质激素治疗6个月，或基于 CNI 的治疗‡6个月，治疗选择取决于风险估计（图30和图31）*(1B)*。

该建议对高风险患者预防进展性肾衰竭以及减少并发症和 NS 风险具有相对较高的价值，对免疫抑制治疗相关的副作用和不便具有相对较低的价值。治疗选择取决于患者特征、药物可用性、药物疗效、患者、医生、社会偏好、报销政策和每种药物的特定副作用特征。基于风险的治疗

Cyclophosphamide (cyclical)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d in months 1, 3, and 5 • Cyclophosphamide 2.5 mg/kg/d in months 2, 4, and 6‡
Cyclophosphamide (continuous)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d every other day in months 1–6, with taper thereafter • Cyclophosphamide 1.5 mg/kg/d in months 1–6‡
Rituximab	• Rituximab 1 g i.v. administered twice within 2 weeks* • Rituximab 375 mg/m^2 given 1–4 times at weekly intervals
Tacrolimus	• Tacrolimus 0.05–0.1 mg/kg/d, target trough level 3–8 ng/ml (3.7–9.9 nmol/l), duration 12 months†
Cyclosporine	• Cyclosporine 3.5 mg/kg/d, target trough level 125–225 ng/ml (104–187 nmol/l)†

图32|MN患者常用的治疗方案。未讨论吗替麦考酚酯。KDIGO 2012指南反对在 MN 患者中使用 MMF 单药治疗。这仍然成立，并且是基于1项 RCT 的结果。[172]在该36例患者的研究中，MMF单药治疗12个月未增加缓解率 (37%vs. 41%)。MMF联合糖皮质激素，疗效更佳。小型 RCT 比较了 MMF 和糖皮质激素与烷化剂[173,174]或CNI [168,175]。在这些研究中，随访时间相对较短，缓解率相当。一项使用历史对照并比较 MMF 与环磷酰胺的研究也报告了相似的缓解率。然而，MMF治疗患者在随访24个月内的复发率明显更高。[176]更详细的评估显示，MMF不太可能发生免疫缓解。[177]MMF的剂量可能是最相关的变量；LN研究使用了更高的剂量 (3 gvs. 2g)，SSNS患者中，药物浓度越高，患者的复发率越低。[178]注：泼尼松和泼尼松龙等效，使用剂量相同，均已用于RCT，具体取决于来源国。本指导原则中的所有后续"泼尼松"均指泼尼松或泼尼松龙。除非另有说明，否则"糖皮质激素"的所有后续用途均指泼尼松或泼尼松龙。‡近期研究使用了i.v.环磷酰胺。这些研究纳入了 eGFR 维持的患者。尚无评价环磷酰胺静脉给药对肾脏终点影响的RCT。使用i.v.环磷酰胺的较早RCT（包括 eGFR 恶化的患者）结果为阴性。[170,171]在 eGFR 正常、应使用环磷酰胺最低可能累积剂量的患者（既往使用环磷酰胺、希望生育的患者）或在无法获得p.o.环磷酰胺的国家中可考虑静脉注射环磷酰胺。*对于持续NS、eGFR稳定的患者，考虑在6个月后重复治疗，尤其是抗 PLA2R 抗体仍为阳性的患者。†环孢素和他克莫司通常与泼尼松联合给药，剂量为 10 mg/日。4个月后，如果无缓解，则退出；12个月后，考虑逐渐减量至较低水平。很少有试验比较 CNI 治疗的剂量和持续时间。Yuan *et al.*比较了他克莫司和泼尼松治疗6个月与24个月。[169]6个月后的缓解率相当 (18/20 vs 18/22)，但在接受6个月治疗的18例患者中仅9例患者与接受24个月治疗的18例患者中观察到24个月后的持续缓解。一项荟萃分析证实了高缓解率和高复发率。这些发现可以与患者讨论，同时同意治疗的持续时间。MN，膜性肾病；PLA2R，M型磷脂酶A2 受体。

算法如图31所示。常用治疗方案详见图32[168–178]。

关键信息

*平衡危害。*许多 *MN* 和 *NSN* 患者会出现自发缓解。任何免疫抑制治疗均与风险相关；因此，免疫抑制治疗仅适用于主诉充分和/或有 *NS* 风险（如水肿、感染、血栓事件、肾衰竭进展）且自发缓解可能性较低的住院患者。*RCT*和队列研究表明，利妥昔单抗和 *CNIs* 可增加完全缓解率和部分缓解率。与环磷酰胺相比，这些药物的获益副作用特征支持其作为 *MN* 患者的初始治疗并维持肾功能。*CNI*治疗后的高复发率是一个值得关注的原因，这些药物单药治疗仅适用于具有中度疾病进展风险的患者。烷化剂不仅可提高缓解率，最重要的是，还可在很大程度上降低肾衰竭风险。烷化剂是一种毒性药物，经常发生严重的短期和长期副作用。尽管证据质量中等，但毒性特征证明

基

于环磷酰胺的免疫抑制治疗应仅限于高风险患者。[179]环磷酰胺优于苯丁酸氮芥。支持环磷酰胺优于苯丁酸氮芥的证据并不有力，但1项 *RCT* [180] 和几项队列研究表明，环磷酰胺的副作用较少。此外，在 *CKD* 患者中，通常需要调整苯丁酸氮芥的剂量和治疗持续时间，这可能解释了使用该药物时观察到的缓解率较低。[181,182]

*证据质量。*ERT基于 *RCT* 评价了证据质量。由于偏倚风险严重且未设盲，认为 *RCT* 中使用口服烷化剂与安慰剂/无治疗或糖皮质激素相比的证据质量为中等（补充表S9 [162、183–191]）。烷化剂是在评价全因死亡率和肾衰竭等关键结局的试验中研究的唯一药物。

利妥昔单抗或 *CNIs* 的 *RCT* 仅评价缓解和副作用的结局。

对于利妥昔单抗，评价利妥昔单抗治疗特发性膜性肾病 *(GEMRITUX)RCT* 检查了使用利妥昔单抗 + 支持疗法与单独支持疗法的比较（补充表S10 [167,192]）。以下

利妥昔单抗的膜性肾病试验 (*MENTOR*) 试验比较了利妥昔单抗与环孢素。对于疗效结局，如完全和/或部分缓解，由于存在严重不精密度，证据质量分别被视为低[167]或中等[193]。由于非常严重的不精密度（*CI*较宽，表明效果的确定性较低；补充表*S11* [192,193]），感染等结局的评估质量较低。

与安慰剂、无治疗、糖皮质激素或烷化剂相比，检查 *CNI* 使用的 *RCT* 的证据质量被认为非常低，因为存在提示明显获益和危害的不精密度和宽*CI*，以及临床结局随访不充分（全因死亡率、肾衰竭；补充表 *S12* 和补充表*S13* [162,168]，[184、188、192、192a、194–202]）。充分随访完全缓解的试验存在非常严重的研究局限性和关于偏倚风险的非常严重的问题，包括参与者和研究者未设盲、结局评估者设盲不明确以及参与者很少和仅纳入摘要出版物。

在罕见疾病中，尤其是具有严重、客观临床结局（如死亡率或肾衰竭）的疾病，证据不能仅限于 *RCT* 的数据。因此，工作组将非 *RCT* 和队列研究的信息作为证据基础的一部分。工作组强调需要使用风险因素评价，这能够以合理的准确性识别高风险患者（实践要点 3.2.1）。基于 *RCT* 和队列研究，有强有力的证据表明烷化剂可降低肾衰竭的风险。有中等质量的证据表明，当根据限制性治疗策略使用时，烷化剂对记录肾功能恶化的患者有效。没有证据表明利妥昔单抗或 *CNI* 可降低肾衰竭的风险。有中等质量的证据表明利妥昔单抗或 *CNI* 可增加完全缓解率和部分缓解率。有证据表明，完全缓解（中等质量）和部分缓解（低质量）可作为 *NS* 患者研究的替代终点。有中等质量的证据表明，与利妥昔单抗或 *CNI* 相比，烷化剂具有更频繁和更严重的副作用。使用 *CNIs* 与高复发率相关。有中等质量的证据表明，与 *CNI* 相比，利妥昔单抗治疗后缓解更持久。

*价值和偏好。*免疫抑制治疗为与副作用相关。可能具有有利临床病程（实践点 3.2.1）或更关注免疫抑制剂不良反应的患者将更有可能拒绝此类治疗。相反，出现 *NS* 严重主诉或 *NS* 并发症（例如血栓栓塞事件、感染、*AKI*）的患者更可能偏好治疗。利妥昔单抗和 *CNI* 的副作用比环磷酰胺少且不太严重。因此，与环磷酰胺治疗相比，大多数医生和患者将更喜欢利妥昔单抗或 *CNI* 初始治疗。肾脏发育治疗失败是 *MN* 最常见和最严重的并发症。肾衰竭患者可通过肾脏替代治疗存活。然而，这种疗法与高发病率和死亡率相关。而且，大多数肾衰竭患者会偏好肾移植，这将导致终生暴露于免疫抑制药物。因此，根据工作组的判断，与仅保守治疗相比，大多数知情良好的肾衰竭（极高风险）患者将选择环磷酰胺治疗。

治疗开始的时间、药物类型和治疗持续时间取决于风险估计、患者特征、患者和医生偏好、报销政策和社会观点（成本和药物可用性）。

*资源使用和成本。*免疫抑制剂治疗的成本较高，包括治疗、监测和副作用管理。肾脏替代治疗与免疫抑制剂相比，生活质量较低，费用较高，副作用相似甚至更多。在一定程度上，免疫抑制治疗可预防进行性肾功能丧失和肾衰竭，从医疗保健系统的角度来看，这种建议可能具有成本效益。在预计病程平稳的患者中，成本效益较低。在中度风险患者中，治疗的副作用将在很大程度上促成成本。因此，在这些患者中，副作用较少的药物将更具成本效益。不同国家和地区的药物可用性不同。

*实施考虑。*主诉或并发症为 *NS* 或有发生肾衰竭风险的 *MN* 患者可能从免疫抑制治疗中获益。这适用于所有患者，与性别和人种无关。因此，该建议适用于所有性别和人种的患者。

依据

该建议替代 *KDIGO 2012* 推荐。虽然承认烷化剂在预防肾衰竭方面的疗效已得到证实，但目前的建议更多地考虑了与使用这些药物相关的严重短期和长期副作用。医生和患者尤其担心长期恶性肿瘤风险。[203]因此，首选有效的替代药物。现在引入基于利妥昔单抗和 *CNI* 的治疗作为合适的替代方案。尽管缺乏利妥昔单抗或 *CNIs* 预防肾衰竭的直接证据，但工作组重视这些药物显示高缓解率的研究结果，并认识到持续缓解与良好肾脏结局的相关性。在 *eGFR* 降低的患者中，仅证实烷化剂有益。

实践要点3.3.4：治疗开始后6个月时抗 *PLA2R* 抗体水平的纵向监测可能有助于评价 *MN* 患者的治疗反应，并可用于指导治疗调整（图33[193]）。

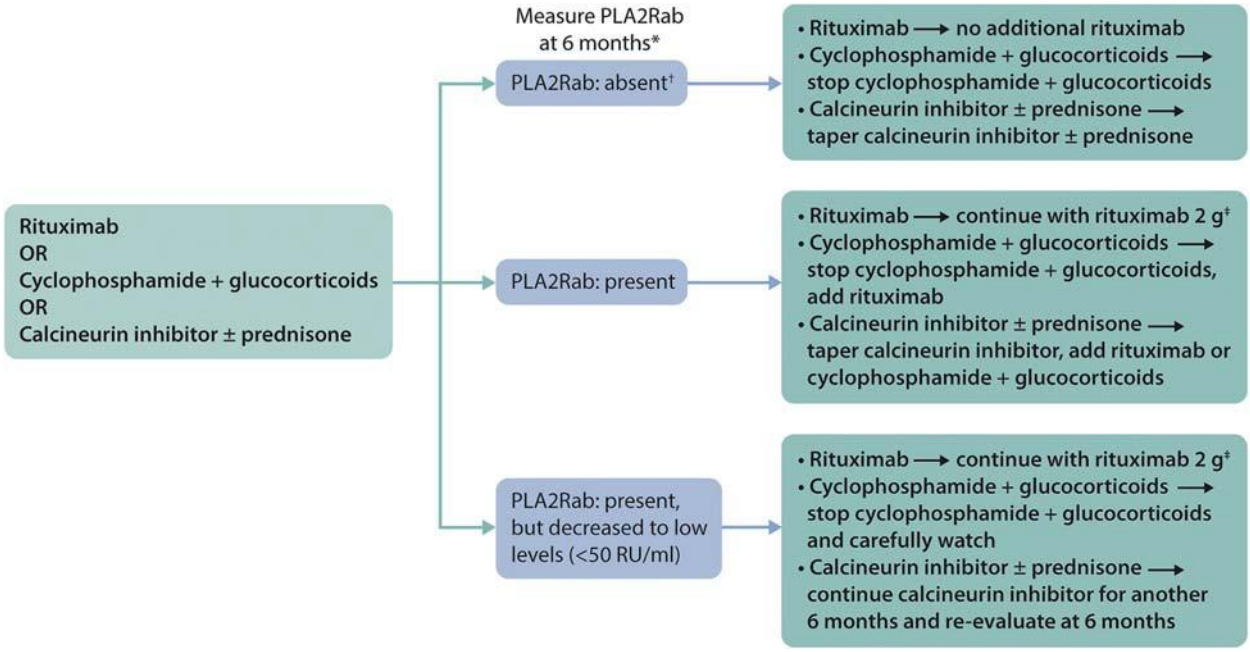


图33治疗开始后 MN 的免疫学监测。当前治疗方案见正文。注：考虑到恶性肿瘤的风险，环磷酰胺的累积剂量不应超过36 g（第1章）。为了保持安全，我们通常将累积剂量限制为25 g（在 80 kg 的男性中：6个月的环磷酰胺周期性给药，剂量为2.5 mg/kg/d，等于18 g，6个月的环磷酰胺每日给药，剂量为1.5 mg/kg/d，等于22 g）。希望怀孕的患者必须使用较低剂量（最多10 g）。CNI不太可能诱导晚期免疫缓解；在持续存在抗 PLA2R 抗体的患者中，这些药物可与利妥昔单抗联合使用。B细胞耗竭不足以判断利妥昔单抗治疗的疗效；即使外周血中 B 细胞不存在或非常低，也可考虑额外给药。但是，在这些患者中，建议咨询专家中心。eGFR应保持稳定；如果不稳定，则始终需要评价其他原因，如果 eGFR 降低归因于 MN 活性，则始终提供额外治疗。*一些中心将在第3个月测量抗 PLA2R 抗体，并在当时调整治疗。在大多数患者中，缓解发生在治疗开始后3个月内。†免疫荧光试验阴性表示免疫缓解。如果通过酶联免疫吸附试验测定，则应使用 2 RU/ml 的临界值来定义完全免疫学缓解。‡利妥昔单抗再治疗的给药方式应与利妥昔单抗1或2次输注（每次1 g，间隔2周）的初始治疗相似。[182]CNI，钙调磷酸酶抑制剂；eGFR，估计肾小球滤过率；MN，膜性肾病；PLA2Rab，抗 M 型磷脂酶 A2 受体抗体。

3.4 特殊情况

实践要点3.4.1：MN和治疗后初始复发患者的治疗算法（图34）

践要点3.4.2：难治性 MN 患者的管理算法（图35）

实

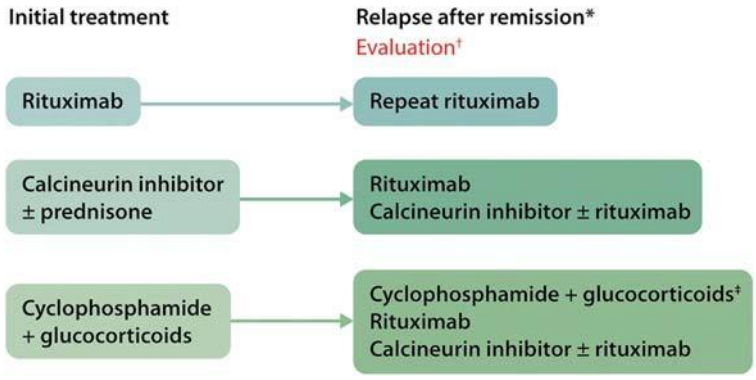


图 34 MN 治疗后初始复发的管理常用治疗方案的详细信息见图32。*复发的定义是可变的。一些作者将缓解后复发定义为出现部分或完全缓解的患者蛋白尿增加 > 3.5 g/日。我们建议在评估中应使用血清白蛋白和 PCR 的过程。如果 PCR 降至2-3.5 g/d之间，血清白蛋白未升高至正常，则后续 PCR 升高应视为耐药疾病，而不是缓解后复发。
在部分缓解（以血清白蛋白正常化为特征）的患者中，复发应定义为蛋白尿增加伴随血清白蛋白水平降低。†在这些情况下，免疫学监测特别重要。如果在"临床缓解"期间，抗 PLA2R 抗体仍为阳性，则表明疾病耐药。因此，在抗 PLA2R 抗体阳性的患者中，建议在缓解和复发时评价抗 PLA2R 抗体。抗 PLA2R 抗体的病程应先于临床病程。在极早期复发的患者中，重要的是要考虑既往治疗失败的原因（例如，依从性、药物水平低、B细胞耗竭不足、存在抗利妥昔单抗抗体）。‡可重复环磷酰胺给药；但医生必须考虑最大耐受剂量：如果需要保留生育能力，累积剂量不应超过10 g。累积剂量不应超过36 g，以限制恶性肿瘤风险。MN，膜性肾病；PCR，蛋白-肌酐比值；PLA2R，M型磷脂酶 A2 受体。

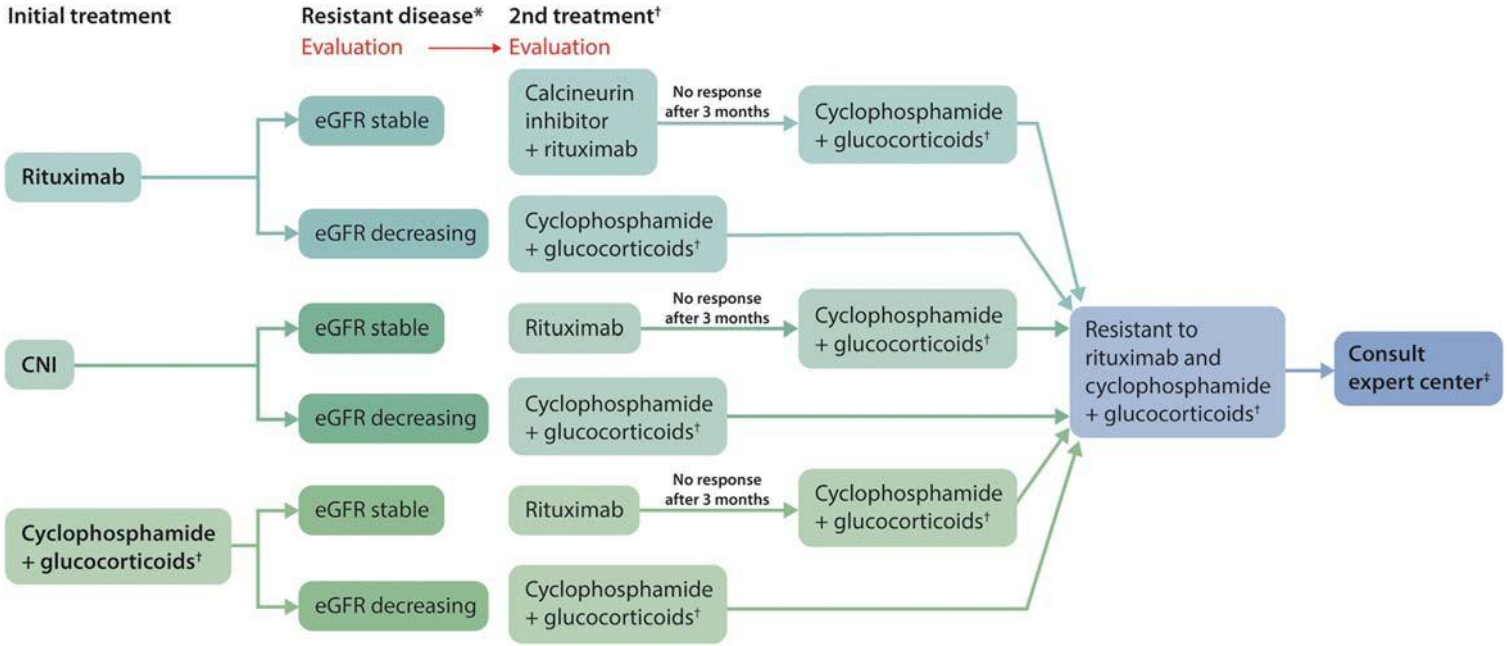


图35|MN耐药疾病的管理。常用治疗方案的详细信息见图32。*评价：在耐药性疾病患者中，应检查依从性并监测疗效（例如，B细胞应答、抗利妥昔单抗抗体、IgG水平、环磷酰胺治疗期间的白细胞减少症、CNI水平）。持续性蛋白尿不足以定义耐药性。如果蛋白尿持续存在，而血清白蛋白升高，应考虑继发性局灶节段性肾小球硬化 (FSGS)。抗 PLA2R 抗体的消失进一步支持了这一点。在血清白蛋白水平正常或接近正常的持续性蛋白尿患者或尽管抗 PLA2R 抗体丢失但仍有持续性蛋白尿的患者中，应考虑进行肾活检以记录活动性 MN。†第二次治疗取决于 eGFR 恶化的严重程度。当选择利妥昔单抗作为第二种治疗时，应在3个月后评价蛋白尿和抗 PLA2R 抗体的缓解。环磷酰胺治疗应考虑最大耐受剂量：如果需要保留生育能力，累积剂量不应超过10g。累积剂量不应超过36 g，以限制恶性肿瘤风险。根据权衡风险和获益，专家中心可能仍会使用更多。‡对利妥昔单抗或环磷酰胺无应答的患者应咨询专家中心。这些中心可以选择试验性治疗（硼替佐米、抗 CD38 治疗和贝利尤单抗）或更高剂量的常规免疫抑制治疗。CNI，钙调磷酸酶抑制剂；eGFR，估计肾小球滤过率；FSGS，局灶节段性肾小球硬化；MN，膜性肾病；PLA2R，M型磷脂酶 A2 受体。

耐药疾病没有公认的定义。在治疗开始时具有可测量抗 PLA2R 抗体的 MN 患者中，耐药性疾病可通过1线免疫抑制治疗（充分的剂量和持续时间）后抗 PLA2R 抗体持续处于高水平或不变来定义。中度蛋白尿的持续存在不应用于定义耐药性疾病，因为蛋白尿可持续至治疗开始后12 –24个月。

尽管抗 PLA2R 抗体的持续存在提示治疗抵抗，但仍有患者发生蛋白尿部分缓解，持续存在低滴度的抗 PLA2R 抗体。应仔细随访这些患者；通常可以暂停免疫抑制治疗。

显然，在抗 PLA2R 抗体阴性的患者中，明确的耐药性更为困难。持续性NS（因此血清白蛋白较低）患者可视为耐药（如果随访持续时间超过6个月）。在低度蛋白尿和血清白蛋白正常化的患者中，持续性蛋白尿可能由继发 F SGS 或其他因素解释。在持续性蛋白尿和血清白蛋白升高但仍有一定程度降低的患者中，可能难以判断。在这种情况下，显示小的致密沉积物的肾活检可用于定义持续性疾病活动。

实践要点3.4.3：MN肾移植受者的评价（图36）

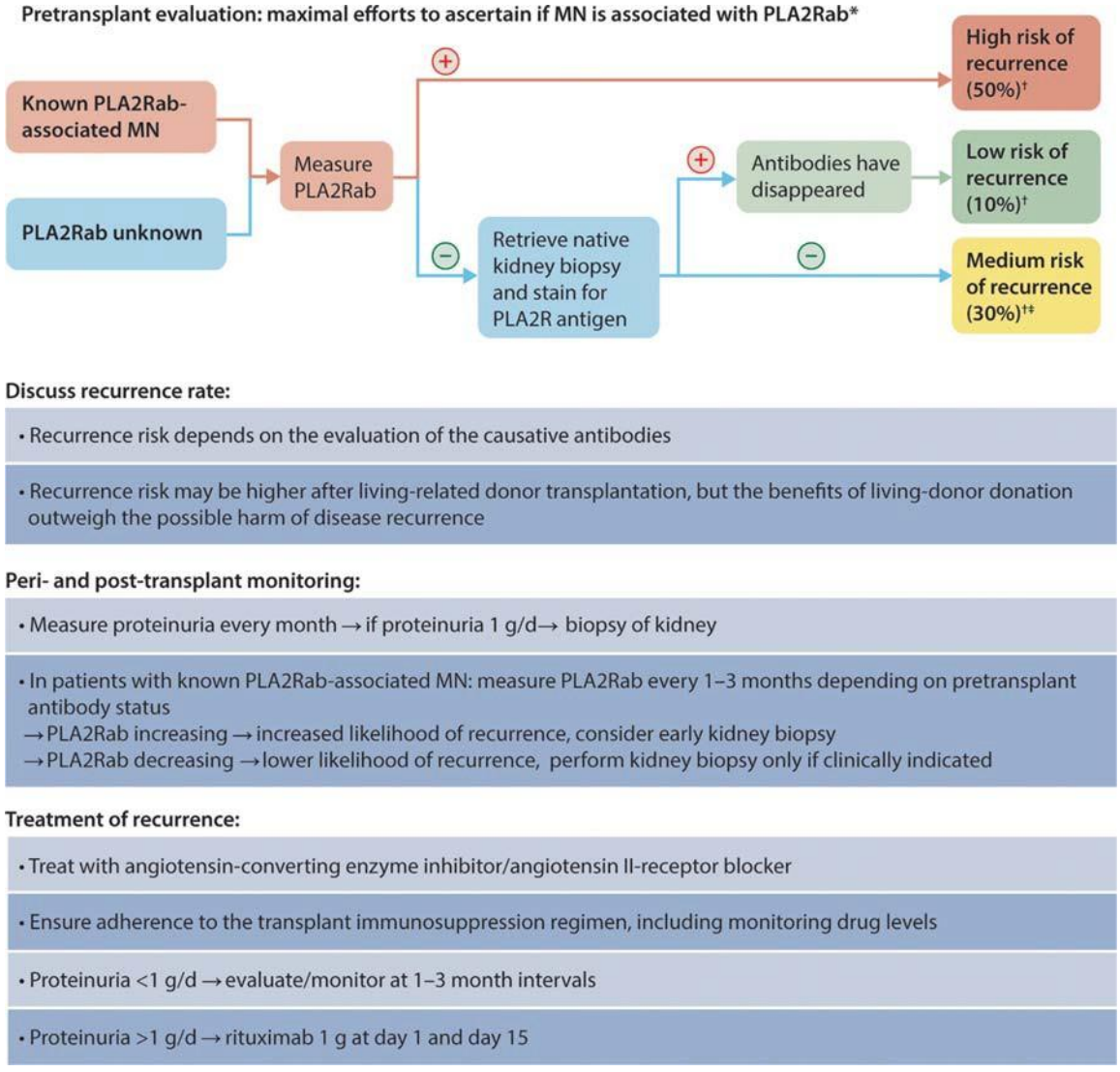


图 36 MN 肾移植受者的评估*可用数据有限，但相同算法可能适用于抗 THSD7A 相关MN。†临床复发。‡这是 MN 和未鉴定抗原患者的估计平均复发率。我们建议在这些患者中，通过评价患者的 THSD7A 抗原/抗体可以更好地估计复发率。MN，膜性肾病；PLA2Rab，抗 M 型磷脂酶 A2 受体抗体；THSD7A，含血小板反应蛋白1型结构域的7A。

移植前评估

确定患者的 MN 是否与抗 PLA2R 抗体有关具有重要意义。既往或近期血清中存在抗 PLA2R 抗体，或在天然肾活检中检测到 PLA2R 抗原，确诊为抗 PLA2R 相关MN。抗 PLA2R 相关 MN 患者移植时无抗体预示复发风险低。相反，如果存在抗 PLA2R 抗体，复发风险较高 (er)。尽管研究表明较高的抗 PLA2R 抗体水平 (> 45 RU/ml) 与风险增加相关，但确定临界值的数据不充分。尽管缺乏关于抗 THSD7A 和肾移植的数据，但很可能可以使用相同的算法来评估抗 THSD7A 相关 MN 患者。

移植前后评估

没有足够的数据支持方案活检或利妥昔单抗抢先治疗，除非患者有多次复发和抗体阳性病史。在与抗 PLA2R 无关的 MN 患者中

抗

体、蛋白尿应在移植后至少6-12个月内每月评价一次。当蛋白尿超过 1 g/日时，需要进行肾活检。在 PLA2R 相关 MN 患者中，建议在移植后第一个6-12个月肾移植后定期测量抗 PLA2R 抗体。监测频率可能从移植前高滴度患者的每月一次至移植前无可测量抗 PLA2R 抗体的患者的每3个月一次不等（这些患者可能再次出现抗体，提示疾病再激活）。抗 PLA2R 抗体的持续高滴度或滴度增加可预防复发，在这种情况下，可考虑对蛋白尿0.3-1.0 g/日的患者进行肾活检。

复发性 MN 患者应接受最大限度的保守、抗蛋白尿治疗。如果蛋白尿
> 1 g/日，我们建议使用利妥昔单抗治疗。

实践要点3.4.4：MN儿童的管理算法（图37）

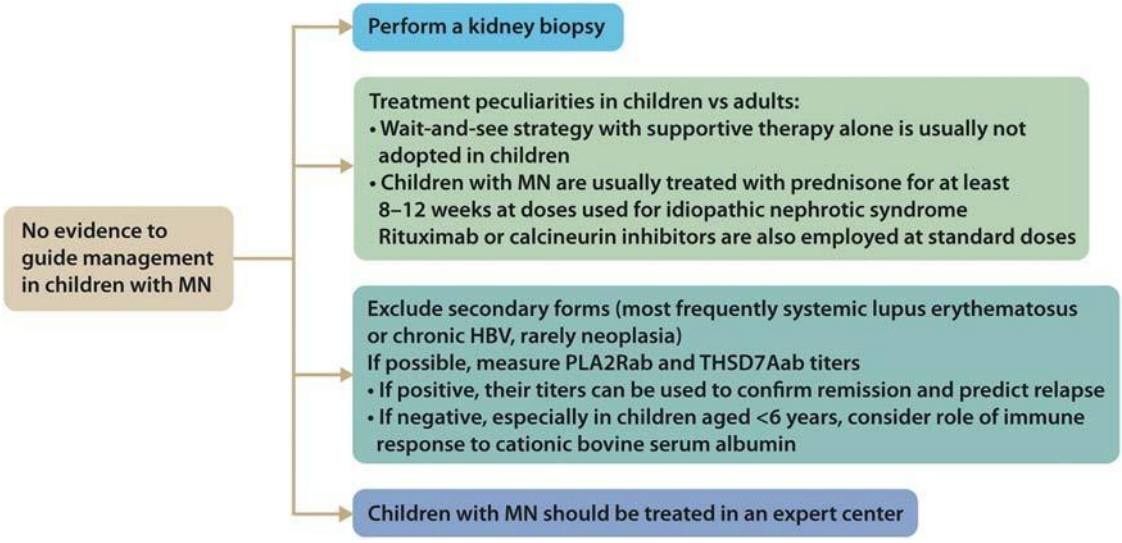


图37|MN儿童的管理。HBV，乙型肝炎病毒；MN，膜性肾病；PLA2Rab，抗 M 型磷脂酶 A2 受体的抗体；THSD7Aab，抗含血小板反应蛋白1型结构域的抗体7A。

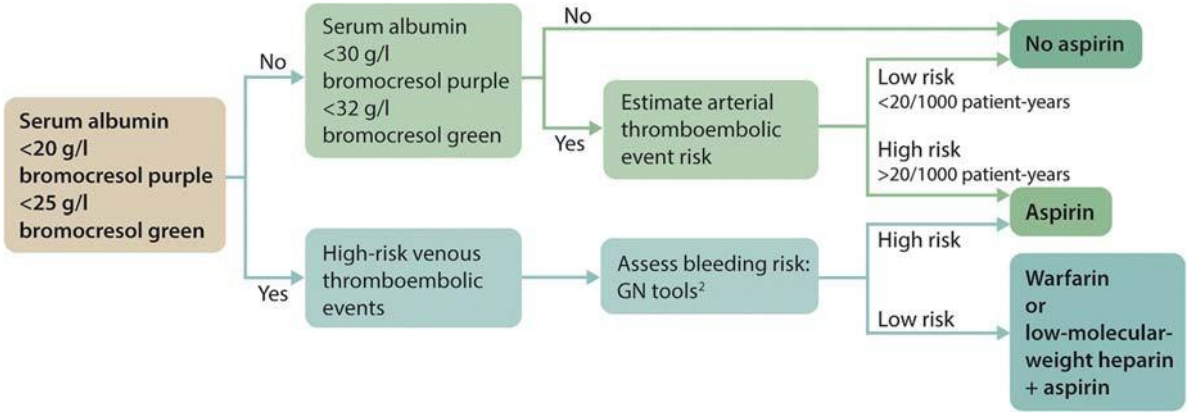


图 38 MN 患者的抗凝治疗摘自*Kidney International*，第89卷，第5期，Hofstra JM，Wetzels JFM。阿司匹林是否应用于膜性肾病患者血栓事件的一级预防？第89:981–983页，版权2016，经国际肾脏病学会许可。[44]膜性肾病 (MN) 患者抗凝治疗的拟定算法。该算法为临床医生提供指导。拟定临界值基于专家意见。在考虑抗凝治疗时，重要的是平衡获益和风险。以下是重要的考虑因素：

1. 血栓事件的风险与血清白蛋白水平有关。值得注意的是，血清白蛋白测定之间存在较大差异。[204]使用溴甲酚绿 (BCG) 时血清白蛋白浓度为25 g/L(2.5 g/dL)，使用溴甲酚紫 (BCP) 或免疫散射比浊法时血清白蛋白浓度为w20 g/L(2.0 g/dL)。很可能大多数研究使用了 BCG 测定法。使用 BCG 时，考虑使用25 g/L(2.5 g/dL) 作为阈值，使用 BCP 或免疫散射比浊法时，考虑使用20 g/L(2.0 g/dL) 作为阈值。
2. 评估静脉血栓形成风险和出血风险 (https://www.med.unc.edu/gntools/bleedrisk.html) .
3. MN 和肾病综合征患者也有发生动脉血栓事件的风险。动脉血栓栓塞 (ATE) 的风险取决于年龄、既往事件史、糖尿病、估计的肾小球滤过率 (eGFR)、吸烟和肾病综合征 (NS) 的严重程度。可使用 Framingham 风险评分进行风险评估，包括既往事件和蛋白尿。[44]
4. 使用阿司匹林不足以预防静脉血栓栓塞 (VTE)；使用华法林足以预防ATE。
5. 华法林治疗：肾病综合征和低 eGFR 的国际标准化比值 (INR) 变异性更高；在开始高剂量华法林治疗后立即出现血栓形成的风险增加。考虑使用低剂量低分子量肝素开始抗凝治疗，然后折叠华法林，治疗时停用肝素。一个很好的替代方案是在转换为华法林之前使用低剂量低分子量肝素阿司匹林3个月，以便判断蛋白尿的病程。[205]
6. 糖皮质激素可增加血栓形成的风险；因此，在开始泼尼松治疗的患者中不应忽略抗凝治疗。
7. 使用 Framingham 风险评分估计 ATE 风险，在 eGFR 较低或蛋白尿较高的情况下增加风险。Framingham风险评分考虑了年龄、吸烟、血清胆固醇和血压。

实践要点3.4.5：MN和肾病综合征患者的预防性抗凝治疗应基于血栓事件风险和出血并发症风险的估计值（图38[44、204、205]）。

肾病综合征与 VTE 和 ATE 风险增加相关。MN患者的风险最大。在疾病发作后的前6–12个月内，血栓形成的风险特别增加。因此，在诊断时讨论抗凝治疗的必要性至关重要

研究建议

诊断。

- 评价抗 PLA2R 抗体和抗 THSD7A 抗体诊断 MN 的准确性；血清学阳性在疾病发展伴临床症状之前有多长时间？
- 比较评价抗 PLA2R 抗体相关 MN 的不同技术，评估诊断 MN 的准确性和最佳截断值水平
- 应使用新技术（激光捕获显微切割后进行肽消化和质谱分析）来

在

约20%的 PLA2R 和 THSD7A 双阴性患者中发现了其他抗原。最近发现的抗原exostosin 1/2、NELL-1和 semaphorin 3B 的示例

预后。

- 评价抗 PLA2R 抗体水平预测 MN 患者结局的准确性；考虑未治疗患者（自发缓解）和接受不同免疫抑制治疗患者的结局。确定最佳截止水平
- 评价抗 PLA2R 变化的预测价值

未接受治疗和接受免疫抑制治疗的 MN 患者在3–6个月期间的抗体水平。提供最高准确度的 De ne 临界值

- 评价基线时抗 THSD7A 水平和随访期间变化预测结局的准确性；考虑未治疗患者（自发缓解）和接受不同免疫抑制治疗患者的结局。确定最佳截止水平
- 开发一种结合风险生物标志物的计算器，以确定疾病进展的风险

- 了解表位扩散和免疫优势的机制，确定表位反应性分析是否具有大于 PLA2R 抗体水平的预测价值
- 建立移植后复发的遗传和临床风险评分
- 评价新发现抗原的作用及其与继发性病因的相关性

治疗。

- 我们的目标是实现免疫完全缓解，还是抗 PLA2R 抗体水平大幅降低？
- 评价 CNI 在疾病进展风险较低的 MN 患者中缩短 NS 期的有效性
- 在高危患者中评价基于 CNI 的联合治疗（包括与利妥昔单抗的联合治疗）的疗效；我们是否应该使用免疫抑制药物的序贯联合治疗？
- 评价利妥昔单抗的最佳给药方案和抗利妥昔单抗抗体的临床影响
- 在疾病进展风险极高的 MN 患者中比较利妥昔单抗治疗与环磷酰胺治疗的疗效
- 评价新型 B 细胞（抗 CD20 抗体、抗 BLyS/BAFF/APRIL 抗体）或浆细胞导向治疗（蛋白酶体抑制剂或抗 CD38 抗体）在对标准免疫抑制治疗耐药的 MN 患者中的疗效
- 评价抗原靶向治疗的潜力和适用性

特殊情况。

- 评价最佳预防性抗凝治疗
- 评价测量 MN 患者 B 细胞（包括记忆 B 细胞和 T 细胞表型）对预测结局和治疗反应的有用性

第4章：儿童肾病综合征

本章对1–18岁的肾病综合征 (*NS*) 患儿提出治疗建议。在1岁以下，所有符合 *NS* 定义的儿童均应转诊至儿科肾病学专家。这些幼儿的正确治疗方法超出了本研究的范围。

4.1 诊断

操作要点4.1.1：与儿童肾病综合征相关的定义是基于图39[206]中概述的临床特征。

- **Nephrotic-range proteinuria:** First morning or *24-h PCR ≥2 g/g (or 200 mg/mmol or ≥3+ dipstick)
- **NS:** Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin <30 g/l (3 g/dl)) or edema when albumin level is not available
- **Complete remission:** First morning or *24-h PCR ≤200 mg/g (or 20 mg/mmol or negative or trace dipstick) on three or more consecutive occasions
- **Partial remission:** First morning or *24-h PCR >200 mg/g but <2 g/g (or >20 and <200 mg/mmol) and, if available, serum albumin ≥30 g/l (3 g/dl)
- **Relapse:** Recurrence of nephrotic-range proteinuria. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick ≥3+ for 3 consecutive days
- Typical dipstick results are expressed semiquantitatively as follows†, or as stated by manufacturer:
  Negative: 0 to <15 mg/dl
  Trace: 15 to <30 mg/dl
  1+: 30 to <100 mg/dl
  2+: 100 to <300 mg/dl
  3+: 300 to <1000 mg/dl
  4+: ≥1000 mg/dl

- **SSNS:** Complete remission after 4 weeks of prednisone or prednisolone at standard dose
- **Infrequent relapsing NS:** <2 relapses per 6 months within 6 months of disease onset or <4 relapses per 12 months in any subsequent 12-month period
- **Frequent relapsing NS:** ≥2 relapses per 6 months within 6 months of disease onset or ≥4 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** Two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission at 4 weeks of therapy with daily prednisone or prednisolone at standard dose
- **Late responder:** Complete remission at 6 weeks.
- **Calcineurin inhibitor-responsive SRNS:** Partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Calcineurin inhibitor-resistant SRNS:** Absence of partial remission after at least 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Multi-drug resistant SRNS:** Absence of complete remission after 12 months of treatment with 2 mechanistically distinct glucocorticoid-sparing agents at standard doses (see below)
- **Secondary SRNS:** A SSNS patient at disease onset who at a subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose

图39|1 –18岁儿童中与 NS 相关的定义。*为排除直立性蛋白尿，应单独采集第1次晨尿进行评估。†van der Watt *et al.*[206]NS，肾病综合征；PCR，蛋白-肌酐比值；SRNS，类固醇耐药性肾病综合征；SSNS，类固醇敏感性肾病综合征。

4.2 预后

实践要点4.2.1：儿童肾病综合征的预后最好通过患者对初始治疗的反应和治疗后第一年的复发频率来预测。因此，通常在初次就诊时不需要进行肾活检，而是保留用于对治疗耐药或临床病程不典型的儿童。

肾病综合征是儿童中最常见的肾小球疾病，发病率为1.15–16.9/100,000。[207]在抗生素和糖皮质激素可用之前，约40%的 NS 儿童死于感染、肾衰竭，偶尔发生血栓栓塞。[208]如果儿童存活，则仅在疾病活动数年后观察到持续的自发缓解。抗生素可降低死亡率，但20世纪50年代糖皮质激素的使用改变了疾病的自然史。[208]自20世纪70年代以来，在疾病发作后，儿童接受标准剂量的糖皮质激素治疗。对该标准给药方案的反应和随后一年的复发次数允许对儿童的 NS 进行分类，该分类比肾脏活检具有更大的预后价值，因此在疾病发作时不常规进行。一般而言，假设对类固醇敏感的 NS 儿童如果进行活检，最常被发现患有MCD，但也描述了伴有 IgM 和 FSGS 的系膜增生（最常与类固醇耐药的 NS 相关的病变）。

在激素敏感的儿童中及时接受和
适当的治疗，肾功能始终得以维持，预后与长期暴露于糖皮质激素和二线糖皮质激素节制药物（处方用于频繁复发和

尤其是类固醇依赖性疾病。该疾病具有慢性、复发-缓解病程，倾向于在青春期后自发消退。然而，在15%–25%的病例中，它可能进展为成年期，保持儿童期发病的 NS 的特殊特征，在复发的情况下对糖皮质激素有快速反应。此外，在随后的复发中，一小部分儿童可能继发类固醇耐药。这些儿童进展为肾衰竭和移植后复发的几率均较高。因此，仅在发病时对具有非典型特征的儿童和所有类固醇耐药儿童进行肾活检（图43）。随后，在病程中，建议对长期（> 2–3年）暴露于 CNI 或继发性类固醇耐药。

因此，在激素敏感型 (SS) 和激素耐药型 (SR) 但对钙调磷酸酶有反应的 NS 患儿中，最佳治疗策略旨在使用最低累积剂量的糖皮质激素和最安全有效的糖皮质激素节制剂来维持缓解。使用维生素 D/钙、胃保护和适当的疫苗接种策略对于将发病率降至最低也很重要。

在耐药型 NS 儿童中，必须立即进行基因检测，以便对肾脏疾病和存在的肾外特征进行适当管理。最小化长期蛋白尿副作用的最佳保守疗法以及透析和移植治疗必须在具有儿科肾病学专业知识的中心进行。

4.3 治疗

治疗方法示意图见图40。

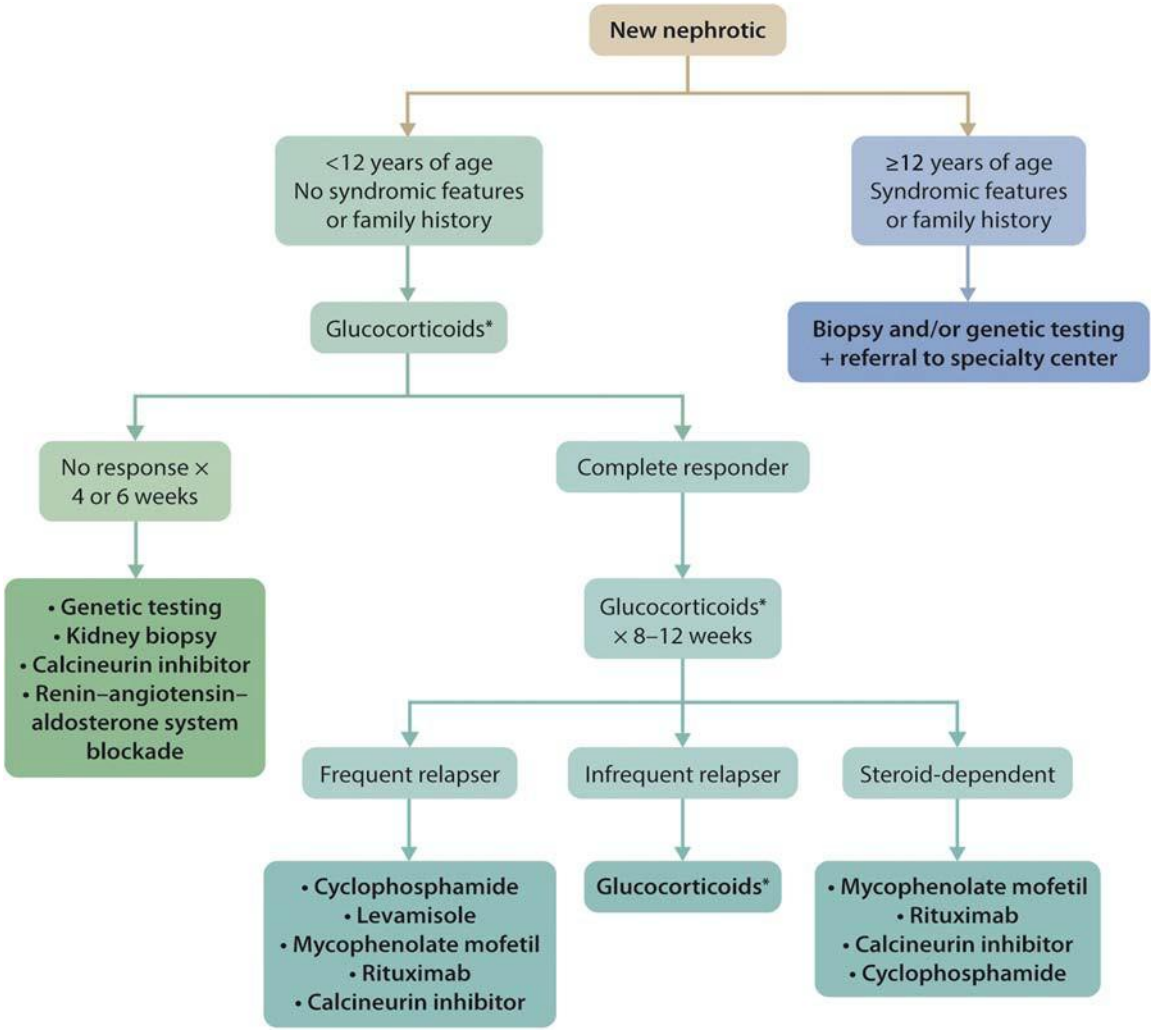


图40新发肾病儿童 NS 的治疗方案。儿童 NS 发病后的治疗方法。适当时参考临床试验。*糖皮质激素：口服泼尼松或泼尼松龙。NS，肾病综合征。

4.3.1 儿童 NS 的初始治疗

建议4.3.1.1：我们建议口服糖皮质激素8周（每日4周糖皮质激素，随后4周隔日糖皮质激素）或12周（每日6周糖皮质激素，随后6周隔日糖皮质激素）*(1B)*。

该建议对短期（8-12周）糖皮质激素治疗的临床结局相当和安全性特征有利的中等质量证据具有相对较高的价值，对长期（> 12周）糖皮质激素治疗的高质量证据具有相对较高的价值。
coid 治疗增加了不良反应的风险，但未进一步增加在复发率方面改善临床结局。该建议对低质量证据的价值相对较低，表明与治疗8–12周相比，长期糖皮质激素治疗可能会延迟至首次复发的时间。

在口服糖皮质激素方面，泼尼松和泼尼松龙等效，使用剂量相同，均得到高质量数据的支持。所有后续用途"口服糖皮质激素"指泼尼松或泼尼松龙。

最近的报告表明，按体表面积给药可能是谨慎的，以避免剂量不足，特别是在年龄较小的儿童中。[209–212]一项比较单次给药与分次给药的 RCT 显示，两者在至缓解时间和后续复发次数方面相当。[213]因此，可能首选每日单次给药以优化依从性。

关键信息

*平衡危害。*如果没有适当的治疗，NS初次发作的自发缓解非常罕见，如果不治疗，其发病率和死亡率相当高。[208]随着糖皮质激素治疗的引入，预后显著改善，从20世纪70年代开始，在疾病发作时对儿童实施标准方案。NS患儿的预后直接

与该治疗的反应相关，随后与他们经历的复发次数相关。大多数最初对类固醇敏感的患者仍对类固醇敏感，从未进展为肾衰竭。因此，最佳管理是基于最小化治疗毒性，最初主要包括口服糖皮质激素，[207,214]保持类固醇敏感性和延长缓解。

自既往 KDIGO 2012 指南发表以来，4项 RCT 评价了治疗儿童 SSNS 初次发作的最佳糖皮质激素剂量：2项比较12周至6个月的研究，1项比较8[215–217]这些研究表明，将初始糖皮质激素治疗从8–12周延长至6个月可能会延迟首次复发，但不会影响频繁复发的发生，也不会影响随后的疾病过程。

为了解释这些最新发现与早期证据之间的差异，2015年 Cochrane 系统评价检查了偏倚风险较低与较高的研究结果是否存在系统性差异。[218]当仅限于偏倚风险较低的研究时，汇总结果表明，长期治疗对发生频繁复发疾病的儿童数量几乎没有差异。对于比较12周至8周治疗的两项研究和比较5 –6个月与8或12周治疗 SSNS 初始发作的两项研究，均是如此。通过对最近发表的 PREDNOS 试验（比较8周至4个月）进行分析，进一步证实了这一点。[219]

就危害而言，Sinha 等人表明不良反应相关 to 糖皮质激素 （高血压、 2个治疗组在随机化、干预结束和12个月随访时（12周vs. 6个月）的库欣样外观、多毛症、肥胖、身材矮小和攻击行为）和感染发作相当。[215]Yoshikawa 等人报告了类似的结果。（中位随访36–38个月），[217]Teeninga et al.（中位随访47个月），[216]和 Webb 等人（随访24个月）。[219]尽管这些研究未证明较短的疗程具有更好的安全性特征，但来自其他疾病的全部证据强烈表明，糖皮质激素治疗的不良事件风险与其持续时间和累积剂量成正比。因此，由于较短的疗程似乎不会导致更频繁的复发，其在安全性方面的影响似乎是有利的，因为它需要在发病时给予较少的糖皮质激素。*证据质量*。RCT的中等质量证据比较了糖皮质激素治疗$12周与糖皮质激素治疗8周（补充表S14 [217–228]）。对于复发频率的重要结局，证据质量较低（非常严重的研究局限性）。删除风险较高或不明确的研究后，在亚组分析中证据质量被评定为较高的分配隐藏偏倚。对于不良事件（库欣综合征），由于严重的研究局限性，证据降级为中度。然而，由于研究的局限性和严重不精密度（CI较宽–表明疗效的确定性较低）或严重不一致（实质性异质性），其他不良事件（感染、其他糖皮质激素相关不良事件）降级为低质量或极低质量证据。但是，这些不良事件较少，因此认为其低质量对证据评级的总体质量并不关键。考虑到所有这些因素，证据的总体质量被评定为中等。

价值和偏好。糖皮质激素治疗的潜在益处，包括降低 NS 的发病率和降低进行性肾功能丧失的风险，被判定为对患者和父母至关重要。工作组还判断，临床重要危害（包括糖皮质激素的副作用）的风险相对较低，对许多患者很重要。由于保持类固醇敏感性和维持缓解与良好的临床结局相关，提供者和患者必须权衡糖皮质激素的副作用与首次发作治疗不足的风险，这可能导致复发和更高的糖皮质激素累积剂量，以及更高的进行性肾功能丧失风险。历史上，认为首次发作的强化治疗可减少复发，因此，在 > 12个月内可减少糖皮质激素的累积剂量。然而，这种态度可能导致过度治疗第一次发作。最近的证据表明，将糖皮质激素治疗时间延长 > 12周会增加伤害风险，但不会在随后几年降低复发风险。工作组判断，所有或几乎所有知情良好的患者和父母都会选择接受8 –
糖皮质激素作为 NS 初始治疗12周，
与较长疗程的糖皮质激素、另一种治疗或不治疗相比。

没有足够的证据可以选择8–12周的糖皮质激素治疗，因此通常的当地实践、可用资源和患者偏好可用于选择8周治疗而不是12周治疗。考虑患者特征也可能有帮助。例如，对于达到快速缓解（泼尼松龙开始治疗后7天内）或有合并症（肥胖、高血压、1型糖尿病等）的儿童，治疗8周而不是12周可能更可取。

资源使用和成本。泼尼松龙价格低廉，应用广泛可用，不需要特殊监测（例如药物水平）。尚无已发表的研究阐述糖皮质激素治疗在类固醇敏感儿童中的成本效益，但考虑到其低成本和临床获益，该治疗在大多数情况下可能具有成本效益。

实施考虑。没有数据评估最佳治疗方法是否会因性别或种族而异。在疾病发作时年龄特别小（即1–4–6岁）的儿童中，发生以下事件的风险可能更高

进展为频繁复发或类固醇依赖性NS，[222]将初始发作的治疗时间延长至16–24周在预防后续复发和相似副作用方面可能是有益的。[215]然而，这仅适用于该年龄组中对泼尼松龙反应延迟（即，治疗开始后10–15天内缓解）的儿童，然而，即使在年轻患者（1–4–6岁）中，如果泼尼松龙快速起效（即 < 7天），也可能首选标准的8–12周泼尼松龙疗程。

依据

该建议对短期（8 –12周）糖皮质激素治疗与不治疗相比的更好临床结局和相对有利的安全性特征给予了相对更高的重视，以及对证据的相对更高重视，表明长期（> 12周）糖皮质激素治疗增加了不良反应的风险，但未进一步改善临床结局。该建议对较弱的证据给出了相对较低的价值，表明与治疗8 –12周相比，长期糖皮质激素治疗可能会延迟至首次复发的时间。证据不充分，无法选择8–12周治疗。

该建议是强有力的，因为工作组判断，与更长疗程的糖皮质激素、另一种治疗或不治疗相比，所有或几乎所有知情的父母和患者将选择接受8周或12周的糖皮质激素作为 SSNS 的初始治疗。

实践要点4.3.1.1：肾病综合征初始治疗的标准给药方案是每日口服泼尼松/泼尼松龙 60 mg/m ^{2}/d 或2 mg/kg/d（最大 60 mg/日），持续4周，然后隔日给予泼尼松/泼尼松龙 40 mg/m ^{2} 或1.5 mg/kg（最大50 mg），持续4周，或泼尼松/泼尼松龙60 mg/m ^{2}/d（最大 60 mg/日），持续6周，然后隔日给予泼尼松/泼尼松龙40 mg/m ^{2}，或1.5 mg/kg（最大50 mg），其他6周。

4.3.2 预防和治疗儿童 NS 复发 SSNS 儿童的长期预后良好，预期可在成年期保留GFR。80%–90%的 SSNS 儿童在糖皮质激素初始应答后复发。其中一半的儿童很少复发。这些儿童中的其余一半将经历–
频繁复发 (FRNS) 或成为类固醇依赖性 (SDNS)。[229,230]许多儿童在感染触发后复发，但许多其他儿童没有可识别的触发因素。[231]预防复发可减少糖皮质激素的总体暴露，并减少长期糖皮质激素的不良反应，包括线性生长受损，肥胖、高血压、眼科病理学、行为变化、骨代谢改变、糖耐量受损、痤疮和其他与库欣综合征相关的身体变化。[232–235]

建议4.3.2.1：对于目前正在接受隔日糖皮质激素或停用糖皮质激素的频繁复发和激素依赖性肾病综合征儿童，我们建议在上呼吸道和其他感染发作期间给予糖皮质激素0.5 mg/kg/d，持续5-7天，以降低复发风险 (1C)。

该建议对较低质量的证据具有相对较高的价值，即超前每日使用泼尼松龙可降低感染期间 SSNS 复发的风险，对低质量的证据具有相对较低的价值，即与治疗相关的免疫抑制风险的潜在不良反应。

关键信息

*平衡危害。*感染长期以来被确定为 FRNS 儿童复发的触发因素。几项试验表明，对于目前未服用糖皮质激素或隔日服用糖皮质激素的 FRNS 或 SDNS 儿童，在上呼吸道感染发作时每日给予糖皮质激素5–7天可减少复发。在 Abeyagunawardena 等人于2017年开展的最新研究中，48例 SDNS 患者（但停用泼尼松$3个月）随机分组，在上呼吸道感染发作时接受泼尼松龙0.5 mg/kg每日5天治疗或安慰剂5天治疗。[236]少数 (34.3%) 治疗组复发，而39.4%的对照组出现单次复发，18.2%出现2次复发。这些短疗程的超前糖皮质激素治疗可能避免需要更长疗程的糖皮质激素，从而降低毒性。

尽管在感染期间更高剂量的糖皮质激素理论上可能会引起有害的免疫抑制，但现有数据未报告接受每日一次与隔日一次糖皮质激素治疗的儿童中感染持续时间或严重程度增加。

这些数据均来自中低收入国家的患者，感染模式可能与较发达国家不同。因此，这些数据需要在更多样化的人群中进行确认。

*证据质量。*在病毒感染期间接受隔日泼尼松龙维持治疗的患者中检查每日使用和增加剂量泼尼松龙的 RCT 证据质量较低（补充表S15 [218, 236–239]）。复发和感染相关复发率是这些研究中检查的唯一关键或重要结局。由于研究局限性和严重不精密度，证据质量被降级，因为只有1项 RCT 检查了这些结局中的每项。

Abeyagunawardena et al.2017年是一项交叉研究，未报告足够的数据纳入配对分析中；因此，未提供补充表。[236]Abeyagunawardena et al.2017 [236]因以下原因降级

对于未完成交叉研究两个部分的患者，31%的损耗水平，并且由于严重不精密度，因为这是唯一一项在停用泼尼松治疗3个月后在 SSNS 儿童中检查泼尼松与安慰剂的试验。

价值和偏好。工作组认为，避免复发和与随后长期高剂量糖皮质激素暴露相关的过高发病率对患者至关重要。工作组还判断，与泼尼松隔日给药至每日给药的短期增加相关的不良反应，或如果患者已停止治疗，则短期重新开始糖皮质激素治疗相关的不良反应，对患者也很重要。鉴于感染引发的复发风险中度降低，且极短期糖皮质激素治疗的不良事件风险增加相对较低，工作组判定，与隔日泼尼松或不治疗相比，所有或几乎所有充分知情的上呼吸道或其他感染患者将选择接受每日泼尼松治疗。

这种抢先策略在儿童中可能更可取 FRNS 患者更容易发生高剂量糖皮质激素的不良副作用——如严重的行为改变、睡眠障碍、肥胖——或有合并症，如糖尿病。

资源使用和成本。糖皮质激素是 NS 最广泛使用的治疗方法之一，而许多其他免疫抑制治疗要么成本高昂，要么无法获得。这种抢先策略可能通过避免与患者复发时所需的更长时间疗程相关的策略进一步降低成本。

实施考虑。没有数据表明治疗方法应因性别或种族而异。

依据

KDIGO 2012 指南建议在感染开始时，将隔日接受糖皮质激素（或未接受糖皮质激素）的 FRNS 儿童转换为每日泼尼松治疗5–7天。自该出版物发表以来，已经有几项随机但小型的临床试验证明，这种治疗方法可使复发减少高达30%，因此需要将该声明作为建议。

实践要点4.3.2.1：复发的初始方法应包括口服泼尼松/泼尼松龙，每日单次给药 60 mg/m²/d 或2 mg/kg/d（最大剂量60 mg/d），直至儿童‡完全缓解3天。

实践要点4.3.2.2：达到完全缓解后，将口服泼尼松/泼尼松龙剂量减少至 40 mg/m² 或1.5 mg/kg（最大 50 mg），隔日一次，持续‡4周。最近，进行了2项关于复发治疗的RCT，更具体的是诱导缓解后隔日口服泼尼松的剂量和时长已发表。一项研究（PROPINE试验）比较了 40 mg/m² 隔日给药5周与使用10周内相同的泼尼松累积剂量和逐渐减量方案。[240]在使用较长治疗方案时，未发现后续复发方面的获益。相反，第二项研究试图通过比较 40 mg/m² 隔日给药4周与 40 mg/m² 隔日给药2周在罕见复发型肾病综合征儿童中的疗效，确定使用较低口服泼尼松剂量的非劣效性。[241]两组儿童的复发率相似。然而，本研究未确立短期方案的非劣效性。这些结果支持如上所述，在诱导 SSNS 儿童缓解后，使用口服泼尼松/泼尼松龙 40 mg/m² 隔日给药约4周。未来更大规模的研究可能确定，在这种情况下，可有效使用较低剂量的口服泼尼松/泼尼松龙。

实践要点4.3.2.3：对于无糖皮质激素毒性的频繁复发肾病综合征或激素依赖性肾病综合征儿童，后续复发可采用相同的糖皮质激素治疗方案。

实践要点4.3.2.4：对于无严重糖皮质激素相关不良反应的频繁复发性肾病综合征儿童，可处方低剂量隔日口服泼尼松/泼尼松龙（最佳£0.5 mg/kg/d）以预防复发。

建议4.3.2.2：对于发生严重糖皮质激素相关不良反应的频繁复发的肾病综合征儿童和所有激素依赖性肾病综合征儿童，我们建议处方糖皮质激素节制药物，而不是不治疗或仅继续糖皮质激素治疗 (1B)。

该建议对观察性数据和广泛的临床经验给予了相对较高的重视，这些数据和经验证明，与不治疗相比，长期糖皮质激素相关的副作用风险较大，且糖皮质激素减量药物预防复发的疗效较好。

关键信息

平衡危害。NS的并发症可分为直接疾病相关和治疗相关。很少有研究将糖皮质激素和糖皮质激素节制疗法与单用安慰剂进行比较。然而，历史观察数据明确表明，在未接受治疗或对任何治疗无反应的儿童中，感染、AKI以及水肿和血栓栓塞并发症的死亡风险较高。[242]

在一项评估环孢素降低复发率疗效的临床试验中入组的 SSNS 儿童的10年随访研究中，至少一半接受评价的儿童发生了糖皮质激素的重度副作用，包括重度生长障碍、肥胖和低骨密度。这些结果归因于2年时停用环孢素后因频繁复发而暴露于糖皮质激素。[233]对儿童期发病的 NS 患者进行的额外长期随访表明，长期暴露于糖皮质激素导致的高血压、骨质疏松症和白内障的患病率较高。[234,243,244]

为避免或减轻糖皮质激素相关不良反应，FRNS或SDNS 患儿需要其他药物治疗，包括烷化剂（环磷酰胺）、左旋咪唑、利妥昔单抗、吗替麦考酚酯 (MMF) 和CNI（环孢素、他克莫司）。

研究一致表明，与糖皮质激素单药或安慰剂相比，二线治疗在降低 FRNS 或 SDNS 儿童复发方面具有获益。最近对26项比较现有免疫抑制药物与安慰剂/无治疗的试验进行了荟萃分析，结果显示苯丁酸氮芥、环磷酰胺、左旋咪唑和利妥昔单抗在6个月和12个月随访时的复发率显著低于安慰剂或无治疗。[245]

这些药物的不良反应包括降低生育力（烷化剂）、肾功能不全、高血压 (CNI)、白细胞减少症和严重感染风险增加（所有二线治疗选择）。尽管存在这些挑战，但该工作组认为，这些治疗的总体获益超过了与长期糖皮质激素暴露相关的几乎普遍的毒性经验。一些不良反应，如左旋咪唑引起的白细胞减少，是不常见的、轻度的和可逆的。此外，存在减轻一些糖皮质激素节制药物的这些潜在副作用的策略，包括将环磷酰胺的累积暴露量限制在 < 168 mg/kg，并监测 CNI 和 MMF 药物水平。

证据质量。质量评价的重点是单独使用糖皮质激素节制药物，但总体质量为中等。比较烷化剂、左旋咪唑或利妥昔单抗与安慰剂或糖皮质激素的 RCT 对重要结局有中等质量的证据。然而，在 FRNS 和 SDNS 患者中比较 CNIs 和 MMF 与左旋咪唑的 RCT 分级较低，因为证据的间接性和研究的局限性（见下文）。尽管这些治疗的证据质量较低，但 RCT 证据的总体质量被分级为中等，因为大多数已被更广泛检查的糖皮质激素节制药物具有更高质量的证据。许多 RCT 未报告长期临床结局，如全因死亡率和肾衰竭，因为这些事件在该人群中罕见。

在 FRNS 患者中，与糖皮质激素或安慰剂相比，使用环磷酰胺或苯丁酸氮芥的6-12个月复发结局的证据质量为中等（研究局限性），12-24个月为较低（研究局限性，少量患者和事件的严重不精密度；补充表S16 [246–253]）。鉴于在12-24个月检查复发的试验中患者较少，6-12个月的复发被认为是最关键的结局。

RCT 显示，在 FRNS 和 SDNS 患者中比较左旋咪唑与糖皮质激素、安慰剂或不治疗的证据质量为中等，因为在 FRNS 患者中仅有1项RCT，在 SDNS 患者中有1项试验（补充表S17 [213,252–260]）。

比较 MMF 与左旋咪唑的1项 RCT 的证据质量较低（补充表S18 [253,261]）。由于参与者、研究人员和评估者结局设盲不充分以及不精确（仅1项研究），重要结局的证据质量被降级。

一项 RCT 在首次 SSNS 发作的患者中比较了环孢素联合泼尼松与泼尼松单药（补充表S19 [253、262、263]）。尚不清楚该人群中有多少患者患有 FRNS 或 SDNS，因此证据质量被降级。此外，由于严重不精密度（仅1项研究），本试验中的证据质量被降级，导致分级较低。

比较利妥昔单抗与安慰剂或标准治疗的试验的证据质量为中等，因为分别存在严重不精密度（少数患者）和严重偏倚风险，对于3个月和6个月时复发的重要结局，认为这是评定证据质量的最关键结局，因为其他结局的受试者数量较少（补充表S20 [209、253、264–269]）。对于12个月时的复发，证据质量降级为中度，因为只有2项研究，并且发现了显著的异质性 (I^2 ¼80%)。感染证据的质量非常低，因为 CI 非常宽，表明存在明显的获益和损害。

在 FRNS 或 SDNS 患者中，尚无 RCT 检查 MMF 单药治疗与无治疗或糖皮质激素单药治疗的比较。

价值和偏好。根据该工作组的判断，与长期糖皮质激素暴露相关的不良反应对患者及其父母至关重要。与不受控制的肾病相关的高发病率，以及许多停用糖皮质激素的 FRNS 儿童疾病复发的频率较高，使得非治疗选择不可行。工作组还认为，由于潜在的风险缓解策略（如药物水平监测和剂量），糖皮质激素减量治疗的潜在不良反应（如感染风险、生育力降低、肾功能不全和高血压）对患者的损害较小

局限性。总体而言，工作组认为避免与长期糖皮质激素暴露相关的不良反应对患者及其父母比糖皮质激素减量治疗的潜在不良反应更为重要。[270,271]

*资源使用和成本。*CNI、烷化剂、MMF和利妥昔单抗比糖皮质激素昂贵得多，可能需要持续的临床和/或实验室监测。一些糖皮质激素节制药物（或他们需要的监测）不可用（例如左旋咪唑）或在所有情况下均可负担。然而，与预防糖皮质激素诱导的不良事件相关的避免成本可能抵消了糖皮质激素节制治疗成本的增加。

*实施考虑。*相对效应

在实践中描述了保留糖皮质激素的治疗。除预期疗效外，治疗决策中还应考虑以下因素：年龄、耐受频繁静脉切开术进行安全性实验室检查的能力、患者对每日口服治疗的偏好以及静脉输注时不频繁住院的情况。

依据

在每个地理区域的多个机构的指南中，限制糖皮质激素对 FRNS 和 SDNS 儿童的长期不良反应的目的是一致的。KDIGO 2012 年指南（最近的 2015 年 Cochrane 儿童 SSNS 治疗综述）、英国儿科协会指南和印度儿科肾病组均建议对类固醇依赖的儿童考虑糖皮质激素减量治疗，尤其是表现出糖皮质激素样毒性的儿童。

实践要点4.3.2.5：理想情况下，在开始使用糖皮质激素节制药物如口服环磷酰胺、左旋咪唑、吗替麦考酚酯(MMF)、利妥昔单抗或钙调磷酸酶抑制剂 (CNI) 之前，患者应使用糖皮质激素缓解。建议在开始糖皮质激素减量治疗后‡2周内同时给予糖皮质激素。

尽管糖皮质激素节制药物的目标是让患者不使用糖皮质激素，但尽管给予了糖皮质激素节制药物，仍可能需要低剂量每日或隔日糖皮质激素来维持 SDNS 的缓解。隔日泼尼松治疗效果不佳的 SDNS 患儿，可给予最低剂量的每日泼尼松以维持缓解，无重大不良反应。

实践要点4.3.2.6：从口服环磷酰胺、左旋咪唑、MMF、利妥昔单抗和 CNI 中选择最合适的糖皮质激素节制药物需要仔细考虑特定患者相关问题，如资源、依从性、不良反应和患者偏好。口服环磷酰胺

和

左旋咪唑可能是经常复发的肾病综合征患者首选的糖皮质激素减量治疗。在类固醇依赖性肾病综合征儿童中，MMF、利妥昔单抗、CNI以及口服环磷酰胺（在较小程度上）可能优于糖皮质激素节制疗法（图41[178]）。

*环磷酰胺。*与类固醇依赖患者相比，频繁复发的患者对环磷酰胺和左旋咪唑的反应可能更优。[272]在143例因FRNS、SDNS或糖皮质激素毒性证据而接受口服环磷酰胺治疗的儿童中，FRNS儿童的持续缓解率高于 SDNS 儿童 (HR：1.72；95%CI：0.99-2.98；P¼0.05)。[273]无-

尽管如此，这种治疗可能在一些 SDNS 患者中发挥作用，尤其是在世界上其他糖皮质激素节制药物不可用的地区。在90例接受单疗程口服环磷酰胺（2 mg/kg/d，持续10-12周）的 SDNS 儿童中，1年时的累积缓解状态为57%。[274]与<4岁的儿童相比，年龄大于7.5岁的 FRNS 儿童在接受环磷酰胺治疗时更有可能获得长期缓解。[274]就诊时年龄较小且有需要更高剂量的类固醇依赖（>1 mg/kg/天的糖皮质激素）以维持缓解似乎与口服环磷酰胺治疗后持续较少的再入院相关。[275]性腺毒性似乎对雄性的影响大于对雌性的影响，数据支持剂量依赖性关系。当环磷酰胺累积暴露超过 168 mg/kg 时，已充分证实无精子症。为此，第2疗程烷化剂不推荐。

*左旋咪唑。*左旋咪唑的不良反应不常见且为轻度，包括白细胞减少症和胃肠紊乱。比较环磷酰胺和左旋咪唑的数据非常有限，在治疗中止后的复发率或感染事件的频率方面，并不能确定一种治疗与另一种治疗相比的疗效。[276]与安慰剂相比，左旋咪唑已被证明可以延迟糖皮质激素停药后的至复发时间，26%接受左旋咪唑治疗的患者至少1年无复发，而安慰剂组仅有6%的患者无复发。[258]本试验中的不良事件很少，主要限于中性粒细胞减少症，其在治疗中止后很容易逆转。在一项139例 FRNS 和 SDNS 儿童的试验中，MMF在停用糖皮质激素后的持续缓解方面并不优于左旋咪唑，但在更严重形式 (SDNS) 的儿童中显示出优效性趋势。[261]

*MMF。*在接受 MMF 治疗的 FRNS 或 SDNS 儿童中报告了停用糖皮质激素后维持缓解的不同结局，这些结局主要限于回顾性观察性数据。最近在60例 FRNS 儿童中进行的一项交叉 RCT 直接比较了 MMF 和环孢素的疗效。MMF治疗期间36%的患者复发，而环孢素治疗期间仅15%的患者复发

Treatment	Dose and duration	Clinical tips
First line:		
• Oral cyclophosphamide	2 mg/kg/d for 12 weeks (maximum cumulative dose 168 mg/kg)	Cyclophosphamide should not be started until the child has achieved remission with glucocorticoids. Moreover, second courses of alkylating agents should not be given. Weekly CBCs are recommended during the treatment course to assess for severe leukopenia or overall bone marrow suppression prompting dose reduction or treatment cessation
• Oral levamisole	2.5 mg/kg on alternate days, with a maximum dose of 150 mg	Monitor CBC every 2–3 months and alanine and aspartate aminotransferases every 3–6 months during therapy with levamisole. Check ANCA titers every 6 months, if possible, and interrupt treatment in case of ANCA positivity, skin rash or agranulocytosis. Maintaining low-dose alternate-day glucocorticoid dosing on the days not taking levamisole may be effective in some children. Levamisole should be continued for at least 12 months
Alternative agents:		
• Mycophenolate mofetil	Starting dose of 1200 mg/m^2/d (given in two divided doses)	Target area under the curve >50 μg•h/ml.* Mycophenolate mofetil should be continued for at least 12 months, as most children will relapse when it is stopped. In children experiencing significant abdominal pain on mycophenolate mofetil, other mycophenolic acid analogs (MPAAs), such as sodium mycophenolate, may be employed at equivalent doses (360 mg of sodium mycophenolate corresponds to 500 mg of mycophenolate mofetil)
• Rituximab	375 mg/m^2 i.v. × 1–4 doses	Rituximab may be used as a treatment for steroid-sensitive nephrotic syndrome in children who have continuing frequent relapses despite optimal combinations of prednisone and glucocorticoid-sparing oral agents, and/or who have serious adverse effects of therapy. Current trials report 1 to 4 doses of rituximab. There are insufficient data to make a recommendation for specific number of needed doses. Where available, CD20 levels should be monitored. Hepatitis B surface antigen, hepatitis B core antibody, and a QuantiFERON test for tuberculosis must be checked prior to rituximab administration. Monitoring IgG levels both before and after rituximab therapy may allow for earlier identification of risk for developing significant infection and identify patients who may benefit from immunoglobulin replacement
• Calcineurin inhibitors†		CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– Cyclosporine	4 to 5 mg/kg/d (starting dose) in two divided doses	Cyclosporine may be preferable in patients at risk for diabetic complications. Target 12 hour trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity
– Tacrolimus	0.1 mg/kg/d (starting dose) given in two divided doses	Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side effects of cyclosporine are unacceptable. Target 12 hour trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity

图 41 SSNS 患儿的糖皮质激素减量治疗*Gellermann *et al.*[178]†CNI通常每日两次给药，但可以每日给药一次，具体取决于制剂。在体型较小的儿童（< 6岁）中，环孢素的日剂量可分为3次给药（每8小时一次），以获得稳定的血液水平。CNI的血液水平不能提供细胞内水平的信息。CNI的目标范围基于移植文献。KDIGO工作组承认肾小球疾病的靶点尚不清楚。大多数临床医生检查这些水平以验证依从性并避免 CNI 毒性。目前，CNI最合理的剂量可能是在个体患者中滴定以获得对蛋白尿的预期作用，平衡剂量递增与血清肌酐，并在以下情况下降低剂量
血清肌酐升高，但未达到平台期或升高超过基线的30%。如果减量后血清肌酐水平未下降，应停用CNI。ANCA，抗中性粒细胞胞浆抗体；CBC，全血细胞计数；CNI，钙调磷酸酶抑制剂；SSNS，类固醇敏感性肾病综合征。

(P¼0.06)。在第一年，环孢霉素组的无复发时间显著长于 MMF 组 (P < 0.05)，但在第二年并非如此(P¼0.36)。值得注意的是，除环孢素组 eGFR 更低和贫血更多表明肾毒性更多外，治疗组之间的不良事件相似。[178]

Gellermann et al 的*事后*分析。比较 MMF 与环孢素的研究提供的数据表明，靶向较高的曲线下面积(AUC) 水平可以减少治疗期间的复发。[178]MPA暴露量较低 (AUC < 50 mg h/ml) 的儿童每年复发1.4次，而 MPA 暴露量较低的儿童每年仅复发1.4次。

高暴露人群每年复发0.27次 (AUC > 50 mg ,h/ml; P < 0.05)。该研究还表明，与 CNI 治疗相比，肾毒性较小。

利妥昔单抗。一些 RCT 和非 RCT 表明，利妥昔单抗在 SDNS 和 FRNS 患者中的反应良好。[265,267,269,277]在 Iijima et al 进行的 RCT 中。在48例 FRNS 或 SDNS 儿童中，存在显著差异（267天vs. 101天无复发 [HR：0.27；95%CI：0.14–0.53]；P < 0.0001）

在接受利妥昔单抗与安慰剂的患者中观察到。[278]在一项30例 SDNS 儿童的随机非劣效性试验中，除1例安慰剂组儿童外，所有儿童在6个月内复发，与接受利妥昔单抗治疗的儿童的中位至复发时间18个月相比（95%CI：9–32个月）。[269]发现利妥昔单抗可使总复发次数从88次降至22次，每例患者的中位复发次数从2.5次（四分位距 [IQR]：2–4）降至0.5次 (IQR：0–1；P < 0.001)。[277]

与安慰剂相比，接受利妥昔单抗治疗的 FRNS 儿童报告的不良事件（如感染）发生率较低。In the Ravani et al.试验中，输注期间恶心和皮疹很常见。[269]NEMO试验中未发生此类事件，事实上，1年后在受试者中观察到生长速度改善和 BMI 降低。尚无研究直接比较利妥昔单抗与环磷酰胺治疗儿童的不良事件发生率。在200例成人 MN 患者中进行的一项回顾性研究报告，在中位随访40个月期间，利妥昔单抗治疗患者的严重 (11 vs. 46，P < 0.001) 和重度 (63 vs. 173，P < 0.001) 不良事件显著少于环磷酰胺治疗患者

非严重 (52 vs. 127，P < 0.001) 不良事件。[279]

CNI（*环孢素和他克莫司*）。中止 CNI 治疗后复发较为常见。既往试验报告，治疗6个月和12个月后，高达70%停用 CNI 的儿童复发。然而，在30%–40%接受环孢素治疗超过12个月的儿童和高达80%治疗超过4年的儿童中报告了输卵管间质病变。基于这些环孢素数据的最佳治疗持续时间尚不明确，他克莫司的数据甚至更稀少。为了降低 CNIs 的成本，同时给予

据

报告，酮康唑可将达到目标谷浓度所需的剂量降低近50%，从而使成本节约近38%，且疗效未降低。

儿童耐类固醇性肾病综合征

在第4周对糖皮质激素未达到完全缓解的儿童中，诊断为SRNS。如果达到部分缓解，则强烈怀疑SRNS，但一小部分儿童将在6周时达到完全缓解（定义为晚期缓解者）。第6周时未发生 SRNS 的患者将被定义为 SRNS 患者。在糖皮质激素治疗开始后4–6周，应开始 RASi，并应继续糖皮质激素给药。可使用静脉注射甲泼尼龙（每日1剂，持续3天）、每日泼尼松龙或隔日泼尼松龙。一旦确诊为SRNS，第一步是考虑免疫抑制可能无用的遗传原因的可能性。因此，如果可能，应迅速实施专家进行的基因检测。SRNS的遗传形式总是在不同的时间过程中进展为肾衰竭，应保守治疗，尽管已发现少数基因突变对免疫抑制治疗（主要是CNI）有一定的反应性。在没有 SRNS 地磁原因的儿童中，相当大比例的儿童将在不同的时间（数周至数月）内对 CNI 作出反应。CNI应答的初始 SRNS 儿童随后或保持稳定缓解，无复发或很少复发，或发生类固醇依赖性NS。对于后一种患者，如前所述治疗SDNS，并考虑转换为 MMF 以维持无类固醇缓解。eGFR < 30 mL/min的患者也可考虑 MMF

1.73 m ^{2}或在缓解状态维持 > 1年后用作 CNI 的替代治疗。[280]罕见情况下，初次诊断为 SSNS 的儿童在4周糖皮质激素治疗后复发且无应答（次要SRNS）。在这些病例中，通常为多重耐药，导致肾衰竭和移植后复发的高风险。

对于 CNI 耐药的 SRNS 儿童，应强烈考虑考虑进入即将进行的评价新型疗法的临床试验。Sparsentan是一种双重内皮素和ARB，在一项仅接受厄贝沙坦治疗的患者的 II 期随机双盲试验中发现其可使蛋白尿减少45%vs 19%，组间严重不良事件无差异。[280a]一项 III 期多中心试验正在进行中。LDL单采的批准后研究正在进行中，并为 CNI 耐药 SRNS 儿童提供了额外的临床试验选择。如果临床试验不可用，利妥昔单抗治疗的作用可能有限。

关于这些方面的更详细建议

关于儿童 SRNS 并发症的护理和管理，请参考最新的国际儿科肾病协会 (IPNA) 指南。[280]

4.4 治疗

建议4.4.1：我们建议使用环孢素或他克莫司作为类固醇耐药肾病综合征儿童的初始二线治疗 (1C)。

该建议对数据的价值相对较高，表明在治疗 SRNS 儿童时，CNI比环磷酰胺、MMF或利妥昔单抗更可能诱导缓解。相反，其给出的证据值相对较低，表明长期暴露于 CNI 可能导致显著肾毒性。

关键信息

*平衡危害。*在 SRNS 患者中，最常用的药物包括环孢素、他克莫司、高剂量i.v.甲泼尼龙和MMF，但 SRNS 中这些药物的疗效低于 FRNS 或SDNS。几项 RCT 表明，与不治疗相比，环孢霉素（联合或不联合糖皮质激素）增加了患者缓解的可能性。[208,281–284]来自欧洲 PodoNet 登记处的研究者报告，在2015年研究中随访的1174例 SRNS 儿童中，几乎62%接受了环孢霉素。[285]这些儿童中至少有一半达到了完全或部分缓解。一项包含138例激素耐药性 FSGS 儿童和年轻成人的 RCT 比较了环孢素与 MMF 联合地塞米松冲击治疗。[286]在本研究中，未发现两组之间的缓解率差异。本研究旨在随机分配500例患者；但是，招募人数较少可能显著不足以测量中度效应。最近对包含790例诊断为 SRNS 的儿童的18项临床试验进行了网络荟萃分析，结果发现，与i.v.或口服环磷酰胺、MMF、来氟米特、苯丁酸氮芥、硫唑嘌呤和安慰剂或不治疗相比，他克莫司和环孢素在达到缓解状态方面更有效，且不良反应更少[287]。

尚未发现环磷酰胺在 SRNS 儿童中的作用，利妥昔单抗的数据表明其在 SRNS 中的作用有限或无作用。[246,277,288,289]接受环孢霉素或他克莫司的 SRNS 儿童发生部分和完全缓解的频率显著高于接受环磷酰胺静脉给药的儿童。[290,291]最近在60例他克莫司治疗6个月后至少达到部分缓解的儿童中进行的一项 RCT 显示，他克莫司预防复发比 MMF 更有效（接受他克莫司治疗的患者在30.3人年中复发24例，而接受 MMF 治疗的患者在21.2人年中复发39例）。[292]

尚未发现环孢素和他克莫司之间的疗效差异，但环孢素的文献更广泛。[293]环孢素和他克莫司的肾毒性风险相似，但牙龈增生和多毛症在

他克莫司组环孢素和葡萄糖不耐受的发生率更高。不同的副作用特征可指导环孢素和他克莫司之间的选择（参见*实施的考虑事项*）。环孢素与 MMF 联合地塞米松的大型试验表明，2个治疗组之间的不良事件发生率相似。

*证据质量。*RCT证据的总体质量较低。仅有少数小型试验检查了 SRNS 患者的治疗。这些试验的样本量不足以确定治疗之间的差异；它们具有各种研究局限性，如高损耗偏倚。然而，尽管有1项比较（环孢霉素与 MMF 联合地塞米松）的证据等级质量较高（证据质量中等），但大多数比较的证据质量较低；因此，证据的总体质量被评定为较低。

在比较环孢素与安慰剂的3项 RCT 中，或无治疗，由于研究限制（失访偏倚）和患者数量较少导致的严重不精密度（n¼49；补充表S21[282–284、294]），证据质量较低。由于证据质量非常低，对不良事件（如感染）的影响尚不清楚，并且考虑到检查该结局的试验中纳入的参与者数量较少 (n ¼17)，因此认为其在确定该比较证据评级的总体质量方面并不关键。

2项比较 CNI 与i.v.环磷酰胺的 RCT 的证据质量较低（补充表S22[290、291、294]）。由于损耗偏倚和严重不精密度，证据质量被降级，因为这些 RCT 中只有少数患者（152名参与者）。

比较环孢素与 MMF 和地塞米松的 RCT 的证据质量中等（补充表S23[286、293–295]）。由于试验招募不足（患者人数较少），无法排除治疗之间的差异，因此将观察结果的质量降级为中度。

一项 RCT 在60例受试者中比较了他克莫司与 MMF 维持疾病缓解的能力（补充表S24[292、294]）。由于研究中未设盲和严重不精密度（患者和事件数量较少），证据质量较低。

*价值和偏好。*工作组对数据的评价相对较高，表明 CNI 治疗在诱导 SRNS 儿童缓解方面优于无治疗和对照药物（如环磷酰胺和MMF）。工作组还对与未治疗的 SRNS 相关的进展性肾衰竭的高风险[285]以及与未治疗的 NS 相关的发病率（例如水肿、感染、血栓并发症）给予了相对较高的重视。工作组对 CNI 治疗副作用相关的发病率（包括肾毒性）的价值相对较低。根据工作组的判断，所有或几乎所有充分知情的 SRNS 患者将接受 CNI 相关发病的风险，以换取 SRNS 导致肾衰竭的风险较低。

Treatment	Dose and duration	Clinical tips
Calcineurin inhibitors	• Oral cyclosporine 5 mg/kg/d (starting dose) in two divided doses. Target 12-h trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity or • Oral tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses for a minimum of 6 months. Target 12-h trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity	CNIs should be continued for at least 12 months as 70% of those who achieve a complete response or partial response will relapse upon discontinuation. They should be discontinued in those without at least a partial response by 6 months. Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side effects of cyclosporine are unacceptable. Cyclosporine may be preferable in patients at risk for diabetic complications. There are no studies that investigate differences in long-term outcomes in SRNS on the basis of treatment duration. Median time to complete response or partial response is variable. Response can be seen as long as 6 months following treatment initiation. Trough levels could be measured to minimize nephrotoxicity
Glucocorticoids	• i.v. methylprednisolone bolus of 500 mg/m^2/d for 3 days prior to starting CNI. Followed by taper: alternate-day oral prednisolone to be tapered gradually over 6 months • Low-dose prednisone (<0.25 mg/kg/d alternate day dosing)	Most clinical trials and observational studies have included low-dose glucocorticoids in combination with CNIs to induce remission. No studies compare the outcomes between children treated with CNIs alone or in combination with low-dose glucocorticoids
Cyclophosphamide	• Not recommended	Two randomized control trials provide moderate-level data demonstrating no benefit using cyclophosphamide to treat children with SRNS. However, in countries with limited resources where CNIs are not available, this approach may be considered
Mycophenolate mofetil	• Starting dose of 1200 mg/m^2/d (given in two divided doses) for 1 year	This approach may be employed in children who have achieved stable remission on a CNI, to maintain remission without accumulating nephrotoxicity
Rituximab	• 375 mg/m^2 i.v.	Giving two infusions (day 1 and day 8) at this dose may be preferable in the presence of nephrotic-range proteinuria to achieve complete B cell depletion. Hepatitis B titers must be checked prior to rituximab administration. Monitoring IgG levels both before and after rituximab therapy may allow for earlier identification of risk for developing significant infection and identify patients who may benefit from immunoglobulin replacement

图42|儿童 SRNS 的治疗。CNI，钙调磷酸酶抑制剂；i.v.，静脉内；SRNS，类固醇耐药型肾病综合征。

*资源使用和成本。*药物成本和治疗药物监测需求带来的经济负担可能会限制环孢素或他克莫司的可及性，尤其是在资源匮乏的地区。在资源丰富的领域，付款人的变异性可能同样挑战广泛的可用性。医生和患者需要权衡治疗的成本负担和潜在长期不良反应与肾衰竭高风险和非治疗相关的其他疾病。

*实施考虑。*针对性基因检测
如可用，可能对某些患者有用。确定致病性足细胞特异性突变可避免在某些情况下不必要的免疫抑制治疗累积暴露，并有助于预测可能的治疗－

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他反应性。在Trautmann et al.的研究中，74例可识别足细胞突变的儿童中有11%在强化免疫抑制方案（包括各种糖皮质激素、他克莫司或环孢素和 MMF 联合治疗）后至少达到部分缓解。[285]尽管足细胞特异性突变患者的治疗缓解率较低，但减轻至少部分缓解的儿童的肾病并发症可能是有价值的。少数突变与治疗反应性相关。例如，已发现携带 WT1 和 PLCE1 突变的患者对低剂量 CNI 具有不同的类固醇反应性和反应性。[296,297]已确定携带COQ2、COQ6和 ADCK4 突变的患者的蛋白尿疾病减轻。

泛醌补充剂[298–300]与 CNI 相关的多毛症和牙龈肥大可能会妨碍治疗依从性，尤其是在青少年中。在肥胖患者或可能有糖尿病风险或已出现葡萄糖不耐受体征（如棘皮症）的患者中，可能需要避免使用他克莫司。如果患者在6个月内未达到部分缓解，则应停止 CNI 治疗（图42）。

依据

在 SRNS 儿童中，与不治疗相比，CNI似乎可增加缓解的可能性，并且一致显示疗效优于环磷酰胺和MMF。单药治疗或联合治疗未能达到部分或完全缓解的患者发生肾衰竭的风险显著更高。比较环孢霉素与他克莫司在 SRNS 儿童中疗效的数据很少且质量较低，因此，在考虑不同的副作用特征后，应根据提供者、患者和家人的偏好决定是否使用一种药物。尽管 CNI 治疗与不良反应相关，但工作组判断，所有或几乎所有知情良好的 SRNS 患者都会选择 CNI 治疗，因为未经治疗的 SRNS 相关的肾衰竭风险较高。

4.5 特殊情况

实践要点4.5.1：图43[301、302]概述了肾病综合征儿童的一般原则。

研究建议

RCT 需要：

- 比较8周与12周口服泼尼松/泼尼松龙作为初始治疗：探索进一步缩短初始糖皮质激素治疗方案，并在疾病发作时评估与糖皮质激素节制药物的联合治疗
- 优化不同形式疾病复发后 SSNS 的后续治疗
- 在感染开始时优化糖皮质激素治疗的给药方案
- 确定 FRNS 和 SDNS 中糖皮质激素节制药物的最佳剂量和选择
- 评价 SRNS 中糖皮质激素治疗的最佳持续时间，尤其是在开始 CNI 治疗时，并根据足细胞病相关基因突变的鉴定对患者进行分层
- 确定糖皮质激素和其他免疫抑制剂在 SSNS 中的作用方式；确定药物基因组学在治疗中的潜在作用；确定生物标志物或遗传风险单倍型，以对疾病亚组进行分层
- 在评估 SSNS 和 SRNS 儿童治疗的临床试验中纳入生活质量指标作为终点

Indication for kidney biopsy*	• Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to glucocorticoids in steroid-sensitive nephrotic syndrome (secondary steroid-sensitive nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, systemic symptoms of vasculitis, hypocomplementemia, etc.) • At onset, kidney failure not related to hypovolemia. Subsequently, decreasing kidney function in children receiving calcineurin inhibitors or prolonged exposure to calcineurin inhibitors (2 to 3 years)
Genetic testing	• Steroid-resistant nephrotic syndrome • Congenital and infantile forms of nephrotic syndrome (<1 year of age) • Nephrotic syndrome associated with syndromic features • Family history of steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis
Vitamin D/calcium	In patients with steroid-sensitive nephrotic syndrome and normal vitamin D levels, supplementation is not required. However, in frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome in children or in the presence of a known vitamin D deficiency, a reduction in bone mineral content can be prevented by oral supplementation with oral calcium and vitamin D.[1,2]
Gastroprotection	There is insufficient evidence of benefit to recommend prophylactic use of proton-pump inhibitors in children with nephrotic syndrome in the absence of risk factors for gastrotoxicity or of gastric symptoms.

图 43 NS 患儿的一般原则。*如果蛋白尿有明显的肾外原因（即淋巴瘤、溃疡性结肠炎的单克隆抗体治疗、人类免疫缺陷病毒），可能不需要进行肾活检。NS，肾病综合征。[1]Gulati 等人[301]，[2]Gruppen 等人[302]

第5章：成人微小病变 (MCD)

微小病变型疾病 (MCD) 是一种更常见于儿童的足细胞病，但也占成人 NS 的10%–25%。[303]大多数患者的 MCD 无基础病因。MCD的发病机制尚不清楚，但有证据支持 T 细胞失调驱动足细胞病。[304]B细胞耗竭治疗药物的有效性也表明 B 细胞在疾病发病机制中发挥作用。[214]罕见，霍奇金病以及锂剂和非甾体类抗炎药等药物可能是 MCD 的基础[305]。本章针对患有 MCD 的成人（$18岁）提出管理建议。

5.1 诊断

实践要点5.1.1：成人 MCD 只能通过肾活检进行诊断。

MCD 具有独特的组织学，其存在不能仅从临床数据推断出。光学显微镜下未见肾小球病变，或仅有轻微的系膜突起。免疫荧光显微镜检查为阴性或显示 C3 和/或 IgM 的低强度染色。电子显微镜检查显示广泛的足突消失，但无电子致密沉积物，在不显著的光和免疫荧光存在的情况下，结果可诊断MCD。一个警告是，如果活检样本较小，早期 FSGS 病变可能会被漏诊。

5.2 预后

实践要点5.2.1：对糖皮质激素有反应的 MCD 患者的长期肾脏存活率极佳，但对无反应的患者不太确定。

类固醇敏感性 MCD 很少（如果有）进展为肾病，但高度蛋白尿引起的 AKI 相对常见。[306]约10%–20%的成人 MCD 患者对类固醇耐药。[307]在重复活检时，在大量此类患者中观察到 FSGS 病变，并且预后更差。[60,306]类固醇耐药性 FSGS 的治疗在第6章中讨论。

5.3 治疗

一般而言，成人 MCD 与儿童 SSNS 相似。然而，成人对糖皮质激素治疗的反应比儿童慢。缺乏评价糖皮质激素与安慰剂相比治疗成人 MCD 有效性的高质量 RCTevidence。成人 MCD 的治疗建议是基于观察性研究、小型 RCT 和 SSNS 儿童 RCT 的外推。

建议5.3.1：我们建议在 MCD (IC) 的初始治疗中使用高剂量口服糖皮质激素。

该建议对低质量证据的价值相对较高，表明与不治疗相比，高剂量糖皮质激素可有效降低与 NS 延长相关的显著发病率。该建议对 MCD 未经治疗自行缓解的可能性以及与糖皮质激素治疗相关的不良事件风险给出了相对较低的价值。

关键信息

*平衡危害。*尽管未经治疗的 MCD 可能会自发缓解，但这种情况相对不常见。约50%–60%的患者缓解超过2–3年随访，而 MN 在6个月内的自发缓解率为30%，[308,309]且与持续性肾病相关的发病率相当高，包括感染、[310]血栓栓塞事件、[311]和高脂血症。[312]

MCD 通常对糖皮质激素有反应，超过80%的患者达到缓解。[306,313]观察性研究一致报告，成人对糖皮质激素作为 MCD 初始治疗的反应率较高。[306,307,313–316]在一项非常早期的糖皮质激素多中心对照研究中，与不治疗相比，125例肾病成人（包括31例仅通过光学显微镜确定的 MCD 患者）接受$20 mg/d泼尼松治疗$6个月的患者显示蛋白尿早期快速减少，与对照组相比。然而，到2.5年时，两组的蛋白尿或血清白蛋白没有差异。[308]同样，在另一项 RCT 中，28例 MCD 患者接受平均 125 mg 泼尼松隔日一次治疗2个月，在77个月随访期间，治疗组和对照组之间的缓解率没有差异。[309]这种差异可能是由于治疗组尽管早期缓解但复发率显著，加上大量安慰剂治疗患者甚至接受了糖皮质激素治疗。

此外，许多高质量研究表明，糖皮质激素可有效治疗儿童SSNS（第4章）。儿童和成人 MCD 的 SSNS 在发病机制方面似乎相似。因此，儿童中糖皮质激素治疗的获益可能至少部分扩展至成人。在儿童中，几项 RCT 显示，糖皮质激素给药8 –12周的缓解率极佳[215–217]。

因此，根据工作组的判断，在几乎所有 MCD 患者中，高剂量糖皮质激素治疗的潜在获益均低于危害风险。

证据质量。检查糖皮质激素治疗 NS 成人 MCD 首次发作的少数 RCT 的证据质量较低（补充表S25[309,317]和补充表S26[317–319]）。这些 RCT 仅包括少量参与者，并且存在各种研究局限性，使其处于偏倚高风险中。此外，由于参与者数量较少，试验表现出严重的不精密度，CI较宽表明对关键和重要结局（如全因死亡率、SCr水平加倍和完全缓解）的影响确定性较低。

价值和偏好。工作组认为糖皮质激素治疗的潜在获益，包括降低 NS 的发病率以及降低进行性肾功能丧失的风险，对患者至关重要。工作组还判断，短期糖皮质激素治疗的危害风险相对较低，包括糖尿病沉淀/恶化、精神疾病和骨丢失，将是许多患者的重要考虑因素。尽管支持使用糖皮质激素的证据质量较低，但该方案的长期临床经验、与未经治疗的肾病相关的显著发病率以及与进行性肾功能丧失或肾衰竭相关的过高发病率和死亡率以及较低的危害风险均表明风险比–benet高度有利。该建议很强，因为根据工作组的判断，所有或几乎所有充分知情的 MCD 患者都希望接受此类治疗。

资源使用和成本。糖皮质激素价格低廉，几乎不需要监测（例如，无需测量药物水平）。在资源匮乏的环境中，这类药物是可负担的，可能是唯一可用的类型。[107]

实施考虑。在某些患者亚组（例如，肥胖患者和糖尿病控制不佳或患有严重精神疾病的患者）中，糖皮质激素的不良反应可能更高。在这些患者中，可考虑其他免疫抑制方案，如 CNI 或环磷酰胺（图44）。人种或性别对 MCD 的治疗反应无已知影响。

依据

由于与长期 NS 和进行性肾衰竭相关的发病率显著降低，工作组认为这应该是一个强烈建议。工作组认为，高剂量糖皮质激素的获益大于潜在危害，该建议可推广至所有 MCD 患者。尽管证据存在局限性，例如缺乏在成人中进行的大型、对照良好的研究，但这些局限性被糖皮质激素的长期临床经验以及来自大型观察性研究的证据所抵消，这些证据表明，与不治疗相比，糖皮质激素治疗确实能更早地诱导成人 MCD 的缓解。该建议很强，因为根据工作组的判断，与不治疗或其他治疗相比，所有或几乎所有充分知情的患者将选择接受高剂量糖皮质激素作为 MCD 的初始治疗。此外，该治疗相对便宜，需要最低限度的监测。

实践要点5.3.1：成人 MCD 的初始治疗算法（图44）

实践要点5.3.2：MCD的高剂量糖皮质激素治疗应不超过16周。

尽管缺乏 RCT 证据，但最长持续时间建议16周以使患者达到缓解。该声明基于观察性研究，表明与儿童相比，成人可能需要更长的 MCD 疗程。糖皮质激素治疗4周后，仅50%的患者会产生应答，但总共治疗16周后，10%–25%的患者可能会产生应答。[306,315]

实践要点5.3.3：完全缓解后2周开始糖皮质激素逐渐减量。

尚不清楚成人缓解后的最佳糖皮质激素逐渐减量方案。一般情况下，在达到缓解后开始逐渐减少糖皮质激素。在2项儿童 RCT 中，初始泼尼松龙治疗2–3个月在至

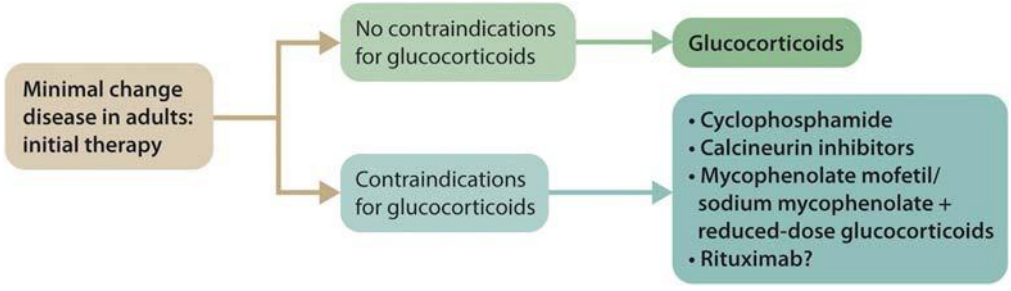

图44成人 MCD 的初始治疗。最佳糖皮质激素治疗方案尚不明确；但建议剂量见图45。药物的选择应基于医生和患者的偏好。MCD，微小病变。

Medication	Regimen	Remission rates (complete and partial)
Initial episode, glucocorticoid treatment		
Prednisone or prednisolone	Dose: 1 mg/kg per day (maximum 80 mg/day) or 2 mg/kg every other day (maximum 120 mg every other day), for a minimum of 4 weeks, and a maximum of 16 weeks (as tolerated). After remission, taper over at least 24 weeks	80%–90%
Initial episode with contraindication to glucocorticoids		
Oral cyclophosphamide	2–2.5 mg/kg per day for 8 weeks	75%
Cyclosporine	3–5 mg/kg per day in divided doses for 1–2 years	75%
Tacrolimus	0.05–0.1 mg/kg per day in divided doses for 1–2 years	90%*
Frequently relapsing/ steroid-dependent patients		
Oral cyclophosphamide	2–2.5 mg/kg/day, adjusted for white blood counts, for 8–12 weeks. 12 weeks may be associated with less relapse in steroid-dependent MCD	75%
Calcineurin inhibitors	**Initial dose:**	
• Cyclosporine	3–5 mg/kg per day in divided doses for 1–2 years	70%–90%
• Tacrolimus	0.05–0.1 mg/kg per day in divided doses for 1–2 years	90%
	• If serum levels are being monitored, suggested initial levels: - Cyclosporine: 150–200 ng/ml (125–166 nmol/l) - Tacrolimus: 4–7 ng/ml (5–8.7 nmol/l) • After withdrawal of glucocorticoids reduce CNI dose if possible Suggested doses: <3mg/kg/day for cyclosporine and <0.05 mg/kg/day for tacrolimus • Attempt gradual taper and discontinuation of CNI after a minimum of one year of therapy if possible • If CNI-dependent reduce dose to lowest possible to maintain remission with monitoring of kidney function (kidney biopsy if kidney dysfunction) Switch to alternate medication if evidence of CNI toxicity	
Rituximab	**Induction regimens:** • 375 mg/m^2 weekly for 4 doses • 375 mg/m^2 × single dose; repeat after one week if CD19 cells >5/mm^3 • 1 g/dose for 2 doses, 2 weeks apart **Relapse after induction:** • 375 mg/m^2 × 1 dose or • 1g i.v. × 1 dose	70% (20% off all immunosuppression, 50% on one other immunosuppressive drug)
Mycophenolic acid analogues	**Initial dose:**	
• Mycophenolate mofetil	1000 mg twice daily	
• Sodium mycophenolate	720 mg twice daily	
	• Attempt gradual taper and discontinuation of mycophenolic acid analogues after a minimum of one year of therapy if possible	

图45成人 MCD 的治疗：初次发作和FR/SD MCD。*未在头对头研究中比较缓解率。CNI，钙调磷酸酶抑制剂；MCD，微小病变。

[215,217]尚无研究在成人中比较糖皮质激素快速减量与缓慢减量。基于病例系列，糖皮质激素通常在达到缓解后逐渐减量 5–10 mg/周，糖皮质激素的总暴露时间约为24周。[306,310,315]重要的是监测患者的糖皮质激素副作用，如果副作用致残或未达到缓解，考虑使用替代药物。

实践要点5.3.4：尽管每日口服糖皮质激素最常用于治疗MCD，但给药途径和频率可根据患者需求进行个体化治疗。

在2项 RCT 中比较了*i.v.*甲泼尼龙 + 低剂量口服泼尼松与标准剂量口服泼尼松单药的作用。未发现这些方法在最终缓解和后续复发率方面存在差异。[318–320]

成人观察性研究显示2种方案的缓解率相似。[306,321]例如，在一项比较65例患者泼尼松 1 mg/kg/d 和23例患者泼尼松 2 mg/kg 隔日一次然后逐渐减量的研究中，治疗组之间的完全缓解率、至缓解时间、复发率、至首次复发时间或不良事件无显著差异。[306]

实践要点5.3.5：对于糖皮质激素可能相对禁忌的患者，考虑环磷酰胺、CNI或 MMF 初始治疗。

关于初次 MCD 发作时不使用糖皮质激素或不使用糖皮质激素的治疗方案的研究很少。这些治疗在有亲属

禁忌症（重度高血糖、既存骨质疏松或骨质减少或糖皮质激素诱导的精神病）或不愿意使用糖皮质激素。环磷酰胺[307、322–324]和环孢素[325]的缓解率约为75%，经验有限（图45）。在116例患者的 RCT 中，麦考酚钠 (SMP) 联合减量泼尼松（每日0.5 mg/kg/d，最大剂量40 mg）在诱导缓解方面与常规高剂量泼尼松单药（每日1 mg/kg/d，最大剂量80 mg）相似，完成治疗后复发率相当。治疗组之间严重不良反应的频率也相似。[326]

在比较口服他克莫司0.05 mg/kg两次的 RCT 中与泼尼松龙 1 mg/kg/天达 60 mg 联合给药时，两组之间的完全缓解率和复发率没有差异。[327]使用利妥昔单抗（375 mg/m ^{2}，每周一次，共4次）作为一线治疗用于治疗6例 MCD 患者，6例患者中的5例完全缓解，1例患者蛋白尿减少75%。[328]尽管 B 细胞计数恢复，但在8–36个月随访期间无患者复发。

5.3.1 复发的治疗

MCD 是一种复发性疾病。大多数患者会在缓解后不久复发，但相当少数的患者会频繁复发或出现类固醇依赖性。高达33%的患者将成为频繁复发者 (11%–29%) 或类固醇依赖性 (14%–30%)。[306,307,316,320]缓解和复发定义在 MCD 临床分类中有用，见图46。尚不清楚糖皮质激素治疗复发性 MCD 的最佳持续时间。一种方案是口服泼尼松，每日剂量为 1 mg/kg

Complete remission
Reduction of proteinuria to <0.3 g/d or PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/l)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Steroid-resistant MCD
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for >16 weeks
Frequently relapsing MCD
Two or more relapses per 6 months (or four or more relapses per 12 months)
Steroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing glucocorticoid therapy

图 46 MCD 缓解、复发、耐药和依赖性的定义MCD，微小病变；PCR，蛋白-肌酐比值。

（最大剂量 80 mg/日）4周或直至缓解，随后每3-5天递减5 mg，1-2个月内停药。

对于后续复发，如果不频繁（例如，每年 < 3次），长期使用糖皮质激素会引起副作用，包括库欣综合征、肥胖、葡萄糖耐受不良、骨丢失和白内障。[329]几种药物对 FR/SD MCD 有效，可减少糖皮质激素的暴露或消除（图45）。

实践要点5.3.1.1：成人频繁复发 (FR)/激素依赖性 (SD)MCD 的治疗算法（图47）

实践要点5.3.1.2：使用糖皮质激素治疗罕见复发（图46）。

如果治疗持续时间有限，不常见的复发可以使用糖皮质激素治疗，而不会产生重大副作用。尚未充分研究糖皮质激素治疗罕见复发患者的剂量和持续时间。在一项研究中，患者接受 20-30 mg 泼尼松龙治疗至少7天或加用环磷酰胺直至蛋白尿恢复至正常范围，表明可能不需要高剂量的糖皮质激素（与 MCD 的初始治疗相同）。[330]随着疗程的延长和重复，可能会发生累积副作用（例如高血糖症和骨丢失）。一项在52例首次 MCD 复发的 MCD 成人患者中比较环孢霉素 (AUC 1700–2000 ng/mL[1414–1664 nmol/L]) 联合泼尼松龙0.8 mg/kg/d与泼尼松龙1.0 mg/kg/d的RCT，结果显示在6个月随访期内，环孢霉素组的蛋白尿减少、血清白蛋白改善、至缓解时间缩短。[331]

建议5.3.1.1：我们建议使用环磷酰胺、利妥昔单抗、CNI或麦考酚酸类似物 (MPAA) 治疗频繁复发/类固醇依赖性MCD，而不是泼尼松单药或不治疗 (1C)。

该建议对避免与长期糖皮质激素相关的发病具有相对更高的价值

FR/SD MCD 中的暴露量。与泼尼松相比，它对支持环磷酰胺、利妥昔单抗、CNI和霉酚酸类似物 (MPAA) 疗效的低质量证据的价值相对较低，对这些替代药物较高成本的价值较低。可根据患者偏好、药物副作用影响、成本和可用性来选择 FR/SD MCD 的治疗，因为提示一种药物类别优于另一种药物类别的证据有限。

关键信息

*平衡危害。*由于 MCD 是一种类固醇敏感性疾病，预期其他免疫抑制药物在该人群中有效。据报告，CNI（环孢素、他克莫司）、环磷酰胺、利妥昔单抗和 MPAA(MMF、SMP) 均为 FR/SD MCD 的有效疗法。

*临床用品。*观察性研究和小型 RCT 显示，所有4类药物均可降低 FR/SD MCD 成人患者的复发率并诱导缓解（图48[277、306、315、332-338、340]）。维持缓解的有效率范围为70%-90%。通常，这些药物在使用糖皮质激素诱导缓解后开始使用。考虑到肾上腺抑制的可能性，接受糖皮质激素维持治疗的患者可能无法完全停用糖皮质激素。

*环磷酰胺。*在发生糖皮质激素副作用的 FR/SD 患者中，环磷酰胺传统上是首选的二线药物。这种做法是根据儿童临床试验外推得出的，因为主要来自观察性研究[306、315、331]和1项比较他克莫司与环磷酰胺的 RCT 的成人数据相对较少[332]。在育龄期患者中，不育风险虽然较小，但仍需要加以解决。在大多数 FR/SD 患者中，口服环磷酰胺单疗程与缓解相关。考虑到累积毒性，应避免长期治疗（> 12周）和重复环磷酰胺疗程。与 CNI 相比，环磷酰胺往往与更持久的缓解率相关。[333]与8周治疗相比，环磷酰胺治疗12周可能与 SD MCD 中更持久的缓解相关。[307]

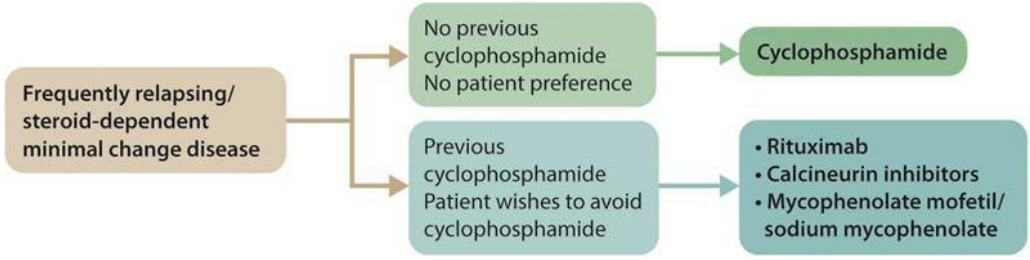

图47成人 FR/SD MCD 的治疗。应根据医生和患者的偏好选择药物。FR/SD，频繁复发/激素依赖性。

Author (ref)	Study design (n with MCD)	Intervention	Outcome
Waldman *et al.*[1]	Observational (39 SD, FR, SR pts)	Cyclosporine trough 150–220 ng/ml (125–183 nmol/l) × 49 ± 14.8 weeks. (12 pts received prednisone 5–10 mg qod)	Remission: 61% Mean time: 5 weeks (2–9)
Meyrier *et al.*[2]	Observational (52/98 SD pts)	Cyclosporine 150–220 ng/ml (125–183 nmol/l) 5 mg/kg/d + prednisone 12–15 mg qod	CR 71% of SD pts at 6 months
Lee *et al.*[3]	Observational (22/27 FR, SD, SR pts)	Cyclosporine 150–220 ng/ml (125–183 nmol/l) 5 mg/kg/d + prednisolone 10 mg/d up to 8 months	CR 84% of SD pts Relapse: 68% at 10 months
Li *et al.*[4]	Prospective cohort study (26 SD pts)	Tacrolimus 4–8 ng/ml (5–10 nmol/l): target trough level 4–8 ng/ml × 24 weeks Cyclophosphamide: intravenous cyclophosphamide (750 mg/m^2, every 4 weeks × 24 weeks)	Tacrolimus: CR 90.9% Cyclophosphamide: CR 76.9% (after 24 weeks therapy) Relapses: tacrolimus: 50%, cyclophosphamide 40%
Ponticelli *et al.*[5]	Randomized, controlled (66 FR, SD MCD pts)	Cyclosporine 150–220 ng/ml (125–183 nmol/l) 5 mg/kg/d × 12 months vs. cyclophosphamide 2.5 mg/kg/d × 8 weeks	Cyclosporine: CR 26/35, PR 5/35 Cyclophosphamide: CR 18/28 Relapse: cyclosporine 75% vs. cyclophosphamide 37%
Mak *et al.*[6]	Observational (22, FR, SD, SR pts)	Cyclophosphamide 2–2.5 mg/kg/d × 8 weeks	CR 86% at 1 year, 74% at 3 years, 63% at 5 years
Waldman *et al.*[1]	Observational (20 SD, FR SD pts)	Cyclophosphamide mean dose 123.6 mg/d for 11.5 + weeks	Remissions: 55% Mean time: 6.4 weeks (5–12)
Munyentwali *et al.*[7]	Observational (17 SD, FR pts)	Rituximab 375 mg/m^2 (1–4 infusions) or 1000 mg × 2 doses, 2 weeks apart	Remission: 65% over mean follow up 26.7 months (5–82)
Iwabuchi *et al.*[8]	Observational (20 SD pts)	Rituximab 375 mg/m^2, 6 monthly × 24 months	CR 100% from 12–24 months Relapses decreased from 108 episodes to 8 (previous 24 months vs. 24 months after rituximab)
Ruggenenti *et al.*[9]	Observational (22 children and adult FR and SD pts)	Rituximab 375 mg/m^2, repeated in 2 weeks if CD20 >5 cells/mm^3	Relapses/patient decreased from 2.5 [IQR 2–4] to 0.5 [IQR 0–1]; P=0.001 during 1 year of follow-up
Guitard *et al.*[10]	Observational (41 SD, FR pts)	Rituximab: 1 g on days 1 and 15 375 mg/m^2 1–4 weekly infusions	CR: 61% PR: 17% NR: 22%
Sandoval *et al.*[11]	Observational (29 FR and SD pts)	MMF: 1500–2000 mg/d or SMP 1440 mg/d. With prednisone tapering to 0–10 mg/d	CR: 86% PR: 7% NR: 7% Mean follow-up of 32.8 months (12–108)
Waldman *et al.*[1]	Observational (10 SD, FR, SD pts)	MMF 1–2 g/d for 36 + 7.9 weeks 10 pts received prednisone 5–10 mg qod	Remissions: 65% Relapses: 35%

图 48 FR/SD 成人 MCD 的治疗-选定的临床研究。[1]Waldman *et al.*[306],[2]Meyrier *et al.*[338],[3]Lee *et al.*[337],[4]Li *et al.*[332],[5]Ponticelli *et al.*[333],[6]Mak *et al.*[315],[7]Munyentwali *et al.*[336],[8]Iwabuchi *et al.*[335],[9]Ruggenenti *et al.*[277],[10]Guitard *et al.*[334],[11]Sandoval *et al.*[340]CR，完全缓解；FR，频繁复发；IQR，四分位距；MCD，微小病变；MMF，吗替麦考酚酯；NR，无应答；PR，部分缓解；qod，隔日一次；SD，类固醇依赖性；SMP，麦考酚钠；SR，类固醇耐药性。

利妥昔单抗。利妥昔单抗在需要糖皮质激素伴或不伴其他维持免疫抑制治疗的 FR/SD MCD 患者的观察性研究中有效。[277,334-336]总体而言，利妥昔单抗诱导缓解的有效性在65%-100%之间，值得注意的是，其与复发次数减少和免疫抑制药物数量减少相关。然而，利妥昔单抗的经验有限，尚不清楚在该人群中的长期疗效/风险。

钙调磷酸酶抑制剂。在观察性研究和1项 RCT 中，在70%-90%的 FR/SD MCD 患者中，CNI与缓解相关。然而，复发率较高，当患者在剂量减少期间复发时，可能需要延长治疗时间。[60,337,338]鉴于 CNI 的经验相对较长，这些药物可能更适合用于接受环磷酰胺疗程后复发的患者或因不育问题而倾向于避免使用烷化剂的患者。监测 CNI 药物水平的价值尚不确定。较早的研究使用了基于固定体重的剂量，而最近使用的目标药物水平的报告。

MPAA。MMF和 SMP 在小型、非对照

在 FR/SD MCD 患者中进行的对照研究，缓解率在65%-85%范围内。[306,339,340]鉴于这种有限的经验，MPAA可能在环磷酰胺和 CNI 治疗后复发的患者中发挥作用，当利妥昔单抗不可用时也有作用。

AE。所有4类药物均与感染风险增加相关。CNI具有潜在肾毒性，但在 MCD 中使用的血清水平较低，这种副作用并不常见。[60]儿童 MCD 中肾小管间质病变的风险因素包括在环孢霉素治疗期间使用环孢霉素 > 24个月和出现重度蛋白尿 > 30天。[61]环磷酰胺、MPAA和利妥昔单抗的潜在副作用在第1章中讨论。在 FR/SD MCD 中使用的剂量下，环磷酰胺通常耐受良好，且仅限于单个疗程时。

证据质量。迄今为止，尚无在 MCD 伴 FR/SD NS 成人患者中检查环磷酰胺或利妥昔单抗使用的RCT。

几项 RCT 检查了 CNI 与糖皮质激素单药相比在 MCD 和 NS 成人中的使用。[331,341,342]这些 RCT 的证据质量较低，因为存在由于各种研究限制和严重不精密度导致的严重偏倚风险问题，因为只有少数研究的参与者数量较少（补充表S27 [317, 331,341-343]）。这些 RCT 未报告关键临床结局、全因死亡率或肾衰竭。

价值和偏好。工作组认为，减少糖皮质激素暴露的潜在获益对患者具有重要意义。但是，4种替代疗法中的每一种都与潜在的权衡相关。包括增加的

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NI 和 MPAA 每日两次给药的负担，以及需要频繁进行血液检查以监测 CNI 的给药和副作用。尽管环磷酰胺的副作用风险相对较低，并且与其他3类相比更便宜，但由于存在不孕风险，育龄期患者可能更倾向于避免使用环磷酰胺。患者可能首选利妥昔单抗，因为药物作为单个疗程给药进行诱导。

资源使用和成本。本节讨论的药物（尤其是利妥昔单抗）比糖皮质激素更昂贵。需要持续监测 CNI 的血清水平，增加成本。环磷酰胺的成本低于其他3类，广泛可用，除监测外周血计数外，不需要任何额外的实验室检查。MPAA使用方便，不需要血清监测，但成本可能是一个限制因素。利妥昔单抗是这些药物中成本最高的，但随着生物类似药的出现，成本有所下降。

实施考虑。无已知信息

基于性别和种族的二线药物治疗反应差异。使用环磷酰胺与不育风险相关。MPAA、环磷酰胺和利妥昔单抗禁用于妊娠妇女。CNI被归类为美国食品药品监督管理局(FDA) 妊娠期 C 类药物。考虑使用环磷酰胺或利妥昔单抗的患者应在给药前检测HBV。

通常，复发的 FR 患者在引入二线药物前再次接受糖皮质激素治疗，直至达到缓解。引入第二种药物后，糖皮质激素逐渐减量，一般在2-4周内可耐受。3-6个月后，如果患者仍然依赖糖皮质激素，那么应该停用新药，并考虑其他疗法。

如果在药物治疗期间复发，建议增加或恢复糖皮质激素治疗，与 MCD 初始发作相同，随后根据反应在2-4周内逐渐减量。用于治疗成人 MCD 的建议用药方案见图45。

依据

工作组认为，由于在 FR/SD MCD 成人患者中使用糖皮质激素时发生不良事件，且低质量证据表明4种药物类别可有效降低复发率，因此该建议很有说服力。工作组认为，这些药物的获益大于与治疗相关的潜在不良事件。大多数知情同意的患者会选择减少/停用糖皮质激素，以减少/避免副作用；然而，最佳二线药物尚不明确。需要在患者充分参与的情况下解决的因素包括

在决定药物选择前，每种药物类别的相对疗效、不良反应、治疗持续时间和成本。

研究建议

- 尽管糖皮质激素治疗通常有效，但相当少数的患者无应答，最终需要二线治疗。识别可能/不可能对糖皮质激素有反应的患者的研究，包括使用生物标志物或基因组学

方

法，可能会得到更精确、更合理的治疗。

- 考察长期糖皮质激素的发病率、糖皮质激素治疗的最佳时长（短期与长期）以及糖皮质激素减量/无糖皮质激素治疗方案在成人 *MCD* 中的疗效的研究
- 利妥昔单抗、*CNI*、环磷酰胺和 *MPAA* 治疗 *SD/FR MCD* 的*RCT*，包括最佳剂量和治疗持续时间
- 探索左旋咪唑在成人 *MCD* 中的作用

第6章：成人局灶节段性肾小球硬化 (FSGS)

本章对出现蛋白尿和局灶节段性肾小球硬化 (*FSGS*) 组织学病变的成人患者提出治疗建议。

定义

围绕 *FSGS* 分类的命名不一致且令人困惑，部分原因是损伤的组织病理学模式也被视为一种独特的疾病。同样，*FSGS*的传统分类未反映围绕临床症状以及肾活检显示 *FSGS* 病变患者的诊断和治疗方法的实用性。因此，工作组建议对 *FSGS* 的命名进行变更，以提高临床实用性，并明确未破坏的病理生理学。图*49*概述了 *FSGS* 的拟定分类，图*52*列出了肾活检中 *FSGS* 病变的次要原因。

主要 FSGS

术语“原发性”和“特发性”*FSGS*可互换使用，导致对 *FSGS* 命名的大量混淆。工作组建议不再使用“特发性”来描述任何类型的*FSGS*，并认可 *FSGS* 未来的以下定义。

我们将原发性 *FSGS* 定义为临床-病理综合征，其中肾脏活检的光学显微镜检查显示 *FSGS* 病变，肾脏活检的电子显微镜检查显示弥漫性足突消失，临床上患者显示*NS*。*NS*定义为蛋白尿 > *3.5 g/d*加低白蛋白血症 (< *30 g/L*)，通常但不一定伴有血脂异常和水肿。当考虑原发性 *FSGS* 的诊断时，不应存在 *FSGS* 的其他可识别原因。尽管原发性 *FSGS* 的临床-病理综合征归因于回路通透性因素，但该因素尚未发现。目前，可合理归因于循环通透性因子的唯一形式的 *FSGS* 是肾移植后快速复发的*FSGS*，可通过血浆置换成功治疗以去除该因子。

FSGS 也可能发生在无遗传或可确定的继发性原因、无 *NS* 且肾脏活检电子显微镜检查显示无弥漫性足突消失的情况下。根据其临床和组织学表现，这种形式的 *FSGS* 与原发性 *FSGS* 不同。我们建议将这种疾病称为 *FSGS-UC*（原因不明）。可以想象，*FSGS-UC*患者有继发性或遗传形式的*FSGS*，目前尚未阐明。

次级 FSGS

当 *FSGS* 病变，伴或不伴弥漫性足细胞足突消失，在已知引起 *FSGS* 的既定病理生理过程背景下发现时，我们将其称为继发性*FSGS*。继发性 *FSGS* 的已知/推定病因见图*52*。

FSGS 的遗传形式

足细胞或肾小球基底膜蛋白发生突变的患者可发生 *FSGS* 病变。在 *FSGS* 成人中寻找遗传原因并不常规

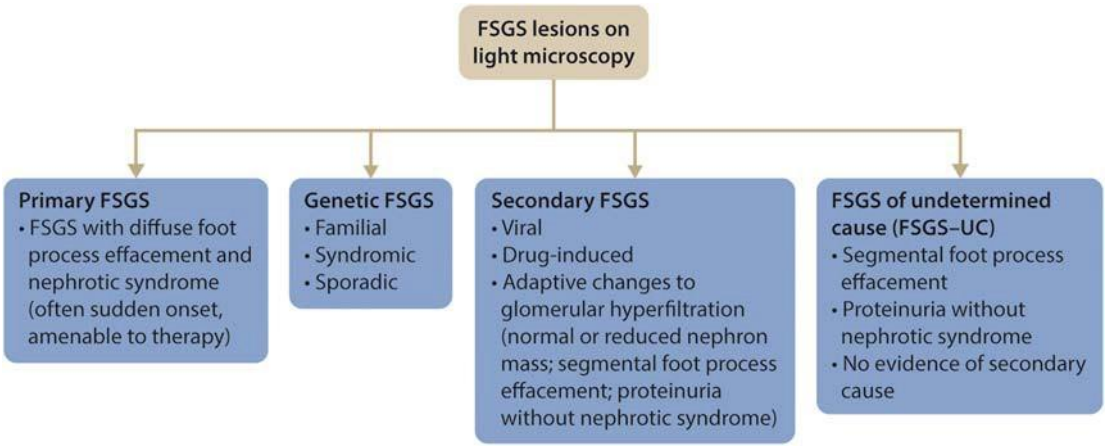

图49|FSGS的拟定分类。FSGS，局灶节段性肾小球硬化。

Complete remission
Reduction of proteinuria to <0.3 g/d or PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/l)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved or an increase in proteinuria by >50% during partial remission
Steroid-resistant FSGS
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for at least 16 weeks
Steroid-dependent FSGS
Relapse occurring during or within 2 weeks of completing glucocorticoid therapy
CNI-resistant FSGS
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite cyclosporine treatment at trough levels of 100–175 ng/ml (83–146 nmol/l) or tacrolimus treatment at trough levels of 5–10 ng/ml (6–12 nmol/l) for 4–6 months
CNI-dependent FSGS
Relapse occurring during or within 2 weeks of completing cyclosporine or tacrolimus therapy for >12 months

图 50 FSGS 缓解、复发、耐药和依赖性的定义CNI，钙调磷酸酶抑制剂；FSGS，局灶节段性肾小球硬化；PCR，蛋白-肌酐比值。

（第6.1.2节基因检测），但应根据具体情况考虑。例如，*FSGS*遗传形式的患者往往年轻，有肾脏病家族史，可有综合征特征，对免疫抑制治疗普遍耐药。如果发现 *FSGS* 的遗传原因，我们将其归类为遗传*FSGS*（图52）。

缓解、复发、耐药和依赖

关于 *FSGS* 成人患者缓解、耐药或复发的定义尚未达成共识。工作组认为，协调成人 *FSGS* 和 *MCD* 的这些定义将简化流行病学比较并统一成人特发性 *NS* 的治疗方法。缓解、复发、治疗耐药和治疗依赖性的建议定义见图50。

6.1 诊断

6.1.1 区分原发性和继发性 FSGS

实践要点6.1.1.1：应评价无肾病综合征的 *FSGS* 成人患者的次要原因（图51；图52）。

提出的 *FSGS* 组织病理学分类表明，肾活检中 *FSGS* 病变的不同变体之间存在差异。[344]尽管某些变体的出现可能提示 *FSGS* 的继发形式，但组织病理学分类在区分原发性和继发性 *FSGS* 方面的预测价值并不一致。[345–347]此外，没有组织病理学特征是原发性 *FSGS* 的特异病症。因此，尽管在电子显微镜下弥漫性足突消失通常发生在原发性 *FSGS* 中，但在原发性 *FSGS* 中受足突消失影响的肾小球表面百分比的变异性在

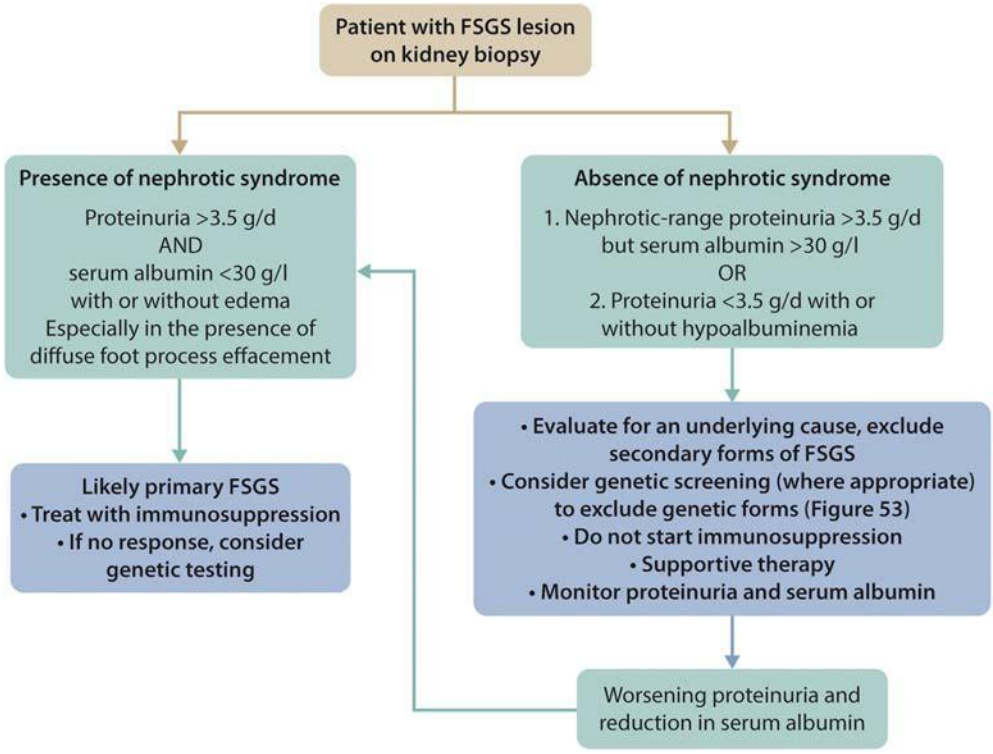

图51|肾活检显示 FSGS 病变且无其他肾小球病理证据的患者评价。FSGS，局灶节段性肾小球硬化。

Secondary to alterations of glomerular epithelial cells	
Viral infections	HIV (established) CMV (probably) Parvovirus B19, EBV, HCV (possibly) Hemophagocytic syndrome (possibly) SARS-COV-2 (with *APOL1* risk genotype)
Drug-induced	Direct-acting antiviral therapy mTOR inhibitors, CNIs Anthracyclines Heroin (adulterants) Lithium Interferon Anabolic steroids NSAIDs
Secondary to adaptive changes with glomerular hypertension	
Reduced nephron number	Reflux nephropathy Renal dysplasia Oligomeganephronia Sickle cell disease Age-related FSGS
Normal nephron number	Obesity-related glomerulopathy Primary glomerular diseases Systemic conditions, e.g., diabetic nephropathy, hypertensive nephrosclerosis

图52继发性 FSGS 的原因。*APOL1*，载脂蛋白L1；CMV，巨细胞病毒；CNI，钙调磷酸酶抑制剂；EBV，EB病毒；FSGS，局灶节段性肾小球硬化；HCV，丙型肝炎病毒；HIV，人类免疫缺陷病毒；mTOR，哺乳动物雷帕霉素靶蛋白；NSAID，非甾体抗炎药；SARS-CoV-2，重度急性呼吸综合征冠状病毒2。

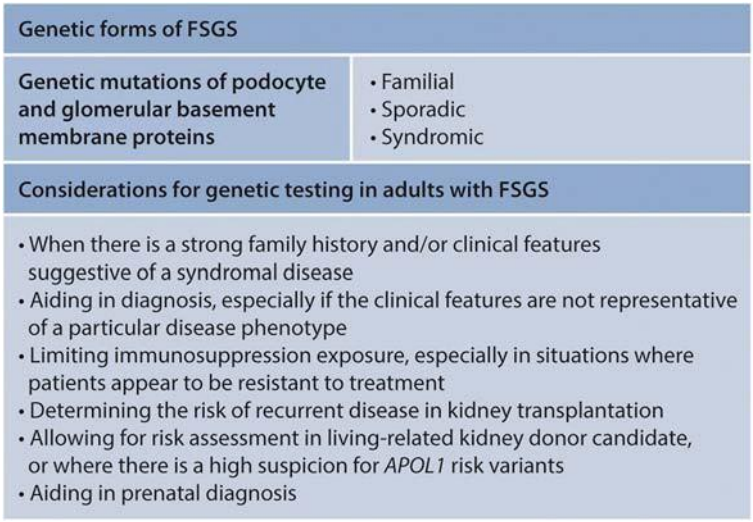

图53|FSGS患者基因检测的实用性。*APOL1*，载脂蛋白-L1；FSGS，局灶节段性肾小球硬化。

FSGS 的继发性形式表明，这种结果并不完全特定[于原发]性 FSGS。[348,349]同样，弥漫性足突消失本身可能无法区分原发性 FSGS 和 FSGS 的遗传形式。相反，弥漫性足突消失的缺失并不能完全排除原发性FSGS，在一个系列中，一些原发性 FSGS 患者的足突消失量可能低至30%。[350]

约54%-100%的原发性 FSGS 患者发生NS。[347,351–353]NS的发生率不同归因于在一些研究中纳入了未识别的继发性FSGS。原发性 FSGS 的典型特征是突然发生明显蛋白尿，在1个系列中，当排除与继发性 FSGS 相关的疾病时，在100%的原发性 FSGS 研究人群中发现NS。[352]因此，在肾活检时未发生 NS 的患者中应重新诊断原发性FSGS，并应寻找基础疾病。

6.1.2 基因检测

实践要点6.1.2.1：基因检测可能对选定的 FSGS 患者有益，这些患者应转诊至具有此类专业知识的专科中心（图53）。

最近的研究报告了家族性 FSGS 患者或糖皮质激素治疗难治的患者中致病性或可能致病性基因变异的结果。[354]然而，基因检测在成人 FSGS 管理中的确切作用尚不确定，因为在许多地区不容易获得，也不具备解释广泛可用的基因检测结果的专业知识。虽然基因检测可能在先天性或婴儿型疾病患者中产生更大的阳性结果，其中在1项研究中分别在100%和57%的患者中检测到遗传原因，[355]但在儿童早期后开始发病的患者中，遗传可能性显著降低。

因此，没有良好的数据支持在所有 FSGS 成人中常规使用基因检测。选定的患者，例如具有家族性肾病和/或综合征特征的患者，当基因检测被认为具有潜在获益时，可以转诊至专门的中心进行进一步评估（图53）。[356]

尽管大多数原发性 FSGS 成人患者对免疫抑制有反应，但治疗耐药是 FSGS 遗传形式的共同特征，尤其是糖皮质激素治疗耐药是所有形式遗传性 FSGS 的一致结果。[354]因此，当考虑对免疫抑制剂反应不佳的个体进行基因检测时，可获得更高的基因诊断率。此外，该组中基因变异的发现应促使讨论停止进一步免疫抑制治疗。

此外，已知原发性 FSGS 复发在一项特定研究中，FSGS通常发生在肾移植后，同种异体移植物结局较差，32%在移植后1.5个月的中位时间内疾病复发。[357]相反，普遍认为 FSGS 在移植后的复发率在地磁形式的疾病中显著较低，一些研究报告没有个体在肾移植后表现出疾病复发。[358,359]因此，在计划接受肾移植的 FSGS 成人中进行基因检测可提供移植结局的预后信息。

此外，活体亲属供者的基因检测对于告知移植后随后发生肾脏疾病的风险非常重要，尤其是在评估时发现存在遗传风险变异但无症状的个体中。在近期具有非洲血统的个体中，已发现 *APOL1* 遗传风险变体的存在与发生 FSGS 的几率增加相关。此外，研究还表明，*APOL1*高风险供肾的衰竭率高于非风险供肾，尚未证实受体 *APOL1* 基因型

与同种异体移植物的存活率相关。[360]因此，在具有*APOL1*风险变异体高风险的供体中，*APOL1*突变的基因检测可为供体的疾病风险和受体的同种异体移植物结果提供信息。

6.2 治疗

6.2.1 FSGS-UC 和继发性 FSGS 的管理

实践要点6.2.1.1：免疫抑制不应用于不明原因*FSGS*(*FSGS-UC*)成人患者或继发性*FSGS*患者。

成人*FSGS*患者应接受所有持续性蛋白尿患者建议的必要支持治疗（第1章），包括使用*RAS*阻断、最佳*BP*控制和饮食盐限制。

由于基础疾病过程导致继发性*FSGS*的患者应根据主要医疗状况的要求进行管理。没有证据或*先验*依据证明在该人群中使用糖皮质激素或其他免疫抑制药物是合理的，并且这种治疗的潜在危害是明确的。[361]

当患者出现不伴*NS*和*FSGS-UC*的肾病范围蛋白尿时，就会出现管理难题。[354]指导这组患者管理的文献有限。工作组建议这些患者接受上述支持治疗，监测*NS*的发生，如果其临床状态发生变化，则考虑重复肾活检。

*FSGS*的肾脏预后与蛋白尿的大量和持续相关。研究表明，在未接受免疫抑制治疗的情况下，非肾病范围蛋白尿患者的10年肾脏生存率 > 90%。[314,362–365]此外，原发性*FSGS*患者的肾病范围蛋白尿降至非肾病水平与肾脏生存率显著改善相关（80%vs. 40%），与持续性*NS*患者相比。[366]这些数据表明，无*NS*患者的肾脏结局仍然有利，不保证患者有接受糖皮质激素治疗的风险。

6.2.2 原发性 FSGS 的初始治疗

建议6.2.2.1：我们建议使用高剂量口服糖皮质激素作为原发性 FSGS *(ID)* 的一线免疫抑制治疗。

该建议对极低质量的证据给予了相对较高的价值，即使用糖皮质激素可使原发性 FSGS 成人患者的蛋白尿得到缓解，增加了无蛋白尿的进展性 CKD 的风险，以及与肾衰竭相关的高发病率和死亡率，以及对高剂量糖皮质激素的不良反应给予相对较低的价值。

关键信息

平衡危害。原发性*FSGS*患者自发缓解的真实可能性和

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*S*未知，因为许多此类患者接受免疫抑制治疗。然而，普遍认为自发缓解率 > 20%。[367,368]事实上，*NS*患者的肾脏预后比非肾病患者差，10年肾脏生存率为57%，而蛋白尿程度较低的患者为92%。[364]因此，许多观察性研究已经证明，治疗诱导的蛋白尿缓解与有利的肾脏存活率相关[364、366、367、369]，而持续性肾病范围蛋白尿患者更可能出现肾功能丧失[364]。

许多在原发性*FSGS*成人中的研究表明，糖皮质激素治疗增加了达到缓解的可能性[366,370–372]；儿童的数据相似。因此，尽管使用糖皮质激素存在固有风险，但工作组认为，该治疗的明显有效性和与未达到蛋白尿缓解相关的肾衰竭风险均支持推荐泼尼松作为原发性*FSGS*成人患者的一线治疗。*证据质量*。检索*Cochrane*肾脏和移植登记研究未发现评价原发性*FSGS*和*NS*成人患者使用高剂量糖皮质激素的*RCT*。证据质量非常低，因为形成该建议基础的证据提取自成人人群的观察性研究。还根据儿童研究外推了使用糖皮质激素的获益，其中*RCT*显示糖皮质激素治疗在*NS*患儿，其中部分为原发性*FSGS*。

价值和偏好。经判断，糖皮质激素治疗的潜在获益（包括*NS*导致的发病率降低以及进行性肾功能丧失的风险降低）对患者至关重要。工作组还判断，长期大剂量糖皮质激素治疗的危害风险，包括代谢并发症、感染风险增加和对骨骼健康的影响对患者很重要。

工作组判断，与另一种治疗或无治疗相比，大多数临床适合且知情充分的患者将选择接受糖皮质激素作为使用*NS*的原发性*FSGS*的初始治疗。一些糖皮质激素不良事件风险较高或对避免此类不良事件有较高价值的患者可选择放弃糖皮质激素作为初始治疗的试验，而倾向于替代免疫抑制。根据工作组的判断，如果有任何充分知情的患者，很少有人会选择不接受免疫抑制治疗原发性*FSGS*。

资源使用和成本。糖皮质激素是最少的可获得昂贵的药物，不需要治疗性药物监测。在资源有限的环境中，这类药物是负担得起的，可能是唯一可用的药物。*实施考虑*。糖皮质激素的不良反应在某些患者亚组中可能更高，包括肥胖患者以及糖尿病、骨质疏松症或精神疾病患者。在这样的

应与患者讨论长期大剂量糖皮质激素治疗的不良反应，并探索 *CNI* 的替代免疫抑制治疗（实践要点 6.2.2.4）。

依据

该建议对使用糖皮质激素缓解 *NS* 原发性 *FSGS* 成人患者蛋白尿的极低质量证据具有很高的价值，从而降低 *NS* 的发病率和肾衰竭风险。该建议对与糖皮质激素使用相关的不良反应给出了较低的价值。

该建议是强有力的，因为考虑到 *NS* 的发病率显著，以及进行性肾功能丧失伴持续性蛋白尿的风险增加，工作组判断大多数患者将选择糖皮质激素作为原发性 *FSGS* 的初始治疗。而且，由于其成本低、广泛可用和医生熟悉糖皮质激素，大多数医生愿意在大多数无糖皮质激素临床禁忌症的患者中考虑将该治疗作为初始治疗。

实践要点6.2.2.1：在原发性 *FSGS* 初始治疗中建议的糖皮质激素给药方案见下文图54。

Treatment	Dose and duration
Glucocorticoids	**Starting dose:** • High-dose glucocorticoid therapy with prednisone at daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg)
	High-dose glucocorticoid treatment duration: • Continue high-dose glucocorticoid therapy for at least 4 weeks and until complete remission is achieved, or a maximum of 16 weeks, whichever is earlier • Patients who are likely to remit will show some degree of proteinuria reduction before 16 weeks of high-dose treatment • It may not be necessary to persist with high-dose glucocorticoid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side effects
	Glucocorticoid tapering: • If complete remission is achieved rapidly, continue high-dose glucocorticoid treatment for 2 weeks or after the disappearance of proteinuria, whichever is longer. Reduce prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If partial remission is achieved within 8 to 12 weeks of high-dose glucocorticoid treatment, continue until 16 weeks to ascertain whether further reduction of proteinuria and complete remission may occur. Thereafter, reduce the dose of prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If the patient proves to be steroid-resistant or develops significant toxicities, glucocorticoids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI should be considered
Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 4–6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated

图54|原发性 FSGS 的初始治疗。*CNI通常每日使用两次，但可以每日给药一次，具体取决于具体制剂。CNIs的血液水平不能提供细胞内水平的信息。CNI的目标范围基于移植文献。KDIGO工作组承认肾小球疾病的靶点尚不清楚。大多数临床医生检查这些水平以验证依从性并避免 CNI 毒性。目前，CNI最合理的剂量可能是在个体患者中滴定以获得对蛋白尿的预期作用，平衡剂量递增与血清肌酐，如果血清肌酐升高但未稳定或升高超过基线的30%，则降低剂量。如果减量后血清肌酐水平未下降，应停用CNI。CNI，钙调磷酸酶抑制剂；FSGS，局灶节段性肾小球硬化。

图54显示了糖皮质激素治疗原发性 FSGS 成人患者的初始剂量。高起始剂量 1 mg/kg 泼尼松 (lo)ne 主要从儿童 RCT 外推而来，已在许多成人观察性研究中使用。由于每日高剂量糖皮质激素治疗的潜在毒性，1项观察性研究在老年FSGS（多种类型）患者中评价了隔日糖皮质激素给药，发现治疗3-5个月后的完全缓解率约为44%，[373]与使用泼尼松 (lo)1 mg/kg/d 的研究报告的缓解率相当。[366,371]

实践要点6.2.2.2：应继续初始高剂量糖皮质激素治疗，直至达到完全缓解，或患者耐受最长16周，以先发生者为准。

在治疗原发性 FSGS 时，应使用糖皮质激素直至缓解，此后逐渐减量。为了避免不适当地增加快速缓解后复发的风险，需要最短的推荐治疗持续时间。相反，由于长期治疗可能不会进一步增加缓解的可能性（或降低复发风险），因此需要最大推荐治疗持续时间来降低糖皮质激素暴露的风险，而不会产生额外获益。

早期研究表明，原发性 FSGS 是一种类固醇耐药性疾病，结局不佳。[314,362,363,374-376]然而，随后的观察性研究表明，初始剂量越高、治疗持续时间越长，对糖皮质激素治疗的反应越好。[314,364,367,369,377]尚未确定成人原发性 FSGS 中高剂量糖皮质激素治疗的最佳持续时间，也未确定考虑类固醇耐药性 FSGS 诊断前的治疗持续时间。然而，患者不可能耐受高剂量泼尼松的长期治疗。

在成人 MCD 患者中进行的观察性研究表明，将高剂量糖皮质激素治疗时间延长至16周可使缓解率增加10%-25%。[307,315,330,378,379]原发性 FSGS 的疗效低于MCD；因此，超过16周的额外治疗获益不太可能。将高剂量泼尼松治疗的最长持续时间定义为16周，避免过早标记治疗失败和使用二线免疫抑制剂进行不必要的治疗，后者通常更昂贵。

基于现有证据，尚不确定糖皮质激素治疗16周的副作用是否显著差于疗程较短的副作用，以及在原发性 FSGS 中副作用是否超过获益，因为研究在不良事件报告方面不一致。

因此，根据工作组的判断，高剂量糖皮质激素治疗的最长持续时间应为16周，因为与较长疗程相关的获益减少和毒性增加。值得注意的是，可能对治疗有反应的患者

通常在16周前显示一定程度的蛋白尿减少，通常在开始治疗后4-8周内出现。[364,367,377]如果蛋白尿持续存在且未显示减少体征，尤其是如果患者出现糖皮质激素副作用，应在16周前停止高剂量泼尼松治疗，并考虑替代治疗。

实践要点6.2.2.3：对糖皮质激素治疗有反应的原发性 FSGS 成人患者应接受糖皮质激素治疗≥6个月。

尚不清楚糖皮质激素治疗的最佳持续时间。在各种研究中，治疗方案的范围为4-24个月，报告的完全缓解率和部分缓解率分别为28%-74%和0%-50%。[314,364,367,369]一项研究发现，接受糖皮质激素治疗 > 16周的缓解率要高得多，为61%，而治疗持续时间 < 16周的患者为15%。[377]同样，另一项研究表明，对糖皮质激素治疗有反应的患者接受的中位治疗持续时间显著更长，为5.7个月。[364]相反，另一项研究发现，如果患者在6个月时对糖皮质激素治疗无反应，超过该持续时间的治疗没有获益。[367]考虑到与长期糖皮质激素治疗相关的显著毒性，拟定总治疗持续时间为6个月。图54还概述了在原发性 FSGS 成人中逐渐减少糖皮质激素剂量的建议方法。

实践要点6.2.2.4：在有糖皮质激素相对禁忌症或不耐受的成人中，应考虑将 CNI 替代免疫抑制作为原发性 FSGS 患者的初始治疗（图54）。成人可能无法很好地耐受长期高剂量糖皮质激素，并且原发性 FSGS 的长期自然史表明，糖皮质激素的副作用对于某些患者可能是不可接受的。[380]此外，肥胖、患有不受控制的糖尿病、精神疾病或重度骨质疏松的患者可能被认为是糖皮质激素的相对禁忌症。理想情况下，此类患者将考虑接受糖皮质激素的替代治疗。然而，尚无 RCT 检查替代免疫抑制剂作为一线疗法治疗成人原发性FSGS。

尽管如此，观察性研究表明，CNI可用于降低总体暴露，甚至避免糖皮质激素治疗的需要。一项对51例原发性 FSGS 成人患者的回顾性综述显示，在肥胖、临界性糖尿病或骨病患者中，低剂量泼尼松龙联合环孢素或硫唑嘌呤。[270]与单独使用高剂量泼尼松龙 (62.5%) 相比，低剂量泼尼松龙联合硫唑嘌呤或环孢素的联合完全缓解率和部分缓解率更高，分别为80%和85.7%。此外，一项小型观察性研究

证实他克莫司单药治疗在6.5 5.9个月后在所有6例患者中均达到部分缓解，避免了完全使用糖皮质激素。[381]此外，使用 CNI 治疗类固醇耐药性原发性 FSGS 的有利结果进一步支持使用 CNI 作为初始治疗选择。

图54概述了使用 CNI 作为原发性 FSGS 成人替代一线治疗的建议治疗方案。将 CNI 视为原发性 FSGS 一线治疗的其他观察性研究考虑的环孢素初始剂量为3 mg/kg/d，平均持续时间为25个月无治疗药物监测，[370]或他克莫司为 4 mg/日，目标谷水平为4-7 ng/mL(5-9 nmol/L)，平均持续时间为13.611.8个月。[381]

6.3 特殊情况

6.3.1 类固醇耐药性原发性FSGS。

建议6.3.1.1：对于类固醇耐药性原发性 FSGS 成人患者，我们建议环孢霉素或他克莫司给药‡6个月，而不是继续糖皮质激素单药治疗或不治疗 (1C)。

该建议对泼尼松治疗无效的患者在降低肾衰竭风险和继续使用糖皮质激素相关的过度风险方面达到蛋白尿前缓解具有很高的价值。该推荐对环孢素或他克莫司治疗肾毒性的成本和风险以及在接受这些药物治疗的患者中监测药物水平的需求价值较低。

关键信息

*平衡危害。*许多观察性研究表明，蛋白尿减少和缓解的实现与肾脏结局改善相关[314、351、366、372]，并且对糖皮质激素的耐药性与原发性 FSGS 成人患者的肾衰竭风险密切相关[314、372]在未达到缓解的患者中，5年和10年肾脏存活率分别为 60%-90% 和 25%-56% 。[314,362,363,382]尽管在不可能产生应答的患者中继续使用高剂量糖皮质激素治疗会产生不必要的副作用，但类固醇耐药患者的肾脏预后较差且蛋白尿持续存在，故需要使用替代免疫抑制策略来尝试达到缓解。CNI环孢素和他克莫司是2种此类替代品。

在2项小型 RCT 中评价了环孢素在类固醇耐药的预设原发性 FSGS 成人患者中的有效性。在1项研究中，在患有SRNS（包括 MCD 和原发性FSGS）的成人和儿童患者中使用环孢素单药治疗6个月，并与支持治疗进行比较。[284]第二项 RCT 仅纳入了 SR 原发性 FSGS 成人患者，并比较了环孢霉素治疗26周与安慰剂治疗。[281]所有患者均接受低剂量泼尼松治疗。在相应的2项研究中，接受环孢素的研究人群中分别有60%和70%达到缓解。

没有在类似情况下评价他克莫司的RCT。然而，非对照研究表明，他克莫司可能是环孢素的替代品。[381,383,384]一项非对照研究考察了他克莫司联合低剂量糖皮质激素治疗原发性 FSGS 和类固醇耐药以及环孢素耐药或环孢素依赖成人患者6个月的情况。[384]分别有40%和8%出现完全缓解和部分缓解。平均缓解时间约3个月。约40%的患者发生急性可逆性 GFR 下降。另一项前瞻性研究评价了他克莫司在类固醇耐药原发性 FSGS 成人患者中的使用，持续48周，发现总体缓解率改善（完全缓解：38.6%；部分缓解：13.6%），平均至缓解时间为15.2周，急性可逆性肾毒性为15.9%。[383]根据工作组的判断，这些有限的观察数据以及他克莫司和环孢素相似的作用机制表明，他克莫司或环孢素均可用于治疗类固醇耐药原发性FSGS。

由于使用环孢素后缓解可能缓慢发生，并且在某些观察性研究中报告需要长达4-6个月的时间，我们建议在将患者标记为环孢素耐药之前，应尝试最短6个月的治疗持续时间。工作组认为，他克莫司的最短治疗持续时间也适合6个月，因为他克莫司通常被认为是一种更强效的免疫抑制药物，对环孢素耐药或环孢素依赖性疾病患者有效，但超过6个月不太可能提高治疗缓解率。

*证据质量。*由以下人员进行系统综述
在类固醇耐药原发性 FSGS 成人患者中比较环孢素（伴或不伴糖皮质激素）与支持治疗或泼尼松治疗的ERT（补充表S28 [284、385]；补充表S29 [281、385]；补充表S30 [385、386]）。

在一项小型RCT(n¼22) 中，比较了环孢素单药治疗与支持治疗，结果显示环孢素在发生ESKD、> GFR下降50%、SCr加倍和感染的效应估计值方面更优。然而，由于研究的局限性和 CI 非常宽（表明存在明显的危害和影响），该证据的质量非常低。设法达到完全缓解的患者太少；因此，无法从该 RCT 中得出环孢素治疗是否对完全缓解产生影响的结论。此外，研究人群具有异质性，包括 MCD 和 FSGS 成人和儿童患者（补充表S28 [284、385]）。

当环孢素联合低剂量泼尼松与单用泼尼松治疗比较时，用

环孢霉素在达到部分缓解方面的获益更大，且肾衰竭风险更低。由于研究的局限性以及该比较仅有1项小型RCT(n¼49)，现有 RCT 的证据质量较低。[281]2组之间部分缓解的影响程度较大（环孢霉素组342/1000例患者vs.泼尼松单药组43/1000例患者）。与之前的系统综述相似，设法达到完全缓解的患者太少；因此，无法根据该 RCT 得出环孢霉素治疗是否对完全缓解产生影响的结论（补充表S29 [281、385]）。同样，在1项小型RCT(n¼25) 中，达到完全缓解的患者太少，无法确定环孢霉素 + 泼尼松龙与甲泼尼龙单药治疗相比是否产生差异（补充表S30 [385、386]）。

*价值和偏好。*疾病缓解和蛋白尿减少在减轻 NS 相关发病率和进行性肾功能丧失风险方面的获益被判定为对患者至关重要。工作组还判断，长期糖皮质激素治疗的有害副作用对患者至关重要，即使与不治疗相比，此类治疗可产生临床获益，但尚不确定。工作组还判断，患者会认为环孢素或他克莫司的肾毒性风险不如长期糖皮质激素治疗相关的副作用重要，或者未经 CNI 治疗的肾衰竭风险更高，特别是如果通过仔细监测药物水平和使用尽可能短的 CNI 治疗疗程来降低 CNI 毒性的风险。

*资源使用和成本。*环孢素和他克莫司治疗的经济负担远高于糖皮质激素治疗或不治疗，因为这两种药物的价格均显著高于糖皮质激素，并且监测药物水平需要额外费用。此外，环孢素和他克莫司（包括仿制药）可能不可用，在资源匮乏的环境中，医疗保健机构可能无法报销。不幸的是，在这种情况下，治疗选择有限，医生需要权衡继续糖皮质激素治疗的风险与治疗中止后进展为肾衰竭的影响。

*实施考虑。*没有头对头

环孢素和他克莫司治疗成人类固醇耐药原发性 FSGS 患者的头比较。然而，一项非对照研究表明，他克莫司治疗对环孢素治疗反应不佳的患者有益。[384]以下章节讨论了对任一 CNI 的偏好。

依据

该建议在降低肾衰竭风险和与持续

泼

尼松治疗无效的患者使用糖皮质激素，以及环孢霉素或他克莫司治疗的肾毒性成本和风险价值较低。

该建议是强有力的，因为尽管没有证实的获益和明显的危害可能性，但工作组判断，所有或几乎所有充分知情的原发性 FSGS 患者如果类固醇耐药，将选择停止糖皮质激素治疗，并将转换为环孢素或他克莫司。

6.3.2 环孢霉素和他克莫司的给药方案操作要点6.3.2.1：类固醇耐药性治疗主要FSGS：环孢霉素和他克莫司的推荐给药方案（图S5）。

图S5概述了类固醇耐药原发性 FSGS 成人患者的拟定治疗方案。环孢素的初始起始剂量为3.5～6 mg/kg/d [281,387]，大多数从 5 mg/kg/d 开始。[60,284,338,388已发现389]剂量 > 5.5 mg/kg/d的环孢素与肾毒性风险增加相关。[60]药物谷水平靶标的变异性更大，从50延伸至600 ng/mL(42–500 nmol/L)。[281,284,387–389]考虑到环孢素的成本、剂量相关肾毒性以及不太可能需要紧急治疗水平，以较低剂量开始治疗并逐渐增加剂量至目标谷水平似乎是合理的。除了1项研究的目标环孢素谷水平为250–600 ng/mL(208–500 nmol/L) 外，[284]大多数研究显示出诱导缓解的能力，谷水平为 100–225 ng/mL(83–187 nmol/L)，但观察到谷水平越高，GFR下降和肾毒性的风险越大。因此，工作组认为应使用100–175 ng/mL(83–146 nmol/L) 的目标谷水平来平衡蛋白尿减少的影响和 GFR 下降的风险，并且在长期内不得超过 225 ng/mL(187 nmol/L) 的谷水平。

一项非对照研究认为他克莫司的初始剂量为0.15 mg/kg/d，目标谷水平为 5–10 ng/mL(6–12 nmol/L)。[384]然而，在该剂量下，平均谷水平在前4周超过治疗目标 (10.3–11.8 ng/mL，12.7–14.6 nmol/L)，水平在治疗目标的第25百分位数 (9.2–9.8 ng/mL，11.4–12.2 nmol/L)，表明较低剂量可能更谨慎。另一方面，另一项前瞻性研究在0.1 mg/kg/d，使他克莫司的平均谷水平达到约7 ng/mL(8.7 nmol/L)。[383]

环孢素和他克莫司之间的决定取决于多种因素，并考虑了药物可用性、药物成本、药物水平监测能力、临床因素、医生偏好和熟悉度等问题。现在两种药物的通用形式都可用，药物成本可能不是问题。从移植文献来看，有人认为他克莫司的免疫抑制作用强于环孢素，尽管

Treatment	Dose and duration
Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated • Consider discontinuing cyclosporine or tacrolimus if the eGFR continues to decline to <30 ml/min per 1.73 m^2
Inability to tolerate or contraindications to calcineurin inhibitors	• Lack of quality evidence for any specific alternative agents • Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered • Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression • Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

图55糖皮质激素抵抗的原发性 FSGS 的治疗*CNI通常每日使用两次，但可以每日给药一次，具体取决于具体制剂。CNI的血液水平不能提供细胞内水平的信息。CNI的目标范围基于移植文献。KDIGO工作组承认肾小球疾病的靶点尚不清楚。大多数临床医生检查这些水平以验证依从性并避免 CNI 毒性。目前，CNI最合理的剂量可能是在个体患者中滴定以获得对蛋白尿的预期作用，平衡剂量递增与血清肌酐，如果血清肌酐升高但未稳定或升高超过基线的30%，则降低剂量。如果减量后血清肌酐水平未下降，应停用CNI。ACTH，促肾上腺皮质激素；CNI，钙调磷酸酶抑制剂；eGFR，估计肾小球滤过率。

这尚未在成人 *FSGS* 研究中得到验证。他克莫司治疗的美容副作用往往较少，这种药物在年轻女性患者中可能更易接受，因为接受环孢素治疗的患者多毛症和牙龈肥大的风险更高，在治疗 > 1年的儿童中报告的发生率分别为70%和30%。[390]

6.3.3 CNI 治疗持续时间

实践要点6.3.3.1：对 *CNI* 治疗有反应的类固醇耐药原发性 *FSGS* 成人患者应接受 *CNI* 治疗至少12个月，以尽量减少复发风险（图55）。

尽管 *CNI* 能有效地诱导类固醇抵抗患者的缓解，但停药后复发的频率很高。在一项评价环孢素对类固醇耐药疾病影响的 *RCT* 中，40%的患者在停用环孢素后1年复发，60%的患者在停用环孢素后78周复发。[281]在另一项 *RCT* 中重复了该结果，69%的患者在停用环孢素后12个月内复发。[284]环孢素治疗的观察性研究也报告了复发率。

范围为60%-80%。与之相似，他克莫司治疗后的复发率较高，约76%的患者在停药后复发。[384]

随着每次复发，进展性 *CKD* 的风险增加，给予另一个疗程免疫抑制的患者将有更大的药物副作用和毒性暴露。必须尽一切努力将复发的风险降至最低。

尚未在类固醇耐药的原发性 *FSGS* 成人患者中确定 *CNI* 治疗的最佳持续时间，尤其是用于预防复发。一项 *RCT* 在儿童和成人类固醇依赖性和频繁复发的特发性 *NS* 中比较了环孢素和环磷酰胺，主要结局为无复发生存期。处方环孢素9个月，每月递减25%，直至12个月完全停药。在成年人群中，接受环孢霉素 (50%) 和环磷酰胺 (60%) 的患者在24个月时的复发率相似。[333]此外，在 *SRNS* 儿童中延长 *CNI* 治疗是一种常见做法，尽管这种做法的影响

尚未确立预防复发、肾毒性风险或长期肾功能的策略。这些有限的数据支持延长 CNI 治疗的时间，以最大限度地降低复发风险，尤其是在替代免疫抑制治疗的证据很少且复发风险显著的情况下。

图55概述了类固醇耐药性原发性 FSGS 的治疗方案，表明对于治疗有效的患者，CNI的治疗水平应维持至少12个月。此后，CNI可逐渐减量，包括临床状态、药物耐受性、医生舒适度和告知减量速度和幅度的财务因素。完全缓解且有药物毒性证据的患者可能需要更快地减少 CNI 剂量。

6.3.4 对 CNI 耐药或不耐受的患者

实践要点6.3.4.1：对 CNI 耐药或不耐受的类固醇耐药原发性 FSGS 成人患者应转诊至专门中心，考虑重新活检、替代治疗或入组临床试验（图55）。

缺乏证据告知对 CNIs 不耐受或耐药的激素耐药的原发性 FSGS 成人患者的治疗。工作组认为，这些患者需要高度专科护理，应转诊至具有适当专业知识的中心。几种免疫抑制药物已试用于成人特发性FSGS，其中许多药物在图55中列出并引用。但是，大多数研究的设计不佳，本质上是观察性的，不足以得出任何有效的结论，并且其结局具有异质性。此外，该组患者的额外治疗可能是无效的，可能会增加免疫抑制治疗不良事件的风险，而不是带来获益。因此，应在这些专业中心评估患者是否需要进一步免疫抑制。

在 KDIGO 2012 GN 指南中，MMF和高剂量地塞米松作为不耐受环孢素患者的替代方案被推荐了2C。该建议是基于一项比较环孢霉素与 MMF 和高剂量地塞米松联合治疗儿童和年轻成人类固醇耐药性 FSGS 的 RCT，该 RCT 显示2组之间的缓解率无统计学显著差异。[286]然而，

本试验未达到500例患者的初始招募目标，且把握度严重不足，最终仅138例患者随机接受任一治疗。因此，不能排除 MMF 方案对环孢素的劣效性。此外，对可能影响研究结果有效性的设计和入选标准存在重大担忧。[391]在考虑这些问题时，KDIGO 2021工作组同意，将 MMF 和高剂量地塞米松作为临床建议删除更为合适，并在其他治疗选择失败时将其视为替代治疗方法。

6.3.5 复发的管理

实践要点6.3.5.1：既往对类固醇敏感的原发性 FSGS 复发成人患者可采用与 MCD 复发成人患者相同的方法进行治疗（图47）。

有极低质量的证据指导原发性 FSGS 复发的治疗。如果疾病复发发生在既往对糖皮质激素治疗敏感的患者中，则建议采用与成人复发性 MCD 相同的方法处理复发（图48）。

研究建议

- 识别并验证类固醇敏感性主要 FSGS 的生物标志物；这包括识别几十年来一直难以捉摸的假定渗透性因子。
- 需要RCT：
  - 在原发性 FSGS 成人患者中评价糖皮质激素治疗（包括每日一次与隔日一次糖皮质激素）的疗效和不良反应
  - 确定原发性 FSGS 成人患者中糖皮质激素治疗的最佳持续时间，并比较与使用初始高剂量糖皮质激素治疗的短期或长期治疗相关的缓解、复发和不良事件发生率
  - 评价 CNI 联合或不联合糖皮质激素治疗成人激素耐药原发性 FSGS 患者的有效性
  - 在类固醇耐药性原发性 FSGS 成人患者中检查 CNI 治疗的最佳持续时间
  - 检查血浆置换和 LDL 置换在治疗原发性 FSGS 和预防肾移植后 FSGS 复发中的作用

第7章：感染相关肾小球肾炎

本章提供了感染相关 GN 的诊断、预后和治疗的实践指南，其可能与细菌、病毒、真菌、原虫和蠕虫感染相关。本指南在全球应用的成本影响见第1章。

7.1 细菌感染-相关 GN

细菌感染相关的 GN 可发生在细菌感染后（潜伏期后的感染后肾小球肾炎，通常在感染后数周）或存在持续、急性或慢性细菌感染。细菌感染相关 GN 包括多个实体[392]：

1. 链球菌感染后GN，在现代有点用词不当，因为链球菌感染仅占这种感染后急性 GN 的28%–47%。12%–24%的病例分离出*金黄色葡萄球菌*或*表皮葡萄球菌*，高达22%的病例分离出革兰氏阴性菌。[393]
2. 分流性肾炎是一种免疫复合物介导的GN，很少发展为脑室心房、脑室颈静脉慢性感染的并发症，或较少见的，

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Risk and risk features	Children, elderly, immuno-compromised hosts, sub-sanitary living conditions	Highest: Ventriculo-atrial Mid: Ventriculo-jugular Least: Ventriculo-peritoneal	Prosthetic valve or structural heart valve lesion; substance abuse; elderly; diabetes mellitus; hepatitis C; HIV; immuno-compromised host	Diabetes mellitus, hypertension, heart disease, malignancy, alcohol or substance abuse, or kidney transplantation
History	Seek evidence of antecedent resolved pharyngitis (1–2 wks) or impetigo (4–6 wks)	May present within months or decades of shunt placement, sometimes after shunt revision. Diagnosis may be confounded and difficult in the 40% with occult infection	Echocardiographic evidence of cardiac valvular vegetations	Demonstration of active blood or tissue infection in a patient with acute GN
Physical exam	In some, active skin or tonsil infections present	Non-specific signs/ symptoms of infection, lethargy, fever, clinical signs of bacteremia	Fever, new or changed cardiac murmur; splenomegaly; characteristic skin lesions	Frequent hypertension. Exam mostly reflects the location/severity of the infection
Laboratory kidney	• Urinalysis (assess for glomerular hematuria and red blood cell casts); ACR; PCR • Measure serum creatinine/eGFR			
Laboratory infection	Culture skin or tonsils if infected Measure anti-streptolysin O, anti-DNAse B, and anti-hyaluronidase antibodies	Organism culture in blood, cerebrospinal fluid, shunt tip (after removal)	Blood culture positive 90%–98%; negative 2%–10%. Fastidious infections, such as *Candida, Coxiella burnetii, Borrelia,* and *Bartonella* may be difficult to culture. Serological tools for diagnosis may be required in such cases	Culture blood/tissues to identify bacterial infection (mostly staphylococcal)
Laboratory immunology	• Assess for low complement (C3, C4), rheumatoid factor, cryoglobulins, factor B antibody levels • Rule out other causes of nephritis if diagnosis in doubt: ANA, ANCA (occasionally PR3-ANCA in shunt nephritis and endocarditis), anti-GBM antibody			
				Serum IgA may be high

图56典型细菌感染相关 GN 综合征的评估。ACR，白蛋白-肌酐比值；ANA，抗核抗体；ANCA，抗中性粒细胞胞浆抗体；eGFR，估计肾小球滤过率；GBM，肾小球基底膜；GN，肾小球肾炎；HIV，人类免疫缺陷病毒；PCR，蛋白质-肌酐比值；PR3，蛋白酶3。

用于治疗脑积水的脑室腹膜分流管。[394]感染微生物通常为*表皮葡萄球菌*、*白色葡萄球菌*或*金黄色葡萄球菌*。ANCA滴度可能为阳性。[394]

3. GN 与感染性心内膜炎相关，尤其是与*金黄色葡萄球菌*已取代*草绿色链球菌*成为感染性心内膜炎的主要原因。与*金黄色葡萄球菌*心内膜炎相关的 GN 发生率范围为22%-78%，静脉内用药者的风险最高。患者表现出低血清补体C3（检测的32名患者中的53%）或C4（检测的32名患者中的仅19%）。ANCA和抗核抗体可以预先发送，[395]并且观察到类似抗 GBM 疾病的肺出血（由于冷球蛋白血症）。[396]在一些患者中，感染相关 GN 可以在没有明显心内膜炎的情况下发生。

4. IgA 显性感染相关 GN(IgADIRGN) 是一种免疫复合物介导的 GN 与甲氧西林耐药*金黄色葡萄球菌* (MRSA)、甲氧西林敏感*金黄色葡萄球菌*、*大肠埃希菌*、*表皮葡萄球菌*和*克雷伯菌*菌血症合并存在基础合并症的患者，尤其是糖尿病（图56）。[397–399]菌血症经常（但并非总是）被发现，尽管表现可能延迟。[398]IgADIRGN已在皮肤和关节感染、肺炎、骨髓炎和心内膜炎患者中报告。在30%-50%的病例中观察到低补体血症。[399]

7.1.1 诊断

实践要点7.1.1.1：肾活检可用于疑似细菌感染相关肾小球肾炎 (GN)，尤其是当感染的培养证据难以捉摸或诊断存在疑问时，可用于评估预后和/或出于潜在治疗原因。在某些情况下，活检可能是对得出正确诊断至关重要，因为合并症可能导致混杂效应（图56）。

肾脏组织学显示急性、通常为渗出性、毛细血管内 GN 伴系膜和毛细血管壁颗粒免疫沉积。在心内膜炎相关的 GN 中，最常见的形态学肾小球改变是新月体 GN > 50%的患者，其次为弥漫性毛细血管内增生性 GN 和系膜增生性GN。C3沉积的强度通常超过IgG，无 C4 的 C3 优势表明替代而不是直接补体途径激活。在电子显微镜下可以发现内皮下和上皮下电子致密沉积物，包括“隆起”。在分流性肾炎中，组织学结果通常是损伤的系膜增生性模式，伴有IgG、IgM和 C3 的颗粒沉积，以及电子致密的系膜和内皮下沉积。

在 IgADIRGN 中，肾活检显示毛细血管内增生伴明显的中性粒细胞浸润 (40%–80%)，少数可能为孤立性系膜增生甚至新月体GN。在免疫荧光显微镜下，存在 IgA 和 C3 共显性模式的系膜染色，通常 k 轻链超过 l。[397]电子显微镜检查显示系膜和毛细血管壁中有电子致密沉积物，后者通常具有上皮下“隆起”和较少出现的内皮下分布[400]。考虑到上述特征性临床和形态学特征，可以完成与物理性 IgAN 恶化的鉴别，但有时可能存在差异（第2章）。

7.1.2 预后和治疗

实践要点7.1.2.1：细菌感染相关 GN 的预后和建议治疗总结见图57[401-403]。

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Prognosis	Short-term prognosis in children is excellent. In endemic regions, persistent albuminuria may occur and some adults develop low eGFR. In the elderly, kidney prognosis is poor for those who develop persistent albuminuria; mortality may be up to 20%	Outcome is good with early diagnosis and treatment of infection. Most patients recover some kidney function but are left with residual chronic kidney disease	Immediate prognosis is good with prompt infection eradication. Some may require valve replacement	Dialysis is frequently required in the acute setting. Recovery is guarded, with <20% returning to pre-morbid levels of kidney function
Treatment	• No randomized controlled trials guide the treatment in any of these conditions • Antibiotics for underlying infection (although this will not alter GN course in postinfectious GN) per local guidelines. Antibiotics can be given in poststreptococcal GN if streptococci are cultured from any site. This is primarily done to prevent the spread of infection within community sites • Treat edema, hypertension, etc. as well as persistent proteinuria and/or progressive GFR decline as per Chapter 1			
	Value of high dose glucocorticoids remains unproven [1]	Most shunts have been replaced with a shunt with a lesser likelihood of infection. Rarely ventriculocisternostomy has been performed after shunt removal	Utility of glucocorticoids and immunosuppression unproven and carries serious potential risks, even in cases with crescentic GN [2]	For severe kidney functional impairment, weigh risks and benefits of immunosuppression. The risk of infection and glucocorticoid-induced complications in this often elderly population with comorbidities can be substantial. A role for immunosuppression remains unproven and these agents should generally not be used
Course	• Follow kidney function, serum C3 and C4, urinalysis, ACR, and proteinuria at appropriate intervals until complete remission or return to baseline			
	Persistently low C3 beyond 12 weeks may be an indication for kidney biopsy to particularly exclude C3GN.[3] Prevention of epidemic poststreptococcal GN may include socioeconomic interventions and mass antimicrobial use to improve living conditions and limit the spread of infection in populations where Group A streptococcus infection and scabies are highly prevalent	The natural history of the PR3-ANCA seen in some patients is unclear and requires follow-up	If the infection can be identified and promptly eradicated, the prognosis is favorable	The prognosis for recovery is poor, especially in diabetic subjects

图57典型细菌感染相关 GN 综合征的预后和治疗。[1]Kapadia 等人[401]，[2]Okuyama 等人[402]，[3]Khalighi *et al.*[403]ACR，白蛋白-肌酐比值；ANCA，抗中性粒细胞胞浆抗体；C3GN，补体性肾小球肾炎；eGFR，估计肾小球滤过率；GN，肾小球肾炎；PR3，蛋白酶3；RCT，随机对照试验。

研究建议

链球菌感染后GN。

- 需要进行 RCT 来评价大剂量糖皮质激素联合或不联合免疫抑制治疗新月体性链球菌感染后 GN
- 需要进行研究以确定链霉菌抗原的性质，作为开发免疫预防治疗的基础
- 在肾脏病变转化的患者中，需要进一步研究阐明免疫复合物介导的链球菌感染后 GN 和 C3 显性但非免疫复合物介导的 C3 肾小球病 (C3G) 之间的区别和重新定位
- 需要进行研究来证实抗 B 因子抗体在链球菌感染后 GN [404] *分流性肾炎诊断中的应用*。
- 需要进行多中心观察性研究，以确定分流性肾炎的发生率、患病率和长期预后，以及具有 PR3-ANCA 抗体的患者的结局*感染性心内膜炎相关*GN。
- 需要进行多中心研究来确定感染性心内膜炎相关 GN IgADIRGN 的发病率、患病率、长期预后和肾小球损伤机制。
- 需要 IgADIRGN 的 RCT 来评估感染控制后糖皮质激素和/或免疫抑制剂的价值或缺乏

7.2 病毒感染相关 GN

7.2.1 丙型肝炎病毒 (HCV) 感染-相关 GN

工作组完全同意各项建议

KDIGO 2018 年慢性肾病中丙型肝炎预防、诊断、评估和治疗临*床实践指南的5.1–5.2.3*[405]。有关具体建议、具体治疗药物的选择和给药以及研究建议，请参考本出版物。

7.2.2 乙型肝炎病毒 (HBV) 感染相关 GN

约2.5–3.5亿人（占世界人口的5%）为慢性 HBV 感染，使其成为最常见的人类病原体之一，[406–408]约3%–5%的慢性 HBV 感染患者发生肾脏疾病并发症[409, 410]

HBV 感染中最常见的肾小球损伤模式是MN。[411,412]IgAN、膜增生性GN(MPGN)、FSGS和新月体性 GN 病变较少见。在罕见情况下，在 HBV 感染患者中观察到MCD，抗病毒治疗后缓解。[413]不同比例的 HBV 感染和 MN 患者显示循环抗 PLA2R 抗体（第3章）。[414,415]

慢性 HBV 感染的肝外表现还包括系统性血管炎（尤其是结节性多动脉炎/Kussmaul-Maier 病）、[406、416]II型（单克隆 gM k 抗多克隆IgG）和 III 型（多克隆IgM、IgA、IgG）冷球蛋白血症。[406–408,417]

本节讨论了与治疗复制型 HBV 感染患者的 GN 相关的问题。由于其整合到宿主基因组中的倾向和在肝细胞中形成治疗抵抗性共价闭合环状脱氧核糖核酸的能力，HBV感染很难用抗病毒药物永久治愈，这与 HCV 感染不同。[418]病毒复制复发在 HBV 感染中相当常见，免疫抑制剂可以重新激活休眠或隐匿性感染。[418,419]

7.2.2.1 诊断

实践要点7.2.2.1.1：蛋白尿性肾小球疾病患者应接受 HBV 感染检测。

HBV 介导的 GN 的诊断需要检测血液中 HBV 感染和复制型病毒的血清学表现，检测肾小球免疫沉积物中的 HBV 相关蛋白抗原，并排除肾小球疾病的其他原因。由于 HBV 感染可能在临床上无症状，包括不存在提示肝脏炎症和肝细胞坏死的肝酶升高，因此可能需要进行肝活检来评估肝损伤的程度，尤其是纤维化。HBV 暴露和感染的血清学鉴定最好通过评估乙型肝炎表面抗原 (HBsAg)、抗 HBc 抗体进行，并且在选定的病例中，HBV脱氧核糖核酸 (DNA) 定量代表复制[型病毒]感染的负担。418,[420]HBe抗原持续升高是复制型感染的体征，并且转化为抗 HBe 可以作为病毒复制缓解的指征。[418]

HBV 感染在MN、IgAN、冷球蛋白血症和结节性多动脉炎 (Kussmaul-Maierdisease) 患者中尤其常见，应对此类患者进行常规感染评估。MCD儿童和成人是否应常规筛查 HBV 感染尚不确定，但在 HBV 感染高流行负担国家或有高感染危险行为或病史的患者中，这可能是明智的。由于常见的合并感染，有高危行为（如静脉注射药物滥用、无保护性交）的患者也应筛查 HCV 和 HIV 感染（见 HCV 和 HIV 章节）。约10%的 HBV 感染受试者合并感染HIV，10%-30%[合并]感染 HCV。406筛选蛋白尿性肾小球疾病患者感染 HBV 的另一个原因是许多此类患者可能成为免疫抑制治疗（糖皮质激素和/或细胞毒性/免疫调节剂）的候选者，可诱导 HBV 复制严重恶化（第1章）。[419]HBs抗原阴性和抗 HBc 可变（阳性或阴性）的隐匿性 HBV 感染可通过聚合酶链反应检测和定量 HBV DNA 进行评价。[420]在无 HBV 感染血清学证据的患者肾组织中偶尔可检测到 HBs 或 HBc 抗原。[421]血清 HBVDNA 水平与临床结果的严重程度中度相关。[422,423]

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7.2.2.2 预后

实践要点7.2.2.2.1：应将慢性 HBV 感染成人患者视为存在发生肾衰竭的风险。

HBV 感染和 MN 成人患者倾向于进展为肾衰竭，自发缓解不常见。[406,411]因此，此类患者需要慎重考虑治疗，而不是尝试用抗病毒药物控制病毒复制。HBV感染辅助治疗的选择将取决于肾脏（肾小球）疾病的特异性表现。HBV相关 MN 儿童的自发缓解率较高，很少进展为肾衰竭（见下文第7.2.2.4节特殊情况）。[406,411]HBV感染也可能促进 IgAN 和 FSGS 的进展，但尚不明确。[424–426]冷球蛋白血症可能与重度和快速进展的肾小球疾病有关，[417,427]通常与血管炎和新月体相关。当伴随 HBV 感染未得到治疗时，结节性多动脉炎的预后特别差。[416]

7.2.2.3 治疗

建议7.2.2.3.1：我们建议复制型 HBV 感染（以 HBV DNA 水平 > 2000 IU/mL表示）和 GN 患者接受
以核苷（酸）类似物治疗作为结果
根据 HBV 感染的标准临床实践指南对一般人群进行修订 (1C)。

由于未经治疗的 HBV 感染（肝细胞癌、肝硬化、GN和/或血管炎）预后较差，并且可获得有效（但无法治愈）的抗病毒药物，除非存在禁忌症，否则几乎所有患有该疾病的患者均应视为抗病毒治疗的候选者。

关键信息

*平衡危害。*通过血清学和病毒基因组研究可以识别慢性复制型 HBV 感染。[418]我们认为慢性复制型 HBV 感染如果不及时治疗，会出现严重的、可能危及生命的长期并发症（肝硬化、肝细胞癌、GN、血管炎）。由于这些风险以及 HBV 感染治疗的微小中度风险，尽管由于在该人群中缺乏高质量的RCT，对复杂性肾小球疾病（即MN）有益的（长期）证据很弱，但复制型 HBV 感染的治疗仍值得。可能存在妨碍这种选择的情况，例如对所有可用的抗病毒药物不耐受，但预计这些情况并不常见。

至少在观察性研究中（低质量证据），根除或控制 HBV 复制性感染可改善伴随 HBV 感染的 GN 结局。一些药物，尤其是 a-干扰素 (IFN)，可能加重基础肾小球疾病，其安全性受到质疑。

适用核苷（酸）类似物治疗 HBV 相关GN。

核苷（酸）类似物可以在可接受的不良副作用水平上有利地改变病毒复制[418,428]；然而，由于病毒的生物学特性（即整合到宿主基因组中，并且能够在肝细胞中以休眠方式持续存在），真正持久的感染治愈是逃避的。

CKD（尤其是MN）可能是易感个体慢性 HBV 感染的直接结果，如果不及时治疗，25%-35%的此类受试者可进展为肾衰竭。[406]

*证据质量。*系统性检索 HBV 感染相关 GN 患者管理 RCT 的医学文献发现1项在 HBV 相关 MN 儿童中进行的小型 (n¼40) 开放性研究[429]。本研究未报告本指南确定的任何关键和重要结局（全因死亡率、肾衰竭、$GFR降低50%、恶性肿瘤、完全缓解、年 GFR 下降）。由于研究不精密度（仅1项研究）和偏倚风险问题，该 RCT 的证据质量较低。此外，该建议的支持性文献来自观察性研究，由于设计偏倚，证据质量被分级为较低。证据的总体质量被评定为较低。

*价值和偏好。*该建议对避免 HBV 病毒复制失控的严重、潜在危及生命的并发症具有较高价值，对核苷（酸）类似物治疗的副作用、成本和不便以及此类治疗可能需要的任何相关监测具有较低价值。根据工作组的判断，所有或几乎所有知情同意的患者将选择接受核苷（酸）类似物治疗，而不是放弃此类治疗。

*资源使用和成本。*该建议需要由于抗 HBV 病毒药物的高成本和评价抗病毒治疗应答的检测成本，导致大量成本，包括自付成本。在世界某些地区，这些药物的供应也可能有限。这些费用可通过避免长期并发症（如肝或肾移植、透析或NS）的治疗费用在一定程度上抵消。需要进行正式的长期成本 t 分析来检验该假设，尤其是在认为是 HBV 感染并发症的肾小球疾病受试者中。

*实施考虑。*世界不同地区 HBV 感染率存在显著差异。预计在 HBV 感染流行的地区，慢性 HBV 感染的肾小球并发症造成的疾病负担将更大。预防 HBV 感染的措施，如疫苗接种、更好的卫生和消除血源性感染（例如，输血或静脉药物滥用）至关重要。对于所有性别、人种和种族，应平等考虑所有措施。

依据

迄今为止，由于在该人群中缺乏适当的RCT，无法对复制性病毒感染和肾小球疾病成人患者提出循证治疗建议。然而，具有抗 HBV 活性和耐药性产生障碍高的强效核苷（酸）类似物现在可用，并被广泛认为是 HBV 感染的首选治疗。[428]拉米夫定与获得性耐药高度相关，不再推荐作为初始治疗。[418]聚乙二醇化 IFN-a 由于疗效有限且倾向于引起严重副作用，因此不太常用，但在较轻的低病毒载量病例中可能有效。[418]通常不推荐使用 IFN 和核苷（酸）类似物的联合治疗，除非在特殊情况下。[418]

关于评估和管理慢性 HBV 感染的临床实践指南最近已经出版，我们大量借鉴了这些出版物，以制定与 GN 相关的 HBV 感染的当前建议。[407,408,418]

目前有几种药物可用于治疗慢性 HBV 感染（恩替卡韦、替诺福韦酯、替诺福韦、阿拉非酰胺、阿德福韦、替比夫定）。已在 RCT 中评估了这些药物对 HBV 感染的疗效[418]。然而，截至2016年，仅发现1项治疗 HBV 相关 GN 的RCT。[429]这是一项 a-IFN 治疗儿童 HBV 相关 MN 的开放性、对照试验，显示短期获益作用和40%的 HBe 血清转换率和蛋白尿改善。副作用常见。本研究被判定为低质量和潜在偏倚。然而，成人观察性研究与这些结果一致。[430]尚未报告使用核苷（酸）类似物的RCT。已经出现了几项荟萃分析，包括观察性研究。[431–435]在6项试验（1项RCT）的1项荟萃分析中，a-IFN和拉米夫定联合或不联合糖皮质激素与仅糖皮质激素或支持治疗相比，蛋白尿缓解率和 HBeAg 清除率（作为控制复制性病毒感染的指标）更高。单独使用糖皮质激素被判定为无效。[434]The Yang et al.分析仅限于 HBV 相关MN，包括3项 IFN-a 试验和2项核苷类似物试验。[432]抗病毒治疗在蛋白尿完全或部分缓解和 HBeAg 清除方面优于对照。核苷类似物和 IFN 之间未观察到结局差异，但未对2种抗病毒方案进行头对头比较。在 IFN 治疗的受试者中常见严重的肾外副作用。核苷类似物（拉米夫定）方案常见耐药的出现。在60%接受 IFN 治疗的患者和85%接受核苷类似物治疗的患者中观察到疑似病毒应答。约6%的对照组可见自发病毒缓解。在一项针对 HBV 相关冷球蛋白血症性血管炎的小型、开放性、非对照试验中观察到相似的抗病毒治疗有利应答。[417]在 IgAN 或 FSGS 患者中进行的 HBV 感染抗病毒治疗研究很少。

进行。观察性队列研究表明，拉米夫定和糖皮质激素联合治疗对患有 IgAN 的 HBV 非活动性携带者有益。[436]已表明 CNI 在治疗 HBV 相关肾小球疾病（MN和FSGS）中发挥作用。[437,438]钙调磷酸酶药物可安全用于存在 HBV 感染的肾小球和其他自身免疫性疾病患者。由于这些药物倾向于通过抑制 HBV 进入而不干扰牛磺胆酸钠共转运多肽 (NTCP) 活性来减少病毒复制。[439,440]在一项初探性研究中，已证明舒洛地特联合抗病毒治疗（恩替卡韦）可能通过补体激活抑制机制对 HBV 相关 MN 的蛋白尿具有叠加获益作用。[441]

HBV 感染和 GN 患者的治疗应根据 HBV 感染的标准临床实践指南进行，需要确定复制型病毒感染（HBeAg 阳性和/或病毒 DNA 水平 > 2000 IU/mL）。[408,418]一些核苷（酸）类似物（特别是阿德福韦和替诺福韦）的肾毒性可能是需要关注的问题。CKD（由于 GN 或其他原因）或 NS 患者使用这些药物时可能需要调整剂量。[428]

实践要点7.2.2.3.1：聚乙二醇干扰素方案不应用于治疗复制型 HBV 感染和 GN 患者。

欧洲肝脏研究协会 (EASL) 临床实践指南建议，基于 IFN-a 的区域不用于 HBV 相关GN，因为 IFN 治疗可能加重此类患者的自身免疫现象。[418]在一例病例中，在开始 IFN 治疗 HBV 感染后出现*新生*MN。[442]这种效应的一致性尚不确定，但由于较新的抗病毒方案能有效诱导病毒应答，且副作用较少，因此使用基于 IFN 的方案的实用性可能受到质疑。

实践要点7.2.2.3.2：免疫抑制剂（如环磷酰胺或利妥昔单抗）可加速 HBV 复制，应避免用于未经治疗的复制型 HBV 感染和 GN 患者。

HBV 感染患者的异质性（如肝功能损害程度、肝外受累程度）使建立 HBV 介导的肾病患者治疗指南变得相当复杂。可增强 HBV 复制的药物（如糖皮质激素、烷化剂、利妥昔单抗），从而加重肝脏疾病表现，构成实际风险（第1章）。[419]可能首选对 HBV 复制几乎无影响（甚至有益作用）的替代药物，如CNI。[437–440]所有接受利妥昔单抗治疗任何适应症的患者均应检查 HBsAg 和核心抗体 (HBcAb)。如果为阳性，治疗 HBV 的疗法必须与肝病学联合使用。应谨慎给予免疫抑制治疗，并了解其风险和获益。

7.2.2.4 特殊情况

实践要点7.2.2.4.1：同时存在 HBV 感染和抗 PLA2R 抗体介导的 MN 的患者应避免使用利妥昔单抗和环磷酰胺，直至通过核苷（酸）类似物治疗获得持续病毒学缓解。

尚未评价抗病毒治疗在模拟 HBV 感染和抗 PLA2R 抗体介导的 MN 患者中的效用，但利妥昔单抗或环磷酰胺为基础的治疗方案在此类患者中存在 HBV 复制加重的风险，应避免使用，至少在通过核苷（酸）类似物治疗获得持续病毒学缓解之前（第3章）。[443]此类患者可能首选 CNI 方案，但缺乏支持此类使用的证据。HBV 感染与 PLA2RMN 的相关性也可能是牙科事件，而不是因果事件，至少在某些情况下是如此。

实践要点7.2.2.4.2：在伴有冷球蛋白血症性血管炎的患者中可尝试血浆置换。

血浆置换在 HBV 相关冷球蛋白血症性血管炎治疗中的作用尚未完全评估，但如果冷球蛋白的血浆水平较高（CryoCrit > 5%，> 500 mg/dL）和存在症状性血管炎，可以尝试使用5%白蛋白或新鲜冷冻血浆替代。[417,427]

实践要点7.2.2.4.3：由于肾病自发缓解的可能性较高，因此应在不进行免疫抑制的情况下对 HBV 感染和 MN 儿童进行保守治疗。

儿童中存在隐匿性 HBV 感染和MN（循环 HBs 阴性，免疫沉积物中有 HBs/HBc 抗原）可能需要抗病毒治疗，因为单纯免疫抑制似乎无效。[444]

研究建议

- 需要 RCT 来确定改变 HBV 相关 GN 进展的最有效抗病毒治疗方案。研究需要考虑肾外疾病累及，并评价不同的药物组合，包括治疗时间和持续时间
- 鉴于 HBV 相关性 GN 自发缓解率较高，应分别评价儿童 RCT

7.2.3 人类免疫缺陷病毒 (HIV) 相关 GN

本节对老年人提出管理建议

> 18岁 HIV 相关肾小球疾病患者。

尚无针对 HIV 相关肾病的RCT。关于与该主题相关的当前问题的总结，我们请读者参考 KDIGO HIV 争议会议的出版物。[445]

根据联合国艾滋病组织的数据，2017年约有3690万人感染HIV。2017年，59%(CI：44%-73%) 的 HIV 感染者正在获得治疗。[445]最近对不同 GFR 估算公式（MDRD、CKD-EPI和Cockcroft–Gault）定义的 HIV 相关肾病进行的审查证明，世界上不同公式和地区的肾病存在差异，但这确实是 HIV 大流行中一个日益严重的问题（图58）。[446,447]

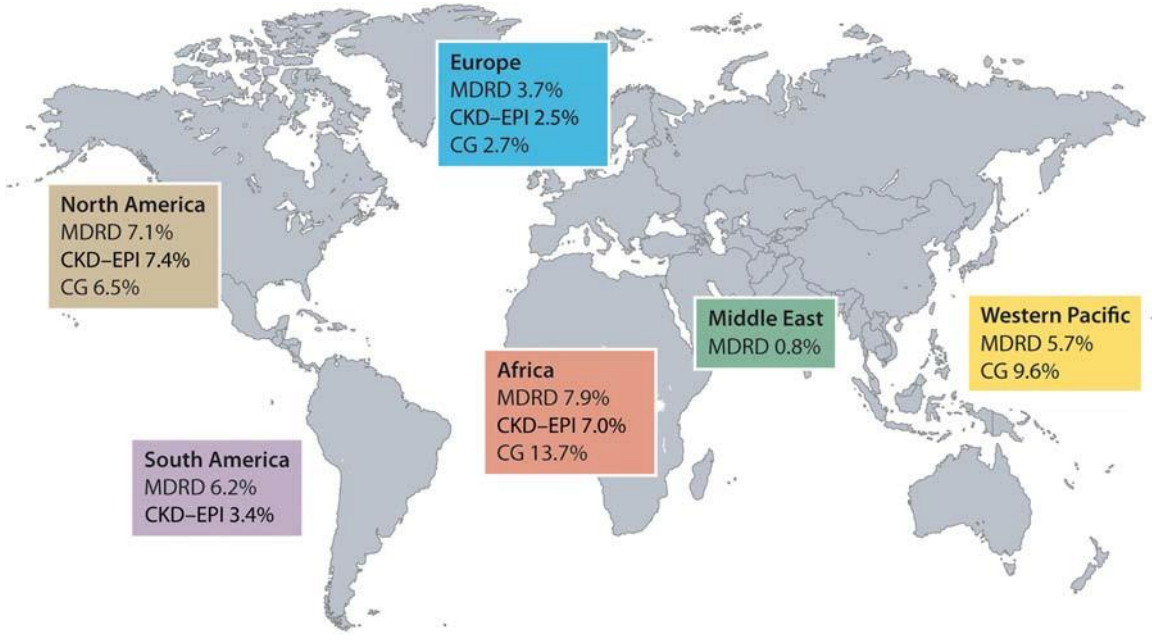

图 58 HIV 感染相关 CKD 的全球分布。转载自Ekrikpo UE,Kengne AP,Bello AK,et al.全球成人 HIV 感染人群中的慢性肾病：系统综述和荟萃分析。*PLoS One*。2018;13:e0195443.[447]版权所有ª2018 Ekrikpo *et al.*这是一篇根据知识共享署名许可 (https://) 条款分发的开放获取文章 creativecommons.org/licenses/by/4.0/）。CG，Cockcroft–Gault；CKD-EPI，慢性肾病流行病学协作组；HIV，人类免疫缺陷病毒；MDRD，肾病患者饮食改良。

7.2.3.1 诊断

实践要点7.2.3.1.1：如可行，应进行肾活检，以评价 HIV 相关肾病的形态学。应使用基于病理学的 HIV 相关肾病描述帮助定义和指导治疗。

KDIGO 争议会议提出了 HIV 相关肾病的病理学分类，以帮助阐明 HIV 相[关肾病]的各种机制。445HIV可对肾脏产生多种影响。肾小球、间质和血管疾病在 HIV 患者中具有独特的表现。感染（实际感染和治疗）可影响肾功能。非 HIV 患者肾脏疾病的传统原因，如高血压肾病或 CKD 和糖尿病，也存在差异。最后，当临床医生关注的肾功能变化时，还必须考虑用于治疗HIV、免疫预防和常见疾病的药物。在 HIV 感染患者中，其中许多病理可以模拟 HIV 相关肾病 (HIVAN)，但每种疾病都需要不同的治疗[448–450]。基于肾活检的方法有助于应对诊断和未来知识的挑战。突出显示近期综述活检诊断的复杂性和优化管理对诊断精确度的需求（图59）。[451]

足细胞病是 HIV 感染患者肾小球中的常见病变，可能表现为塌陷性肾小球病 (HIVAN)，尤其是在具有非洲遗传背景、无塌陷特征的 FSGS(FSGS-UC) 或 MCD 患者中。[1,2,451]许多免疫复合物介导的疾病也在 HIV 背景下描述过，包括IgAN、狼疮样GN、MN、和MPGN.[451]由于在这些病例中缺乏关于 HIV 因果关系的确定性，因此建议不使用术语 HIV 相关免疫复合物肾病 (HIVICK)。某些基因，如APOL1，可增加 FSGS 和 HIVAN 的风险，但不会增加 HIV 免疫复合物疾病的风险。无论基因变异的数量如何，活检的病理学均相同。[452]需要更多关于遗传因素的信息（图60[453]）。

HIVAN 可能存在肾小管间质性疾病，但也可能是由于药物所致，或可能是对感染的反应。在高效抗逆转录病毒治疗 (HAART) 之前，血管疾病的患病率更高。[454,455]超过三分之一接受肾活检的 HIV 患者患有糖尿病肾病；或MN、MPGN或IgAN；或另一种免疫复合物 GN 模式。[448,456]a

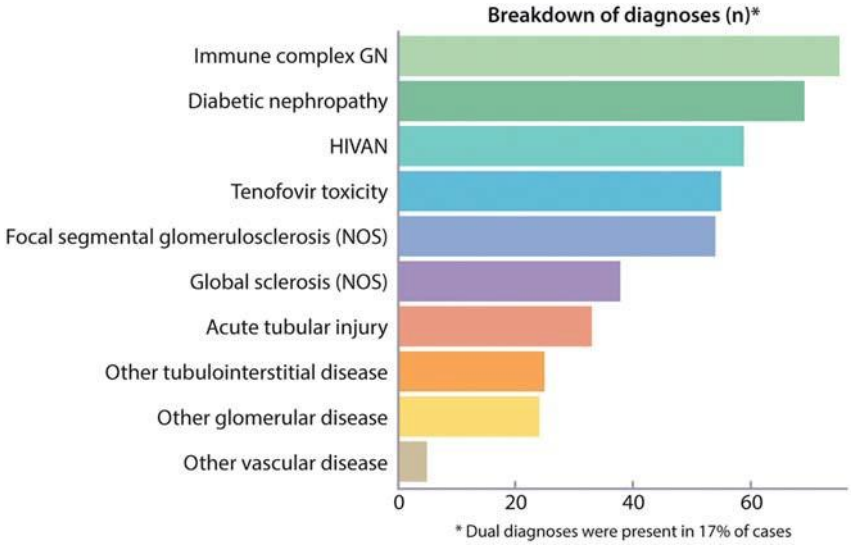

图59|现代 HIV 患者的肾活检结果谱。转载自*Kidney International*,volume 97,issue 5,Kudose S,Santoriello D,Bomback AS,et al.经国际肾脏病学会许可，现代 HIV 感染患者的肾脏活检结果谱，第1006–1016页，[a]2020。[451]回顾性审查了2010-2018年的26,737份本地活检样本；437份(1.6%) 来自 HIV 患者（平均年龄：53岁；66%男性；58%黑人；25%白人；17%西班牙裔；＜ 1%亚洲人；80%接受抗逆转录病毒治疗[ART]；合并症包括：57%高血压、31%糖尿病、27%丙型肝炎合并感染）。研究结论：ART使 HIV 相关肾病的格局向多样化的免疫复合物GN、糖尿病肾病和非塌陷性肾小球硬化转变，但尚未根除 HIV 相关肾病。GN，肾小球肾炎；HIV，人类免疫缺陷病毒；HIVAN，人类免疫缺陷病毒相关肾病；NOS，未特指。

	Overall disease frequency	*APOL1* 0 risk alleles	*APOL1* 1 risk allele	*APOL1* 2 risk alleles
		~ 42%	~ 45%	~ 13%
HIVAN (without ART)	10% 1:10	2.5% 1:40	4% 1:25	50% 1:2
HIV– FSGS	0.8% 1:125	0.2% 1:500	0.3% 1:333	4.25% 1:24
HIV+ FSGS	No data	No data	No data	No data

图60|HIV背景下 HIVAN 或 FSGS-UC 的终生风险，按 *APOL1* 风险等位基因数显示。摘自*Seminars in Nephrology*,volume 35,issue 3,Dummer PD,Limou S,Rosenberg AZ,et al.APOL1肾病风险变体：演变中的情况，2015年，Elsevier.[453]*APOL1*，载脂蛋白L1；ART，抗逆转录病毒治疗；FSGS-UC，局灶节段性肾小球硬化-原因不明；HIV，人类免疫缺陷病毒；HIVAN，HIV相关肾病。

罕见疾病–弥漫性滤过性淋巴细胞增多综合征 (*DILS*)（存在于 *HIV* 患者中）已被报告为 *HIV* 肾损伤的原因。[457]*HIV*相关血栓性微血管病已被报告为 *HIV* 的首次表现，[454,455]，其与血尿和蛋白尿相关。该疾病的机制尚不明确，但似乎与 *ADAMTS 13* 水平相关。[458]

7.2.3.2 预后

实践要点7.2.3.2.1：导致 *GN* 相关 *HIV* 感染长期结局的因素很多，包括病毒复制持续存在、抗病毒治疗应答、肾小球损伤的遗传易感性（例如，*APOL1*风险等位基因）、与其他病毒合并感染和形成免疫复合物。

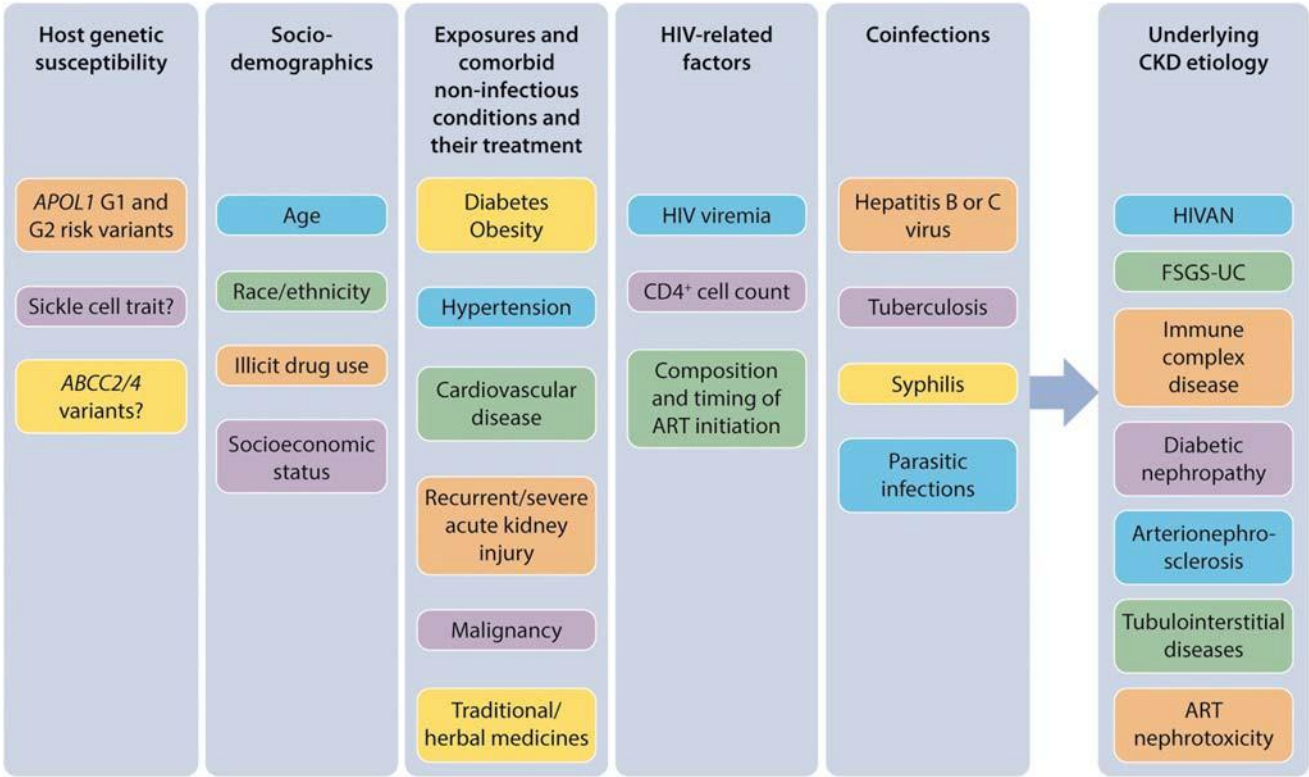

图 61 HIV 阳性个体中 CKD 的风险因素和基础病因。转载自Swanepoel CR,Atta MG,D'Agati VD,et al.HIV感染背景下的肾病：肾病：改善全球预后 (KDIGO) 争议会议的结论。*肾脏国际*2018;93:545–559,https://www.kidney-international.org/article/S0085-2538(17)30823-2/fulltext,Copyright[a]2017,International Society of Nephrology.Elsevier Inc.出版。这是 CC BY-NC-ND 许可下的开放获取文章 (http://creativecommons.org/licenses/by-nc-nd/4.0/)。[445]ABCC，ATP结合盒转运蛋白；*APOL1*，载脂蛋白L1；ART，抗逆转录病毒治疗；CKD，慢性肾病；FSGS-UC，局灶节段性肾小球硬化-原因不明；HIV，人类免疫缺陷病毒；HIVAN，HIV相关肾病。

疾病或血栓性微血管病。因此，个体患者的预后估计可能非常困难。

尚无指导预后的RCT。需要考虑的因素总结如下（图61[445]）。有限的数据显示，合并症（HBV、HCV、TB和梅毒）会损害长期预后。[459–463]AKI也是 HIV 患者 CKD 长期进展为肾衰竭的风险因素。[464]APOL1风险等位基因是否应在患有 HIVAN 的西非血统患者中常规评估仍不确定。

7.2.3.3 治疗

建议7.2.3.3.1：我们建议所有 HIV 和 CKD 患者均开始抗逆转录病毒治疗，尤其是活检证实的 HIV 相关肾病 (HIVAN)，无论 CD4 计数如何，根据肾功能程度调整 *(1C)*。

CKD 的存在不是 HIV 感染抗逆转录病毒治疗 (ART) 的禁忌症。当前共识数据是基于2项关于启动 ART 时间的大型RCT，即抗逆转录病毒治疗的战略时机 (START)、HIV感染成人的早期抗逆转录病毒治疗和/或早期异烟肼预防结核病 (TEMPRANO)，证明在诊断时早期启动 ART 有益，不考虑 CD4 计数。[465,466]本工作组认为获益大于支持该建议的风险，并且在可能的情况下，此类感染患者也对早期治疗具有较高价值。

关键信息

*平衡危害。*这些建议来自 HIV 文献中 ART 的益处和外推至 GN 患者似乎支持的低质量数据。

*证据质量。*证据质量较低，没有在 HIVAN 患者中进行指导的RCT。确定支持该建议的证据是间接的，因为它是在一般 HIV 人群和观察性研究中进行的，其设计显示偏倚。

*价值和偏好。*工作组高度重视尽量减少 HIV 感染的有害影响，并高度重视 ART 和肾脏活检相关不良事件（肾脏和非肾脏）风险。

*资源使用和成本。*治疗 HIV 以预防肾脏副作用的成本远低于肾移植和肾脏替代治疗，并且许多终末期治疗在全球范围内均不可用。我们没有可作为我们建议基础的特定成本数据。

*实施考虑。*目前，除了在 HIV 阳性患者的标准治疗中考虑的信息外，没有足够的信息来指导基于性别或种族背景的选择。

依据

目前，尚无针对 HIV 相关肾病的RCT。[467]支持性数据表明 ART 治疗对 HIV 相关肾病有益。在 HIV 患者中，蛋白尿和/或肾功能下降与死亡率增加和结局恶化相关。[468]多项 RCT 的数据表明，ART在非 CKD HIV 患者的肾功能保护和改善方面均有益。[452,467,469,470]ART期间 HIV 病毒载量降低与肾功能改善相关，病毒载量增加与肾功能恶化相关。[453,471,472]

HIV 相关 GN 的治疗多从 HIVAN 外推而来。观察性研究、非对照或回顾性研究的数据[465–467、473–475]和 RCT 的数据[476]表明，HAART（定义为使用≥3种药物的联合 ART 治疗）对 HIVAN 患者的肾功能保护和改善均有益。自20世纪90年代引入 HAART 以来，HIVAN的发生率也大幅降低。[477]在多变量分析中，使用 HAART 使 HIVAN 风险降低了60%，在发生获得性免疫缺陷综合征 (AIDS) 之前开始 HAART 治疗时，没有患者发生HIVAN。[477]使用 HAART 也与 HIVAN 患者肾脏存活率改善相关。[478]

在 CD4 淋巴细胞计数较低和基线肾功能受损的 HIV 患者中，抗病毒治疗与 GFR 改善相关，支持 HIV-1 复制在晚期 HIV 疾病中对 CKD 的独立作用。[479]早期观察性研究也表明 ACEi 有益。[480]在 ART 前或初始阶段进行的几项回顾性观察性或非对照研究报告，在 HIV 相关肾病患者中使用糖皮质激素取得了不同程度的成功。[478,481,482]只有一项研究在15例 HIV 和 NS 儿童中使用环孢素。[483]这些早期观察性研究表明 ACEi 和糖皮质激素在 HIV 介导的肾病中有益，但研究是在引入 ART 之前进行的；在现代 HAART 治疗的时代，目前尚不清楚在当前管理背景下是否仍存在这种获益。[480]尚无 RCT 评价 ART 治疗在 HIVAN 患者中的价值。[467]有极低质量的证据表明 ART 可能对 HIV 相关免疫复合物肾病和血栓性微血管病患者有益。[484–487]，但其他数据表明抗病毒治疗在 HIVICK 中无特殊获益。[448]

接受 ART 的患者的结局

替代治疗与 HIV 阴性对照相同。[486]HIV患者现在可以接受移植作为治疗选择。

实践要点7.2.3.3.1：必须决定使用糖皮质激素作为 HIVAN 的辅助治疗

根据具体情况，因为长期风险和获益尚不确定。

损害的可能性不容忽视。在 HIVAN 中的一项研究比较了传统 ART 与 ART 加糖皮质激素方案（1 mg/kg 至60 mg）和 ACEi 或 ARB 治疗。该研究表明 GFR 显著增加、不良事件（感染和全因死亡）增加和间质炎症减少[488]。该结果与其他研究一致，其他研究表明糖皮质激素可改善 HIVAN 的功能[475,480,489]。糖皮质激素的风险与获益必须单独平衡。

研究建议

- RCT 需要：
  - 评价 ART 在 HIV 相关肾小球疾病（足细胞病和免疫复合物疾病）中的疗效
  - 评价其他治疗（例如，RASi、糖皮质激素等）联合 ART 在 HIV 相关肾病治疗中的作用
  - 帮助确定 HIV 相关肾病的最佳肾脏替代治疗和移植方案
  - 确定评估 APOL1 和其他遗传风险变体的作用及其优化 HIV 相关肾病治疗的临床应用。

7.3 血吸虫病、线虫病和疟疾感染引起的肾病

人们越来越认识到慢性寄生虫感染是 CKD 和肾衰竭的原因，尤其是在世界热带和亚热带地区以及社会经济抑郁和卫生条件不足的地区。本节涵盖可能引起肾小球病（特别是血吸虫、线虫病和疟疾）的多种寄生虫感染的诊断、预后和治疗。

7.3.1 血吸虫性肾病

血吸虫病（别名。Bilharziasis）是由吸虫（血蜱）引起的慢性感染，见于亚洲、非洲和南美洲。血吸虫病是由宿主对血吸虫卵的免疫反应所致。据推测，血吸虫性肾小球疾病来源于这种免疫应答。

临床肾小球疾病最常被描述为与*曼氏血吸虫*引起的肝脾血吸虫病相关。[490]非洲肾脏病协会（AFRAN；图62）描述了5种血吸虫性肾小球病理学模式。已提出第6种模式来描述与血吸虫性 GN 和 HCV 合并感染相关的病理学（图62）。应认识到，在高度流行区，GN与血吸虫病的关联可能是巧合，而不是因果。

许多患者可能有无症状和自限性肾小球疾病。GN最常见于男性青壮年。组织学研究已证实10%-12%的病例存在肾小球病变。[491]

*曼氏血吸虫*更常与血吸虫性 GN 的症状表现相关，并且是10%-15%的患者发生慢性、进行性肾小球病的独立风险因素。肾小球病变和蛋白尿的严重程度与肝巨噬细胞功能障碍和免疫复合物清除率降低相关。[492]

AFRAN classification	Etiology
I Mesangial proliferative	*Schistosoma haematobium* *Schistosoma mansoni*
II Proliferative exudative	*Schistosoma haematobium* *Schistosoma mansoni* *Salmonella*
III Membranoproliferative	*Schistosoma haematobium* *Schistosoma mansoni*
IV Focal segmental glomerulosclerosis	*Schistosoma mansoni*
V Amyloidosis	*Schistosoma haematobium* *Schistosoma mansoni*
VI Cryoglobulinemia	*Schistosoma mansoni* Hepatitis C

图62血吸虫肾小球病理的6种模式。AFRAN，非洲肾脏病协会。

7.3.1.1 诊断

实践要点7.3.1.1.1：检测适当的地方性混合感染（*沙门氏菌*、HBV、HCV、HIV），因为靶向治疗可能改变基础 GN 的侵袭性或血吸虫病后遗症。

合并感染可影响肾小球疾病的严重程度以及相关并发症。血吸虫病合并*沙门氏菌*感染与快速发生的 GN 和 NS 相关。[493]合并沙门氏菌感染的治疗有利于改善 GN 的病程。[493–496]血吸虫病合并 HBV 或 HCV 感染与更快进展为肝硬化或肝癌相关。血吸虫病合并 HIV 感染与较高的 HIV 病毒活性相关。

实践要点7.3.1.1.2：在存在病毒合并感染 (HCV、HBV、HIV) 的情况下，对疑似患有血吸虫性 GN 的患者进行肾活检。

对于任何有明显或进展性肾病（蛋白尿 > 1 g/日、低补体血症、血尿、GFR降低）的患者，通常建议进行肾活检。如果蛋白尿为轻度（< 1 g/日）且患者无血尿或 GFR 降低，则可合理推迟肾活检，因为定向抗寄生虫治疗也可治愈轻度血吸虫性GN。血吸虫性 GN 的明确诊断需要鉴别肾小球中的寄生抗原（仅专门实验室）。

It is important to differentiate MPGN due to schistoso- miasis from MPGN caused by HBV or HCV. HIV can also be a common cause of FSGS.

7.3.1.2 Treatment

Practice Point 7.3.1.2.1: Treat patients with schistosomal infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism. There are no indications for use of immunosuppressive agents in schistosomal nephropathy.

Specific antiparasitic treatment can alter the development or progression of kidney disease when started in the initial phase of infection. Class I and Class II schistosomal GN are likely to spontaneously resolve and/or respond to antiparasitic therapy. The proliferative forms of schistosomal GN (Class III, IV, V, VI) are more likely to progress to kidney failure despite antiparasitic therapy.

Two antiparasitic drugs are available to treat schistosomi- asis, and treatment is recommended for all patients that are infected. No dose adjustment is necessary for kidney or he- patic impairment (Figure 63). The drugs should be given with

food, separated by at least 4–6 hours. The tablet should not be chewed. Praziquantel dosing is effective in curing 60%–90% of patients with schistosomiasis. Oxamniquine is used for praziquantel-resistant patients or those with refractory schistosomal disease.[497] Successful treatment can prevent development of glomerular disease. However, established schistosomal GN does not respond to either antiparasitic agent.[490] Praziquantel is pregnancy category B, and is excreted in human breast milk, so it should not be used in lactating women. Oxamniquine is contraindicated in pregnancy.

There is no established role for glucocorticoids or immunosuppressant therapy in schistosomal GN. However, immunosuppression may rarely be necessary in severe Class VI schistosomiasis GN, coinfection with HCV, and severe mixed cryoglobulinemia syndrome.[405]

7.3.1.3 Special situations

Practice Point 7.3.1.3.1: Monitor patients with hepatic fibrosis from schistosomiasis for the development of kid- ney disease.

Patients with chronic hepatosplenic schistosomiasis and hepatic fibrosis are at higher risk of developing chronic schistosomal GN and should be monitored for hematuria/proteinuria and SCr changes.[498] In the opinion of the Work Group, annual testing may be reasonable.

Practice Point 7.3.1.3.2: Evaluate patients with a history of schistosomiasis and an elevated SCr and/or hematuria for bladder cancer and/or urinary obstruction.

Infection with *S. haematobium* can lead to genitourinary symptoms due to chronic granulomatous inflammation, leading to ulceration, strictures, and obstructive uropathy. Imaging may be needed to determine if hematuria or kidney disease stems from a chronic obstruction, given that chronic schistosomal disease can also cause acute/chronic GN. Pa- tients are also at an increased risk for bladder cancer. Monitor periodically with urine cytology or cystoscopy (gold stan- dard), especially in the setting of hematuria.[498]

Research recommendation

- Studies are required to evaluate the right sequencing/timing of treatment of antibiotics for salmonella and antiparasitic therapy for schistosomiasis.

7.3.2 Filariasis and glomerular disease

Filarial worms are nematodes that are transmitted to humans through a mosquito vector and dwell in the subcutaneous tissues and lymphatics. Glomerular disease has been reported in association with *Loa loa*, *Onchocerca volvulus*, *Wuchereria*

Dosing	Praziquantel	Oxamniquine
Adult	20 mg/kg, 3 times a day, for 1 day	15 mg/kg, single dose
Pediatric >1 year old	20 mg/kg, 2–3 times a day, for 1 day	20 mg/kg, single dose

Figure 63 | Dosing of antischistosomal agents.

bancrofti, and *Brugia malayi* infections in Africa and some Asian countries. There are limited observational studies and no RCTs in filarial nephropathy.

The incidence, prevalence, and natural history of glomer- ular involvement in various forms of filariasis are poorly documented. This condition is usually found in areas with poor vector control and inadequate healthcare facilities. Glomerular involvement is infrequent. Light microscopy re- veals diffuse proliferative MPGN, MCD, or chronic-sclerosing GN, or the collapsing variant of FSGS.[499] Microfilariae may be found in the arterioles, glomerular and peritubular capil- lary lumina, tubules, and interstitium.[499]

Immunofluorescence and electron microscopy show im- mune deposits along with worm antigens and structural components.[500,501] Urinary abnormalities have been reported in 11%–25% and NS is seen in 3%–5% of patients with loiasis and onchocerciasis, especially those with polyarthritis and chorioretinitis.[501,502] Proteinuria and/or hematuria was detected in over 50% of cases with lymphatic filariasis, and 25% showed glomerular proteinuria.[503,504]

7.3.2.1 Treatment

Practice Point 7.3.2.1.1: Treat patients with filarial infection and GN with an appropriate antiparasitic agent in suffi- cient dosage and duration to eradicate the organism.

A reduction in proteinuria can be observed following antifilarial therapy in patients with non-nephrotic proteinuria and/or hematuria. An increase in proteinuria or decline in kidney function can follow initiation of diethylcarbamazine or ivermectin,[504,505] probably due to an exacerbation of the immune process secondary to antigen release into circulation after death of the parasite.[506] Therapeutic apheresis has been utilized to reduce the microfilarial load and prevent antigen release before starting antifilarial treatment.[507] The renal response to antifilarial therapy is inconsistent in those with NS. Deterioration of GFR may continue despite clearance of microfilariae with treatment.

Potential kidney toxicity of treatment regimens requires careful monitoring of kidney function. Please refer to the WHO treatment guidelines for filariasis.[508]

Diethylcarbamazine is contraindicated in pregnancy (animal studies have shown an adverse effect on the fetus, but no well-controlled studies have been done in humans). However, po- tential benefits may warrant use of the drug in pregnant women, despite potential risks. Diethylcarbamazine is considered safe during lactation. Ivermectin is in pregnancy category C. Iver- mectin is also excreted in breast milk, and its use is not recom- mended during lactation unless the risk of delayed maternal treatment outweighs potential risk to the nursing infant.

Research recommendations

- Epidemiologic studies of kidney involvement in regions endemic for filaria
  - Studies on the effect of population-based treatment with filaricidal agents on the course of filarial kidney disease

7.3.3 Malarial nephropathy

Malaria caused by *Plasmodium* parasites transmitted through the female *Anopheles* mosquito is the most prevalent endemic disease in the world (Figure 64).

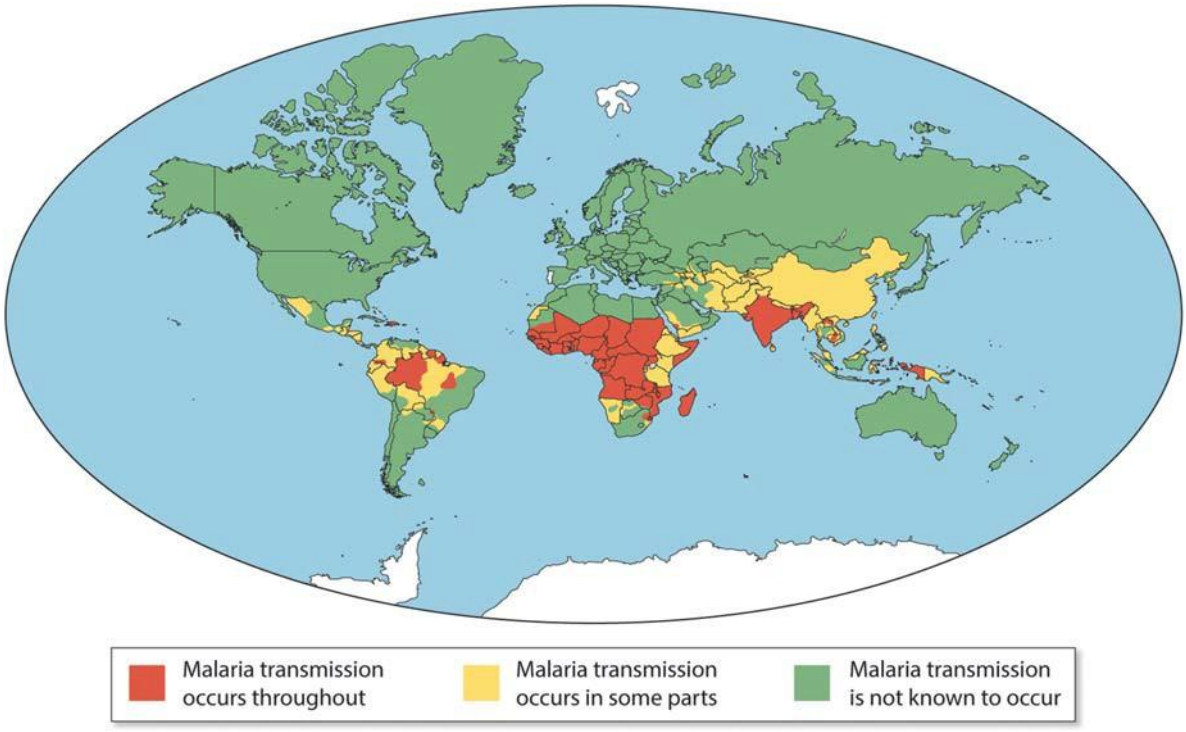

Figure 64 | Global distribution of malaria transmission. Reproduced from Centers for Disease Control and Prevention-CDC. Available at: http://www.cdc.gov/malaria/about/distribution.html. Accessed January 27, 2021.

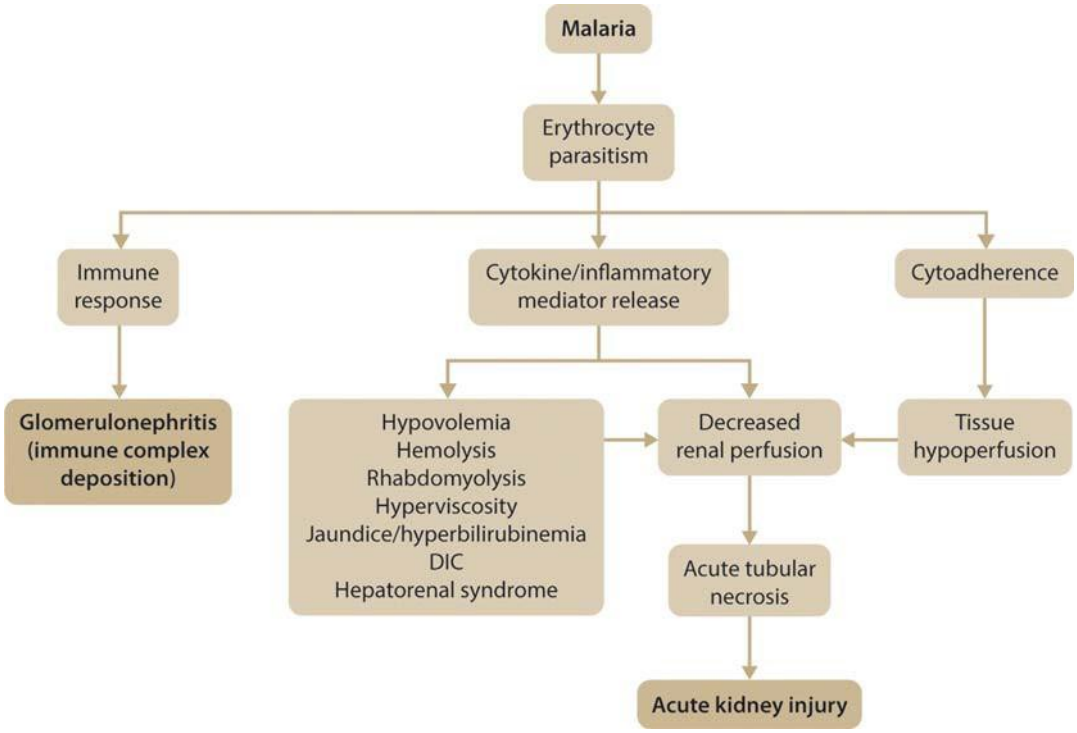

Figure 65 | Pathophysiology of kidney involvement in malaria.[510] DIC, disseminated intravascular coagulation.

Stage 1	Mild focal and segmental
Stage 2	Moderate focal and segmental
Stage 3	Diffuse or segmental lesions with interstitial and tubular changes
Stage 4	Marked sclerosis, and interstitial/tubular atrophy

Figure 66 | Histopathologic staging of quartan malarial nephropathy.

Safe	Unsafe
Chloroquine	Halofantrine
Amodiaquine	Tetracycline/doxycycline
Quinine	Primaquine
Azithromycin	
Sulfadoxine–pyrimethamine	
Mefloquine	
Chlorproguanil–dapsone	
Artemisinin derivatives	
Atovaquone–proguanil	
Lemefantrine	

Figure 67 | Antimalarial drugs and pregnancy.[521]

Malarial infection can cause a diversity of kidney injuries, both acute and chronic. Malarial infection–related GN is believed to be primarily a condition mediated by immune- complex formation.

Malaria-associated AKI can be classified as AKI from acute tubular necrosis (ATN), acute malarial-associated GN (revers- ible), or chronic and progressive GN (irreversible).[509] Immune- system activation between the malaria antigen and host red blood cells can lead to immune complex complement-mediated GN, acute interstitial nephritis, or acute GN (Figure 65).[510]

The exact incidence of GN in malaria is unknown, but it is estimated to be around 18%.[511] Acute malaria-associated GN can occur with *Plasmodium falciparum* or *Plasmodium vivax* infections, but is more common with *P. falciparum*. These patients will present with NS (transient mild proteinuria, microscopic hematuria, and occasionally low complement levels), and histopathology revealing MPGN or mesangio- proliferative GN.[509]

Chronic infection with *P. malariae* (and to a lesser extent *P. vivax*, *P. ovale*) has been associated with irreversible and progressive GN. In the past, this has been known as tropical nephritis or "quartan malarial nephropathy" (QMN; Figure 66).[512,513] Nephrotic syndrome, sometimes with impaired kidney function, is a common clinical manifestation. QMN is principally encountered in young children.[510] Nowa- days, the lesion is much less common, and most children in the tropics with NS have MCD, FSGS, HBV or HIV infection, sickle cell disease, or SLE, rather than QMN.[511,514,515]

7.3.3.1 Treatment

Practice Point 7.3.3.1.1: Treat patients with malarial infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism from blood and hepatosplenic sites. There are no indications for use of immunosuppressive agents in malarial nephropathy.

The outcome of GN due to malarial infection is difficult to predict, as eradication of the parasitic infection is not always followed by recovery. GN and CKD can develop despite malarial eradication, detectable 3–5 years after primary infection.[516] Complete kidney recovery can be seen in approximately 64%–79% of cases of AKI or acute GN asso- ciated with *P. falciparum* and *P. vivax*.[516–519]

There does not appear to be any role for glucocorticoids or immunosuppressant therapy in malarial nephropathy,[512,513] although controlled trials are lacking. Treatment should focus on malarial eradication.

P. falciparum infection: Artemisinin-based combination therapy (ACT) is recommended over monotherapy due to the development of artemisinin resistance. The patient should also receive a single low dose of primaquine to reduce malaria disease transmission. No testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is required due to low risk of serious toxicity.

P. malariae infection: ACT, or chloroquine in areas without chloroquine-resistance.

P. ovale, *P. vivax* infections: ACT, or chloroquine in areas without chloroquine-resistance. Primaquine should be added to prevent relapses, adjusted to a patient's G6PD enzyme activity.

Severe malaria requires treatment with i.v. or intramus- cular artesunate for at least 24 hours, followed by a complete 3-day course of ACT once the patient is able to tolerate oral medications.

The WHO also provides detailed recommendations for treatment of malaria.[520]

7.3.3.2 Special situations

In cases of severe malaria in children aged <6 years, when injectable medication cannot be given, the child should receive rectal artesunate and then be referred to a healthcare facility where the full level of care can be provided.

Halofantrine is both embryotoxic and cardiotoxic. Tetra- cycline/minocycline is associated with impairment of bone growth and teeth discoloration in the fetus and during in- fancy. Both are contraindicated during pregnancy and/or breastfeeding. Primaquine and tafenoquine can cause hemo- lysis in individuals with G6PD deficiency and are contra- indicated in G6PD-deficient individuals, pregnant women (since the G6PD status of the fetus cannot be determined), infants <6 months of age (since G6PD testing can be confounded by fetal hemoglobin in early life), and for women breastfeeding infants <6 months old (Figure 67[521]).

Research recommendations

- Studies on the incidence and prevalence of malarial ne- phropathy and its response to antimalarial therapy, espe- cially in endemic areas of West Africa
- RCTs to investigate the role of glucocorticoids and immu- nosuppressive agents when malarial nephropathy pro- gresses, despite eradication of the malarial parasite
- Studies to assess the safety and efficacy of antimalarial treatments in pregnancy, as pregnant women are often excluded from clinical trials[521]

Chapter 8: Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury

This chapter replaces the 2012 guideline chapter for idio- pathic MPGN. Given the advances in our understanding of underlying etiology and the recognition that MPGN is not a disease but a pattern of glomerular injury, this updated chapter discusses the evaluation and management of the glomerular disease that often have a membranoproliferative pattern of injury, including C3G.[522]

The treatment of MPGN depends upon identification of an underlying cause. In most cases, the MPGN lesion derives from deposition of immunoglobulins and complement as either immune complexes (secondary to an underlying infection/autoimmune process), or monoclonal immuno- globulins, or is due to dysregulation of the alternative com- plement pathway.

In a few cases of immune complex–mediated MPGN, an identifiable underlying cause cannot be found despite extensive evaluation. This may be seen in children and young adults, but is rarely seen in adults. These patients are considered to have an "idiopathic" immune complex–mediated MPGN or immune complex–mediated MPGN of unknown etiology.

Because previous controlled trials included patients based on the old and now discarded electron-microscopic classifi- cation of MPGN, and not on the current classification that uses immunofluorescence microscopy in combination with presumptive disease pathobiology, there is insufficient high- quality evidence to form recommendations for the manage- ment of the various diseases that have MPGN histology. Therefore, practice points will be given to assist in clinical decision-making for these patients.

Nomenclature

The membranoproliferative pattern of GN is a light- microscopic pattern of kidney injury, characterized princi- pally by an increased number of intraglomerular cells and diffuse thickening of the glomerular capillary walls. The clinical presentation is not specific, and patients commonly present with proteinuria (frequently associated with the NS), hypertension, glomerular hematuria, and abnormal kidney function. Hypocomplementemia (C3 and/or C4) is often, but not always, present. An MPGN pattern of injury may be found in many unrelated disorders (Figure 68). Identification of the pathogenic mechanisms specific for a disease is critical for appropriate management.

Membranoproliferative lesions were historically classified based on the location of deposits on electron microscopy examination as:

- *Type I MPGN* (MPGN I)—characterized by *subendothelial* and *mesangial* electron-dense deposits consisting of both immunoglobulin and C3
- *Type II MPGN* (MPGN II—Dense deposit disease [DDD])— characterized by electron-dense *intramembranous* deposits, predominantly consisting of complement
- *Type III MPGN* (characterized by *both subepithelial and subendothelial deposits*)

This historical classification was not based on disease pathogenesis, and as a result, different pathogenic processes fell under the collective designation of MPGN.

Advances in our understanding of underlying disease mechanisms leading to the development of a mem- branoproliferative pattern of kidney injury have resulted in a new pathobiology-based classification. The new classification relies on immunofluorescence examination; deposits are defined as primarily immunoglobulin (monoclonal), poly- clonal immunoglobulin and complement, or predominantly complement (Figure 69).[523,524]

On the basis of the immunofluorescence findings, MPGN can be broadly divided into an immunofluorescence-negative subgroup, a complement-dominant subgroup, and an immunoglobulin subgroup, with or without complement. When MPGN is immunoglobulin-positive, regardless of the presence of complement, evaluation for infection, autoim- mune disease, and monoclonal gammopathy should be done. Complement-dominant MPGN is further divided into C3/C4 glomerulopathy. A complement-dominant pattern requires evaluation of the alternative pathway of complement. Absence/trace Ig or C3 suggests a TMA.

It should be understood that the presence of an MPGN lesion implies that the pathogenic process has been present for some time and that other patterns of injury, including endocapillary proliferative GN, mesangioproliferative GN, and crescentic GN, may occur as a result of the same process. Thus, the type of lesion initially seen on light microscopy will depend, in part, on the timing of the kidney biopsy in relation to disease chronicity.[525]

Immune complex–mediated GN (ICGN) with an MPGN pattern ICGN is characterized by the deposition of immune com- plexes containing both polyclonal immunoglobulins and

Immunoglobulin-/ immune complex-mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** • Viral: hepatitis C (including HCV-associated mixed cryoglobulinemia), hepatitis B • Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis • Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, histoplasmosis **Deposition of immune complexes as a result of an autoimmune disease:** • SLE • Sjögren's syndrome • Rheumatoid arthritis • Mixed connective tissue disease **Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder** **Fibrillary glomerulonephritis** **Idiopathic** • None of the conditions above are present
Complement-mediated	**C3 glomerulonephritis and C3 DDD:** • Mutations in complement regulatory proteins: CFH, CFI, CFHR5 • Mutations in complement factors: C3 • Antibodies to complement factors: C3, C4, and C5 nephritic factors • Antibodies to complement regulatory proteins: CFH, CFI, CFB **C4 glomerulonephritis and C4 DDD**
Membranoproliferative pattern without immune complexes or complement	• Healing phase of HUS/TTP • Antiphospholipid (anticardiolipin) antibody syndrome • POEMS syndrome • Radiation nephritis • Nephropathy associated with bone marrow transplantation • Drug-associated thrombotic microangiopathies • Sickle cell anemia and polycythemia • Dysfibrinogenemia and other pro-thrombotic states • Antitrypsin deficiency

Figure 68 | Causes of a membranoproliferative pattern of injury. CFB, complement factor B; CFH, complement factor H; CFHR5, complement factor H–related protein 5; CFI, complement factor I; DDD, dense deposit disease; HCV, hepatitis C virus; HUS, hemolytic–uremic syndrome; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

complement (excludes IgAN). This lesion classically results from chronic antigenemia with or without circulating im- mune complexes. ICGN may manifest with the MPGN pattern of injury or other proliferative glomerular lesions.

ICGN is usually due to:

- Infections: Hepatitis C and B viral infections are among the most common underlying causes of ICGN, but bacterial and protozoal infections can also cause ICGN.
- Autoimmunity: ICGN can be associated with certain autoimmune disorders, such as SLE, Sjögren's syndrome, and rheumatoid arthritis.

GN with monoclonal immunoglobulin deposits

Proliferative patterns of kidney injury secondary to deposition of monoclonal immunoglobulins are observed in patients with monoclonal gammopathies. These disorders are

infrequently found in patients with overt hematologic disease, such as multiple myeloma, Waldenström macroglobulinemia, or B cell lymphoma. They most commonly occur in the setting of an indolent clonal, plasma cell, or lymphocytic disorder, and may be classified as a monoclonal gammopathy of renal significance (MGRS).[526] Kidney injury results from direct glomerular deposition of the monoclonal immuno- globulin. Examples include immunotactoid glomerulopathy, type I and type II cryoglobulinemic GN, and proliferative GN with monoclonal Ig deposits (PGNMID). Of note, in approximately 70% of the cases of PGNMID, a clone cannot be detected.[527] Each type can be differentiated by the distri- bution and ultrastructural appearance of deposits (i.e., amorphous or organized), by electron microscopy.[528] A complete discussion of these entities is beyond the scope of this guideline.

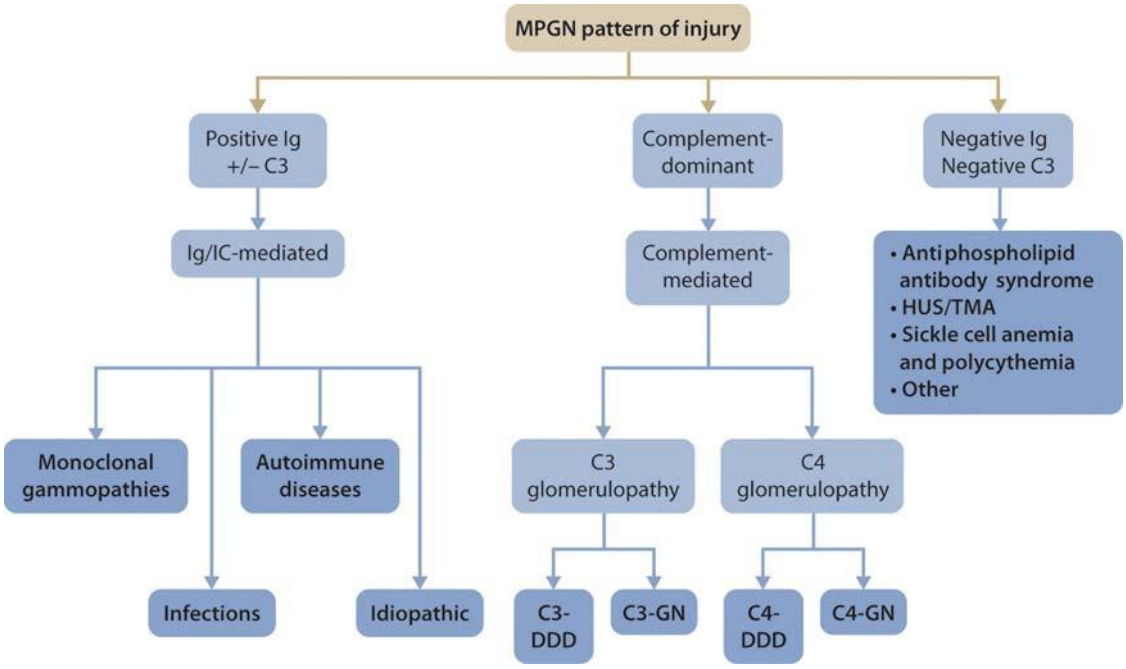

Figure 69 | Pathophysiology of membranoproliferative lesions. DDD, dense deposit disease; GN, glomerulonephritis; HUS, hemolytic– uremic syndrome; IC, immune complex; Ig, immunoglobulin(s); MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

Glomerulonephritis with C3- and C4-dominant deposits

C3G is a rare entity that is defined by C3-dominant glomeru- lonephritis (a proliferative histologic lesion with C3 deposition at least 2 orders of magnitude greater than any other immune reactant) on immunofluorescence.[529] This category includes both DDD and the newer designation of C3 glomerulone- phritis (C3GN).[530] Although DDD is defined by highly electron-dense osmophilic, predominantly intramembranous deposits, C3GN is characterized by mesangial and capillary wall deposits of lesser intensity. Other C3-dominant glomerular lesions (e.g., infection-related GN) must be excluded. Masked monoclonal immunoglobulin deposits should be considered in patients with a pattern of C3GN when immunofluorescence shows a small amount of immunoglobulin deposition admixed with C3 deposits. Immunofluorescence studies on paraffin- embedded tissue after pronase digestion may unmask glomerular deposits of monoclonal Ig.[531] An MPGN pattern is inconstantly observed in C3G, and hypocomplementemia is present in only about 50% of cases.[532,533] The underlying dis- ease mechanism of C3G is presumed to result from dysregu- lation of the alternative complement pathway.[534] A similar entity of complement-mediated GN that is characterized by bright C4d staining but with no or minimal C3 or immuno- globulin deposits on immunofluorescence (C4 glomerulopathy [C4G]) has recently been described.[535] Further studies are required to determine its underlying cause.

8.1 Diagnosis

Practice Point 8.1.1: Evaluate patients with immune complex-mediated GN (ICGN) for underlying disease (Figure 68).

First, consider infection such as HBV and HCV infection, chronic bacterial infection (e.g., endocarditis, shunt nephritis, abscesses), fungal, and particularly in the developing world, parasitic infections (e.g., schistosomiasis, echinococcosis, malaria). Streptococcal serology should be performed in pa- tients with recent history of infection. Second, consider autoimmune disorders such as SLE (particularly in the chronic phase of LN) and, less often, Sjögren's syndrome or rheumatoid arthritis. Besides autoimmunity, an underlying immune abnormality may be a trigger for ICGN. ICGN may be associated with malignancy; therefore, age-appropriate cancer screening may be warranted.

Practice Point 8.1.2: Evaluate patients with GN and monoclonal immunoglobulin deposits for a hematologic malignancy.

Patients with PGNMID, as determined by immunofluo- rescence, should undergo a complete evaluation for a hema- tologic malignancy or an indolent plasma cell or lymphocytic disorder, regardless of age, that includes: (i) serum and urine protein electrophoresis; (ii) serum and urine immunofix- ation; (iii) measurement of serum-free light chain levels; and
(iv) hematology consultation to further evaluate for the presence of an underlying B cell/plasma cell clone producing the monoclonal immunoglobulin.[526] Working with a hema- tologist is important not only to further evaluate these pa- tients (i.e., with a bone marrow biopsy, if indicated) but also because a number of the drugs used to treat these patients are not commonly used by practicing nephrologists.

Practice Point 8.1.3: If no underlying etiology is found for ICGN after extensive workup, evaluate for both

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, and CFHR1-5 MLPA
Plasma cell disorders‡	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

Figure 70 | Evaluation of abnormalities of the alternative pathway of complement. Adapted from *Kidney International*, volume 89, issue 2, Angioi A, Fervenza FC, Sethi S, et al. Diagnosis of complement alternative pathway disorders, pages 278–288, Copyright a 2016, with permission from the International Society of Nephrology.[539] ‡The presence of a circulating monoclonal gammopathy is less common below the age of 50 years. Ability to detect a monoclonal protein will depend on the sensitivity of the assay used. †Some complement assays may require referral to specialist/research laboratories, and interpretation of complement assays may require expert consultation. AP50, complement alternate pathway activation 50%; Bb, activated factor B; C3d, complement component 3d; C4d, complement component 4d; CFB, complement factor B; CFH, complement factor H; CFHR1-5, complement factor H–related protein 1-5; CFI, complement factor I; CH50, complement hemolytic activity 50%; FB, factor B; FH, factor H; FI, factor I; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MLPA, multiplex ligation-dependent probe amplification; sMAC, soluble membrane attack complex.

complement dysregulation and drivers of complement dysregulation (Figure 70).

Data support a role for complement dysregulation in ICGN.[536,537] In addition, cohort data demonstrate that classic C3G may masquerade as ICGN (i.e., significant immunoglobulin may be present) when an infectious trigger is present at the time of kidney biopsy.[538] Substantiating a role for excess complement activity may inform a treatment approach, over and above supportive measures, and/or standard immuno- suppression for active GN. A complete complement workup includes an assessment of overall complement activity, mea- surement of serum levels of complement proteins, and in select cases, screening for autoantibodies against complement regulatory proteins and genetic studies (Figure 70[539]).

Practice Point 8.1.4: Rule out infection-related GN or post- infectious GN prior to assigning the diagnosis of C3 glo- merulopathy (C3G).

Both infection-related GN (i.e., in the presence of active infection) and postinfectious GN (i.e., in patients with a pre- ceding infection that has resolved) are presumed to be nonrecurrent, acute disease processes requiring only a limited workup. Treatment is best focused on resolving the infection while supporting kidney function. Immunosuppression is unlikely to be required except in extreme cases (i.e., rapidly progressive loss of kidney function and/or crescentic glomerular disease) and only after concurrent infection is controlled.

Practice Point 8.1.5: Evaluate for the presence of a mono- clonal protein in patients who present for the first time with a C3G diagnosis at ‡50 years of age (Figure 69).

C3G in its classic form is a disease of children and young adults[538,540] related to autoantibody (nephritic factor)- mediated dysregulation of the enzyme complexes of the alternative pathway of complement, or to other key comple- ment pathway proteins, and to a lesser extent to mutations in genes encoding Factor H, Factor I, Complement Factor H– related (CFHR) proteins, or C3.[534] Recently, the association between the production of a monoclonal protein in older adults and the development of C3G has been described.[533,541] In patients over the age of 50 years with C3G, the prevalence of monoclonal gammopathy ranges from 31% to 83% versus approximately 3% in age-matched controls.[533] However, C3G with an associated circulating monoclonal protein has sometimes been reported in patients aged 20–47 years, demonstrating that the disease affects a large age span.[538] The association rests on the epidemiologic findings, as direct ev- idence demonstrating monoclonal gammopathy as the cause of C3G is lacking in most patients. However, it appears that a number of monoclonal proteins have complement dysregu- lating features, primarily through direct activation of the complement alternative pathway.[541] The impetus for evalu- ating a given patient for a clonal B cell disorder stems from the limited data suggesting that a therapeutic strategy that addresses the clone may provide a treatment benefit for a paraprotein-associated C3G.[542] The comprehensive evalua- tion of a patient suspected of having a monoclonal protein is beyond the scope of this presentation.

8.2 Treatment

8.2.1 ICGN

Prior guidelines supported the use of oral cyclophosphamide or MMF plus low-dose, alternate-day, or daily glucocorticoids

as a therapeutic approach to ICGN, particularly in those with idiopathic disease and NS and/or rapidly progressive diseases. The same advances in our understanding of underlying disease mechanisms that have driven a nomenclature change have also highlighted the confounding heterogeneity of prior disease cohorts. Additionally, idiopathic ICGN is an exceptional con- dition in adults. Data no longer support the global application of broad-spectrum immunosuppression as in prior recom- mendations, but rather a more individualized approach. The optimal management of many of the disorders that have an MPGN injury pattern remains to be defined. Unless otherwise indicated, the practice points offered below are based upon very low–quality evidence, clinical experience, and expert opinion. Treatment is often influenced and determined by the severity of proteinuria and kidney dysfunction.

Practice Point 8.2.1.1: When the cause of ICGN is deter- mined, the initial approach to treatment should focus on the underlying pathologic process.

After identification of the underlying trigger for ICGN, the most effective therapy is to treat the primary disease process (Figure 68). In addition, all patients with ICGN are likely to benefit from the usual, routine care considered for patients with other active glomerular disease (Chapter 1).

Practice Point 8.2.1.2: Indolent ICGN, whether idiopathic or linked to a primary disease process, is best managed with supportive care and carefully considered use of immunosuppression.

Patients with indolent disease may present late when active inflammation has subsided. Such patients may have a bland urine sediment with a variable degree of proteinuria and elevation in SCr. Such patients should be treated with RASi alone, unless the kidney biopsy shows signs of active inflam- mation. Patients who present with advanced kidney disease and severe tubulointerstitial fibrosis on kidney biopsy are less likely to benefit from immunosuppressive therapy even if there is still some active inflammation in the kidneys, so assessment of the extent of chronicity on the kidney biopsy may help in deciding whether or not to treat with immunosuppression.

Practice Point 8.2.1.3: For patients with idiopathic ICGN and proteinuria <3.5 g/d, the absence of the nephrotic syndrome, and a normal eGFR, we suggest supportive therapy with RAS inhibition alone.

No evidence exists to support a benefit from immuno- suppressive therapy in adults. Given that disease progression can occur, regular monitoring of SCr, proteinuria, and the urinalysis is recommended.

Similarly, there are no data available to inform the threshold for starting immunosuppression for the treatment of ICGN (as defined by the new nomenclature) in children who are not experiencing the NS. The authors recognize that in practice, immunosuppression may be initiated at lower levels of urine protein than may be considered in adults, and MMF is more likely to be utilized as a glucocorticoid-sparing option.

Practice Point 8.2.1.4: For patients with idiopathic ICGN, a nephrotic syndrome, and normal or near-normal SCr, try a limited treatment course of glucocorticoids.

Prednisone (or its equivalent) can be initiated at 1 mg/kg/ d (maximum dose of 60–80 mg/d) for 12–16 weeks. If the patient responds, prednisone may be gradually tapered to alternate-day therapy over 6–8 months. If there is <30% reduction in proteinuria after 12–16 weeks, we recommend tapering and discontinuation of prednisone.

Patients with a contraindication to glucocorticoids or unwilling to take glucocorticoids can be treated with a CNI. We do not encourage the extended use of glucocorticoids, where a glucocorticoid-sparing option may be available, particularly in children.

Practice Point 8.2.1.5: For patients with idiopathic ICGN, abnormal kidney function (but without crescentic in- volvements), active urine sediment, with or without nephrotic-range proteinuria, add glucocorticoids and immunosuppressive therapy to supportive care.

Prednisone (or its equivalent) can be initiated at 1 mg/kg/ d (maximum dose 60–80 mg/d) for 12–16 weeks. Patients who respond with stabilization or improvement in kidney function or $30% reduction in proteinuria are considered to have a satisfactory response to initial therapy. In such pa- tients, gradually taper and discontinue prednisone.

Patients that experience worsening kidney function and/or <30% reduction in proteinuria after 12–16 weeks are considered to have had an unsatisfactory response. In such patients, reduce the dose of prednisone to 20 mg/d and add MMF. If, after 6–12 months of combined therapy, there is no improvement in kidney function, hematuria, or proteinuria, discontinue therapy, and consider a repeat kidney biopsy. If the kidney biopsy continues to show active GN, consider using cyclophosphamide or rituximab.

Initiate daily oral cyclophosphamide (2 mg/kg/d; maximum 200 mg/d in adults) with prednisone (10 mg/d) for 3–6 months. The cyclophosphamide dose should be reduced by 25% in older adults (age >60 years) and adjusted appro- priately for abnormal kidney function.

Alternatively, in adults, initiate rituximab at 1 g followed 14 days later by a second dose of 1 g and repeat this 2 g regimen at 6 months.

In patients with persistent disease activity despite at least 6 months of MMF plus low-dose prednisone or after 3–6 months of daily oral cyclophosphamide plus prednisone or rituximab, discontinue glucocorticoids and immunosuppres- sion and continue supportive therapy.

Practice Point 8.2.1.6: For patients presenting with a rapidly progressive crescentic idiopathic ICGN, treat with high-dose glucocorticoids and cyclophosphamide.

Initiate treatment with i.v. methylprednisolone (1–3 g) followed by oral glucocorticoids and oral cyclophosphamide using a regimen similar to that used for patients with ANCA- associated vasculitis (AAV; Chapter 9).

Practice Point 8.2.1.7: For most patients with idiopathic ICGN presenting with an eGFR <30 ml/min per 1.73 m^2, treat with supportive care alone.

Unless kidney biopsy shows an active necrotizing cres- centic glomerulonephritis (NCGN) or other reason that could support use of immunosuppression (i.e., minimal interstitial fibrosis or concomitant acute tubulointerstitial nephritis), these patients should be treated conservatively with referral for kidney transplant evaluation in due course.

Practice Point 8.2.1.8: Patients who fail to respond to the treatment approaches discussed in 8.2.1.4 and 8.2.1.5 should be considered for a clinical trial where available.

8.2.2 C3 glomerulopathy

An optimal treatment strategy for C3G using currently avail- able therapeutics has not been established. Expert opinion has encouraged the usual supportive measures (Chapter 1), as well as the use of immunosuppression in the setting of moderate- to-severe disease, defined as moderate-to-marked prolifera- tion on biopsy and proteinuria (>2 g/d).[543] This opinion is based primarily on 4 retrospective cohorts and on an extrap- olation of data from other non-related proliferative glomeru- lonephritides. Well-controlled data are unavailable.

Practice Point 8.2.2.1: In the absence of a monoclonal gammopathy, C3G in patients with moderate-to-severe dis- ease should be treated initially with MMF plus glucocorti- coids, and if this fails, eculizumab should be considered.

Consider treating patients with C3G who have proteinuria >1 g/d and hematuria or have had declining kidney function for at least 6 months.

The reported effectiveness of immunosuppressive treat- ment in C3G has been variable. Medjeral-Thomas *et al.* reported 32 patients with C3G who received immunosup- pressive treatment (glucocorticoids alone or combined with other drugs). Immunosuppression did not seem to reduce progression to kidney failure as compared to no treatment.[544] Similar results were obtained by Servais *et al.* in a cohort of 85 patients with C3G.[537]

More recent data showed encouraging results with MMF. Rabasco *et al.* reported a relative treatment advantage with MMF in a cohort of 60 patients with C3G.[545] In a mean follow-up of 47 months, the 22 patients who received MMF plus glucocorticoids showed lower rates of ESKD (0% vs. 16.6%) and doubling of SCr (0% vs. 39%) as compared to patients exposed to other immunosuppression. In addition, the rates of remission in the MMF group were significantly higher (19 of 22 patients vs. 9 of 18 patients; $P < 0.05$). The response to immunosuppression seen in this retrospective cohort provided the support for the current expert opinion on treatment approach for C3G.[543]

Similarly, Avasare *et al.* reported the kidney outcomes for 30 patients with C3G after MMF.[546] After a mean follow-up of 3 years, two-thirds had an either stabilized or reduced SCr level and reduced proteinuria. Ravindran *et al.* reported the kidney outcomes on a subcohort of 144 patients with

C3G.[533] Of 24 patients given MMF (median follow-up 9.6 months), 3 had improved kidney outcome measures, and 4 had stable disease. Fifteen patients worsened. Finally, Bom- back *et al.* reported the results of a subcohort of their 111 patients with C3G.[532] Of the 42 patients exposed to MMF, 19 achieved either a complete or partial remission.

The benefits of terminal complement blockade with the anti- C5 monoclonal antibody eculizumab remain unestablished. A trial involved 3 patients with DDD (including 1 kidney trans- plant recipient) and 3 patients with C3GN (including 2 kidney transplant recipients), all of whom had proteinuria >1 g/d and/ or AKI at enrollment. Complement testing identified pathogenic variants in Complement Factor H (CFH) and CD46 in one patient each and C3 nephritic factors in 3 patients. After 12 months of twice-weekly eculizumab, 3 patients had a renal response (decrease in SCr levels and/or proteinuria), and 1 pa- tient with stable laboratory parameters had histopathologic ev- idence of improvement. Eculizumab normalized soluble C5b-9 level in all patients with elevated levels of this biomarker of terminal pathway activity at baseline, suggesting it may represent a potentially useful marker of response.

In a recent retrospective study, 26 patients with C3G were treated with eculizumab for a median duration of 14 months. Of these, 6 patients (23%) had a global clinical response, 6 (23%) had a partial clinical response, and 14 (54%) had no response. As compared to those with partial response or no response, re- sponders had lowereGFRs, more rapidly progressive disease, and more extracapillary proliferation on kidney biopsy samples. Age, extent of kidney fibrosis, frequency of NS, and features of alternative pathway activation did not differ. These results are consistent with the fact that eculizumab mainly targets glomer- ular inflammation and has no effect or limited effect on the complement dysregulation that governs C3G.[547]

In the absence of clear evidence, the use of eculizumab can be considered in patients with progressive disease who fail to respond to other therapies.

Practice Point 8.2.2.2: Patients who fail to respond to the treatment approaches discussed in 8.2.2.1 should be considered for a clinical trial where available.

Research recommendations

- Further define the diagnostic criteria for C3G (utilizing biomarkers and histology characteristics) to allow for the separation of C3G from confounding conditions
- RCTs of immunosuppression in patients with fully char- acterized idiopathic ICGN and C3G without monoclonal gammopathy
- In-depth study of the role of complement in each of the diseases included in this chapter
- Optimize the evaluation of suspected paraprotein- associated C3G
- RCTs of clone-targeted chemotherapy versus immunosup- pression for the treatment of paraprotein-associated glomerular disease

Chapter 9: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

9.1 Diagnosis

Small-vessel vasculitis encompasses a group of diseases characterized by necrotizing inflammation of small vessels (i.e., arterioles, capillaries, and venules) and little or no deposition of immune complexes in the vessel wall (pauci- immune). Medium or large vessels may occasionally also be involved. Pauci-immune small-vessel vasculitides include granulomatosis with polyangiitis (GPA), microscopic poly- angiitis, and eosinophilic granulomatosis with polyangiitis (eGPA).[548] The kidney lesion associated with these conditions is a pauci-immune focal and segmental NCGN. Active pauci- immune small-vessel vasculitis is typically associated with circulating ANCA, and GPA, microscopic polyangiitis, and eGPA were grouped under the term "ANCA-associated vasculitis" (AAV) in the 2012 Chapel Hill definitions of pri- mary systemic vasculitis.[548] NCGN may occur with or without extrarenal manifestations of disease.

Patients with systemic vasculitis may present with extra- renal manifestations affecting one or several organ systems, with or without kidney involvement. Commonly involved systems are the upper and lower respiratory tract, skin, eyes, and the nervous system. Pulmonary hemorrhage affects 10% of patients with AAV and is associated with an increased risk of death.[549] The need to treat extrarenal vasculitis may in- fluence treatment choices for kidney vasculitis.

The clinical manifestations associated with NCGN include microscopic hematuria with dysmorphic red blood cells and red cell casts, and proteinuria that is usually moderate (1–3 g/d). Pauci-immune NCGN is frequently associated with a rapidly declining GFR over days or weeks. A slowly progressive course has also been described when active vasculitic lesions may be hard to find on histology, and some patients with kidney vasculitis, especially if pre- senting with extrarenal disease, are diagnosed when the GFR is still normal.

AKI can present together with alveolar hemorrhage and is often referred to as a "pulmonary–renal syndrome." Although several diseases can manifest as a pulmonary–renal syndrome, simultaneous lung and kidney injury should raise concern for vasculitis. In this situation, serologic testing and interpreta- tion are of great diagnostic importance. A positive test for anti-GBM antibodies suggests anti-GBM disease (formerly Goodpasture's syndrome) and a need for urgent plasma ex- change without waiting for a positive diagnostic biopsy (Figure 71), whereas a positive test for ANCA is compatible with a diagnosis of AAV. Some patients are positive for both ANCA and anti-GBM antibodies. The diagnosis of AAV relies on the combination of clinical findings and results of imaging studies and laboratory tests (such as C-reactive protein level, complete blood count, kidney parameters, and urine sedi- ment analysis). In addition, myeloperoxidase (MPO)- and proteinase 3 (PR3)-ANCA testing and, when feasible, biopsy of the kidney or other affected organs should be performed. About 90% of patients with small-vessel vasculitis or NCGN have ANCA, directed primarily to the neutrophil granule proteins MPO or PR3.[550] The 2017 revised

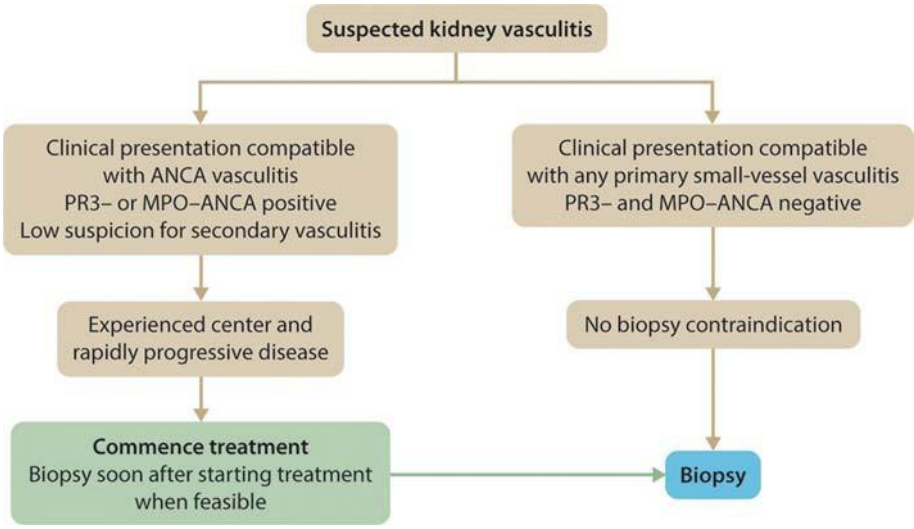

Figure 71 | Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

international consensus on testing of ANCA in GPA and microscopic polyangiitis states that high-quality antigen- specific immunoassays are the preferred screening method for MPO- and PR3-ANCA.[551]

Practice Point 9.1.1: In the case of a clinical presentation compatible with small-vessel vasculitis in combination with positive myeloperoxidase (MPO)- or proteinase 3 (PR3)- ANCA serology, waiting for a kidney biopsy to be per- formed or reported should not delay starting immuno- suppressive therapy, especially in patients who are rapidly deteriorating (Figure 71).

In AAV, a kidney biopsy is of importance for both the primary diagnosis and recurrent disease. This also relates to recurrent disease after kidney transplantation (Figure 72 and Figure 73). Biopsy remains the gold standard, and in GPA, the diagnostic yield of a kidney biopsy can be as high as 91.5%.[552] The kidney biopsy provides prognostic information through assessment of glomerular, tubulointerstitial, and vascular histopathology.[553] Therefore, a kidney biopsy should always be considered in patients suspected of active kidney involve- ment, but in the context of positive MPO– or PR3–ANCA serology and a clinical picture compatible with small-vessel vasculitis with low suspicion for secondary vasculitis, an immediate biopsy may not be necessary and should not delay the initiation of treatment.

The treatment recommendations in this guideline derive from studies of patients with AAV and/or NCGN. About 10% of patients presenting with signs and symptoms of micro- scopic polyangiitis, GPA, or NCGN are persistently ANCA- negative. These patients are treated similarly to patients who are ANCA-positive, although no study has focused specifically on the treatment of patients who are ANCA- negative. Considering patients who are ANCA-negative, it is important to realize that several nonvasculitic diseases may closely mimic small-vessel vasculitis. These include systemic rheumatic diseases, for example, SLE, infections, and malig- nancies (Figure 74[554]).

Practice Point 9.1.2: Patients with ANCA-associated vasculitis (AAV) should be treated at centers with experi- ence in AAV management.

A center with experience in AAV management is equipped with adequate facilities for rapid diagnosis and management. For diagnosis, adequate serologic and histologic tests should be available. All treatment modalities should be available, including rituximab and plasma exchange. The center should have experience with these treatment modalities and their complications. Finally, a center should have access to an intensive care unit and an acute hemodialysis facility.

9.2 Prognosis

9.2.1 Survival

Factors influencing remission, relapse, kidney and overall survival in AAV have been described.[555–557] Important factors associated with survival are age and kidney function and/or kidney involvement at diagnosis. Without immunosuppressive therapy, AAV is associated with poor outcomes. Consequently, immunosuppressive treatment is pivotal to improve survival of individual patients with active systemic AAV, including older adults (>75 years of age) for whom immunosuppressive treatment has been associated with improved survival.[558]

Disease activity of ANCA-associated vasculitis represents signs or symptoms attributable to active disease in any organ system

Remission is defined as the absence of manifestations of vasculitis and GN. For GN, it is defined as a stable or improved glomerular filtration rate. While hematuria and proteinuria are present at times of active disease and can resolve completely, their persistence does not necessarily imply active disease

Relapse is defined as the occurrence of increased disease activity after a period of partial or complete remission. A return or increase of hematuria with proteinuria may indicate a kidney relapse. Relapse can be divided into major or minor, with major relapses defined as life- or organ-threatening. Examples of major relapse include diffuse alveolar hemorrhage, subglottic stenosis, GN or vasculitis threatening vision

Treatment-resistant disease is defined as the persistence of or appearance of kidney and/or systemic manifestations of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy

Figure 72 | Definition of disease activity, remission, relapse, and treatment-resistant disease in AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis.

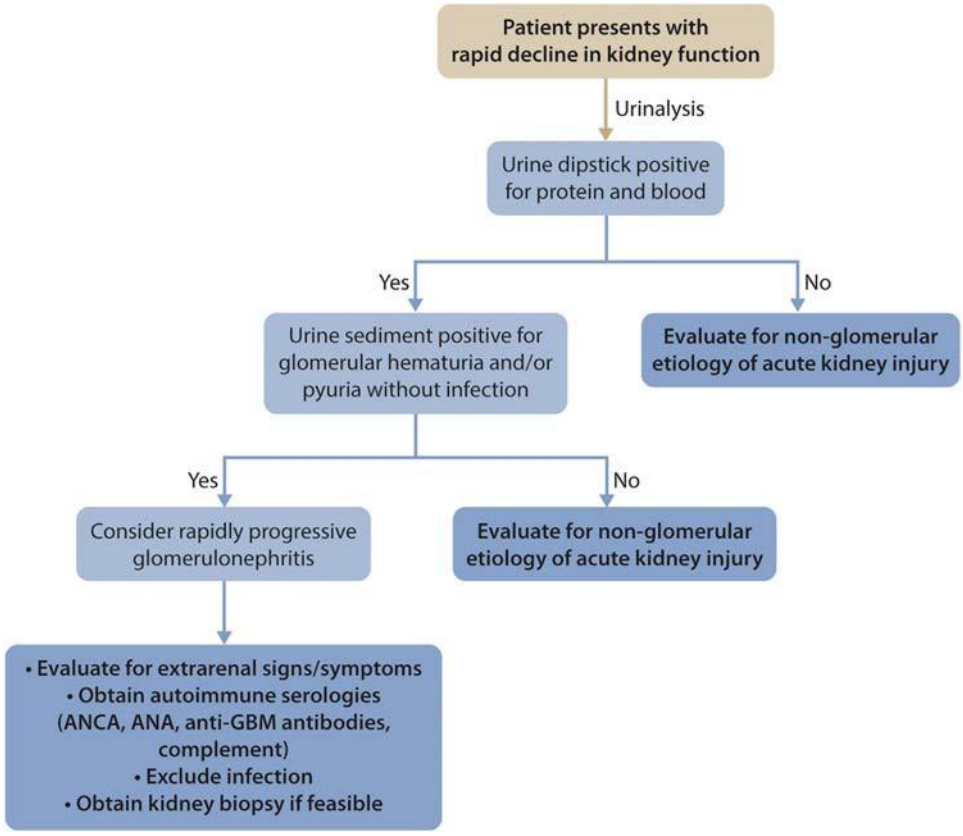

Figure 73 | Diagnostic strategy in rapidly progressive glomerulonephritis. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

Organ system	Microscopic polyangiitis (%)	Granulomatosis with polyangiitis (GPA) (%)	Eosinophilic granulomatosis with polyangiitis (eGPA) (%)
Cutaneous	40	40	60
Kidney	90	80	45
Pulmonary	50	90	70
Ear, nose, and throat	35	90	50
Musculoskeletal	60	60	50
Neurologic	30	50	70
Gastrointestinal	50	50	50

Figure 74 | Frequency of organ involvement in AAV. Reproduced from *The New England Journal of Medicine*, Jennette JC, Falk RJ, Small-Vessel Vasculitis, Volume 337, Pages 1512–1523, Copyright a 1997 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[554] AAV, ANCA-associated vasculitis.

9.2.2 Kidney prognosis and treatment response

Kidney histology is predictive of long-term risk of kidney failure; prognostic histologic scores have been developed (e.g., by Berden *et al.*[553] and Brix *et al.*[559]; Figure 75[553]).

In validation studies of the histopathologic classification by Berden, >50% normal glomeruli in the focal class were associated with a favorable outcome, whereas >50% sclerotic glomeruli were associated with a poor outcome.[560] Also, in the kidney risk score developed by Brix *et al.*, a higher per- centage of normal glomeruli (>25%) was associated with favorable kidney outcomes.[559] However, regarding the

crescentic class (>50% cellular crescents) and mixed class, discrepancies in outcome have been reported.

Importantly, kidney recovery can be seen in the face of advanced kidney damage, and induction treatment should not be withheld on the basis of unfavorable histologic findings.

Assessing response of kidney vasculitis can be difficult in the presence of persistent hematuria and proteinuria, which are seen in 50% of patients. A stable or falling creatinine level is a guide; control of extrarenal disease and normalization of in- flammatory markers (e.g., C-reactive protein) are also helpful but do not exclude ongoing kidney activity. Also, other causes

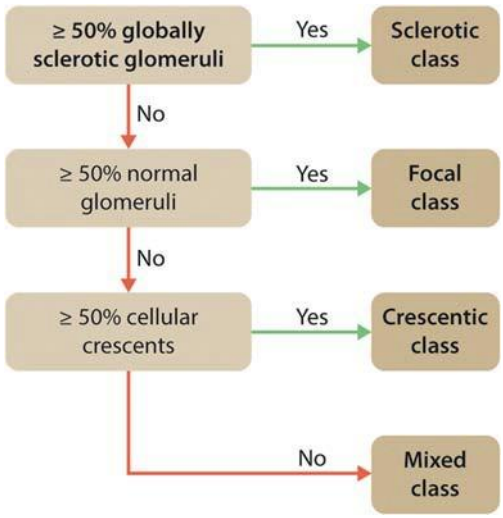

Figure 75 | Histopathologic classification of ANCA-associated glomerulonephritis. Biopsies should be scored for glomerular lesions in the following order: globally sclerotic glomeruli, normal glomeruli, and glomeruli with cellular crescents. Biopsies that do not fit into a category based upon a predominant glomerular phenotype will be included in the mixed category.[553]

of AKI, not related to AAV, should be considered; therefore, a kidney biopsy should be considered at presentation and during follow-up in case of poor treatment response (Figure 71).

Histologic activity is unlikely in the absence of hematuria. Persisting proteinuria can reflect disease activity or chronic parenchymal damage from preceding inflammation. Such chronic damage confers an adverse long-term kidney prog- nosis. The significance of persisting hematuria is unclear. In a retrospective study, no difference was found in the occurrence of ESKD between patients with and without persisting hematuria, but more patients with hematuria experienced a relapse of kidney disease.[561] More impor- tantly, a return of hematuria after initial resolution may indicate kidney relapse.

9.2.3 Relapses

Practice Point 9.2.3.1: The persistence of ANCA positivity, an increase in ANCA levels, and a change in ANCA from negative to positive are only modestly predictive of future disease relapse and should not be used to guide treatment decisions.

PR3- and MPO-AAV are characterized by the occurrence of relapses. Patients who are PR3-ANCA-positive experience more relapses than those who are MPO-ANCA positive.[562] The achievement of ANCA-negativity after induction treat- ment is associated with a lower risk of relapse.[563,564] Both a rise or persistence of ANCA are only modestly predictive of future disease relapse.[565] Also, a change in ANCA status from negative to positive has been associated with a higher inci- dence of relapse, and more frequent clinical assessments should be considered. However, regarding the relapsing phenotype of AAV, ANCA measurements should not guide treatment decisions in individual patients.

9.3 Treatment

Treatment of AAV is generally divided into an initial phase, commonly termed "induction," followed by a "maintenance" phase.

9.3.1 Induction

The best evidence is available for patients with new-onset AAV. In patients with severe (SCr >4 mg/dl [>354 mmol/l]) kidney disease, limited data for induction therapy with rituximab are available.

Key information

Balance of benefits and harms. Cyclophosphamide, in combination with glucocorticoids, has been used as induction therapy in several RCTs. In 2 RCTs, rituximab alone or in combination with 2 cyclophosphamide pulses was shown to be equally as effective as cyclophosphamide, with a similar rate of infectious complications (Supplementary Table S31[566–569]). However, *post hoc* analysis of the Rituximab in ANCA-Associated Vasculitis (RAVE) trial found a superior remission rate for the PR3-ANCA subgroup at 6 months treated with rituximab, with an odds ratio (OR) of 2.11 (95% CI: 1.04–4.30) in analyses adjusted for age, sex, and new-onset versus re- lapsing disease at baseline.[570] In patients with PR3-AAV and relapsing disease, more patients achieved remission at 6 and 12 months with rituximab, with an OR of 3.57 (95% CI: 1.43– 8.93) at 6 months and an OR of 4.32 (95% CI: 1.53–12.15) at 12 months.[570] No association between treatment drug and remission was observed in patients with MPO-AAV (RAVE trial; Supplementary Table S32[567,569]).

Regarding the route of cyclophosphamide administration, oral and i.v. cyclophosphamide resulted in similar outcomes. With i.v. cyclophosphamide, a reduction of the total cyclo- phosphamide dosage is achieved compared to oral cyclo- phosphamide. In the Pulse Versus Continuous Cyclophosphamide for Induction of Remission in ANCA- Associated Vasculitides (CYCLOPS) study, this resulted in a lower rate of leukopenia (Supplementary Table S33[569,571]). Nevertheless, more patients tended to experience relapses after i.v. cyclophosphamide during long-term follow-up.

In patients with non-life-threatening disease, excluding those with rapidly progressive kidney disease, MMF might be an alternative to cyclophosphamide for the MPO-ANCA subgroup. MMF had a similar remission rate to cyclophosphamide for patients with both PR3- and MPO-ANCA (Supplementary Table S34[569,572–575]), but a much-increased relapse risk in those with PR3-ANCA in the Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC) trial.[574]

Methotrexate, with glucocorticoids, has been used for AAV without kidney disease in the absence of irreversible tissue

Recommendation 9.3.1.1: We recommend that glucocorticoids in combination with cyclophospha- mide or rituximab be used as initial treatment of new-onset AAV (1B).

damage but is associated with a higher relapse rate and higher late accrual of damage compared to cyclophosphamide (Supplementary Table S35[569,576,577]).

Glucocorticoids are major contributors to adverse events. Intravenous methylprednisolone (doses of 1–3 g) is widely used for more severe presentations but has not been tested in an RCT. Oral prednisolone/prednisone starting at 1.0 mg/kg/d has been used in most RCTs, again without direct RCT support. The rate of reduction of glucocorticoids varies between studies, with some aiming for withdrawal by month 5, while others continue 5–10 mg/d after 6 months.[578] The Plasma Exchange and Glucocorticoids for the Treatment of ANCA-Associated Vasculitis (PEXIVAS) trial demonstrated that for patients with GFR <50 ml/min per 1.73 m^2, a more rapid reduction was as effective but safer than a "standard" glucocorticoid tapering regimen.[579] In the RAVE trial, the rituximab group had a lower glucocorticoid exposure, and observational studies have supported early glucocorticoid removal when rituximab is used (Figure 79).

Complement-targeted therapy might be another strategy to reduce glucocorticoid exposure. An oral C5a receptor antagonist, avacopan, has been shown in the A Phase 3 Clinical Trial of CCX168 (Avacopan) in Patients with ANCA- Associated Vasculitis (ADVOCATE) phase 3 trial to be an effective alternative to glucocorticoid treatment in AAV with potential to improve kidney outcomes.[580]

Quality of evidence. The overall quality of evidence is moderate. The RCTs that compared rituximab with cyclo- phosphamide reported important outcomes of remission and relapse, and the quality of the evidence was rated as moderate for these outcomes because of serious imprecision (Supplementary Table S31[566–569]). The critical outcome, all- cause mortality, was included; however, there were no cases reported for kidney failure in the 2 trials. Only the RAVE trial was blinded for both participants and personnel and is regarded by the panel as the best evidence available. Effects on complete remission at 6 months, relapse rate, and serious adverse events are graded as moderate. In a secondary paper, complete remission in ANCA subgroups was reported; this is graded as low due to imprecision (only 1 study). There were no differences in kidney outcomes, and those with SCr >4 mg/dl (>354 mmol/l) were excluded. Finally, follow-up was short at 18 months.

The studies comparing continuous oral versus i.v. pulse cyclophosphamide were not blinded (participants and study personnel; Supplementary Table S36[569,581–583]). Overall, the quality of evidence on the important endpoints of complete remission and leukopenia is graded as moderate because of study limitations. Other outcomes exhibited low quality of evidence because of serious imprecision due to very few events (relapse, all-cause mortality). The Work Group con- siders the CYCLOPS study the best available study on this topic because of the addition of azathioprine to both

treatment arms; consequently, it was evaluated separately (Supplementary Table S33[569,571]). The quality of the evidence was low for all critical outcomes, due to imprecision, as there was only 1 study.

The RCTs comparing MMF versus cyclophosphamide had few events for many critical and important outcomes (all-cause mortality, ESKD, malignancy, serious adverse events), and hence the quality of the evidence was low (Supplementary Table S34[569,572–575]). However, for the outcomes of infection and relapse, the quality of the evi- dence was rated as moderate due to study limitations from some studies (unclear blinding of outcome assessors). The MYCYC[574] and Tuin *et al.*[575] studies had an independent, blinded adjudication committee assess the primary endpoint of complete remission at 6 months, but the other studies had concerns regarding blinding and hence the quality of the evidence for this outcome has been rated as moderate.

Values and preferences. This Work Group places a relatively high value on achieving complete remission of disease, which was the primary outcome of most evaluated studies. However, extended immunosuppressive therapy should be associated with a minimum of adverse events. In subgroups of patients for whom fertility is a concern, and in relapsing patients, rituximab may be preferred.

Intravenously pulsed versus oral continuous cyclophos- phamide results in a similar outcome. However, the cumu- lative dosage of cyclophosphamide is lower with i.v. cyclophosphamide. Patients treated with i.v. pulse cyclo- phosphamide may have an increased risk of relapse, as re- ported in the CYCLOPS study.

Glucocorticoids are disliked by patients and are major causes of adverse events. Use of rituximab or the combi- nation of rituximab with cyclophosphamide may be asso- ciated with a lower glucocorticoid requirement, particularly desirable in those at higher risk of glucocorticoid toxicity.[567,584] C5a receptor inhibition with avacopan is a potential alternative to glucocorticoid treatment, which in addition to its efficacy in controlling disease, has been shown to improve patient quality of life when compared to prednisone in AAV.[580]

Resource use and costs. Rituximab is typically more expensive than cyclophosphamide, although secondary costs for cyclophosphamide (infusions and monitoring) and reduced cost of generic rituximab can make the total costs similar. Ease of administration, simpler monitoring, glucocorticoid sparing, and reduced early toxicity associated with rituximab compared to cyclo- phosphamide are additional factors that influence cost and resource use.

Regarding i.v. versus oral cyclophosphamide, with intra- venous cyclophosphamide, a reduction of the total cyclo- phosphamide dosage is achieved compared to oral cyclophosphamide. However, oral cyclophosphamide is less

expensive. In patients treated with either i.v. or oral cyclo- phosphamide, frequent monitoring for treatment toxicity, in particular leukopenia, is important.

Considerations for implementation. The choice of treatment regimen depends on patient comorbidity, age, and preference, as well as local availability and cost.

Rationale

Cyclophosphamide, in combination with glucocorticoids, has been applied as induction therapy in multiple RCTs. In 2 RCTs, rituximab has been shown to be equally effective in inducing remission to cyclophosphamide.[566,567] Rituximab compared to cyclophosphamide probably has little or no difference in relapse rate at 1–6 months (RR: 0.63; 95% CI: 0.35–1.14). Rituximab and cyclophosphamide have similar rates of severe adverse events, including infections. However, risks of long-term comorbidities, such as malignancy, HBV and HCV reactivation, and secondary immunodeficiency, appear to differ between rituximab and cyclophosphamide and may influence choice.[585,586]

In the RAVE study, patients with relapsing disease more often achieved remission at 6 and 12 months in the rituximab group compared to the cyclophosphamide–azathioprine group.[570,587] Analysis of the data according to ANCA status showed that patients with PR3-AAV were significantly more often in complete remission at 6 months than patients treated with cyclophosphamide–azathioprine.[570]

An important consideration when interpreting the RAVE trial is that it excluded patients with severe kidney disease (SCr >4 mg/dl [>354 mmol/l]). A recent single-center retrospective study found that rituximab was comparable to cyclophosphamide in remission induction at 6 months.[588] However, no prospective data on the efficacy of remission induction of rituximab in severe kidney disease are available. In contrast, the Rituximab versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) study included such patients and showed that rituximab combined with 2 cyclophosphamide pulses and glucocorticoids was compa- rable to cyclophosphamide for remission induction and number of adverse events.[566]

Regarding the administration route of cyclophosphamide, 4 RCTs compared induction therapy with i.v. pulse versus continuous oral cyclophosphamide.[569,571,581–583] Intravenous cyclophosphamide and oral cyclophosphamide resulted in a similar rate of complete remission, but less leukopenia was

seen in patients given i.v. cyclophosphamide. In the CYCLOPS study, a higher rate of relapse was reported with i.v. pulse cyclophosphamide.[571] This reflects the 50% reduction in cyclophosphamide exposure seen with i.v. regimens; shorter-course oral cyclophosphamide regimens are also associated with higher relapse risk.

In patients with non-severe disease, MMF and metho- trexate have been compared to cyclophosphamide. Regarding MMF versus cyclophosphamide, no significant differences were found, but cyclophosphamide tended to show better efficacy and fewer relapses.[569,572–575] Compared to cyclophosphamide, methotrexate was associated with a higher relapse rate (RR: 1.50; 95% CI: 1.03–2.17).[569,576,577,589] Effects on other critical and important outcomes are unclear, as they were not reported or occurred infrequently.

Glucocorticoids are part of induction therapy. In the PEXIVAS study, all patients received oral prednisone/pred- nisolone at 1 mg/kg/d for the first week, followed by rapid or slow tapering schedules. This led to about a 50% dif- ference in oral glucocorticoid exposure during the first 6 months The lower-dose regimen was noninferior for efficacy and is safer, and therefore is preferred.[579,590] All patients in the PEXIVAS trial received an initial dose of i.v. methyl- prednisolone of 1–3 g; the optimal dose is yet to be determined.

Cyclophosphamide dose should be reduced for kidney impairment and age, as these patients are at increased risk for infection (Figure 80).

Low-dose sulfamethoxazole/trimethoprim (TMP-SMX), or alternative, is advised for pneumocystis pneumonia prophy- laxis for the duration of the cyclophosphamide course or for 6 months following rituximab induction. Longer-term use may be considered in those receiving repeated rituximab infusions, for those with structural lung disease, or those requiring ongoing immunosuppressive or glucocorticoid therapy.

In a retrospective study, the IgG level before rituximab correlated with hypogammaglobulinemia post-rituximab.[591] Therefore, IgG levels should be measured at baseline and every 6 months for patients treated with rituximab. A low level at baseline (defined as IgG <3 g/l; Figure 80) may predict a greater risk of secondary immunodeficiency with rituximab.[591]

Practice Point 9.3.1.1: A recommended treatment algo- rithm for AAV with kidney involvement is given in Figure 76.

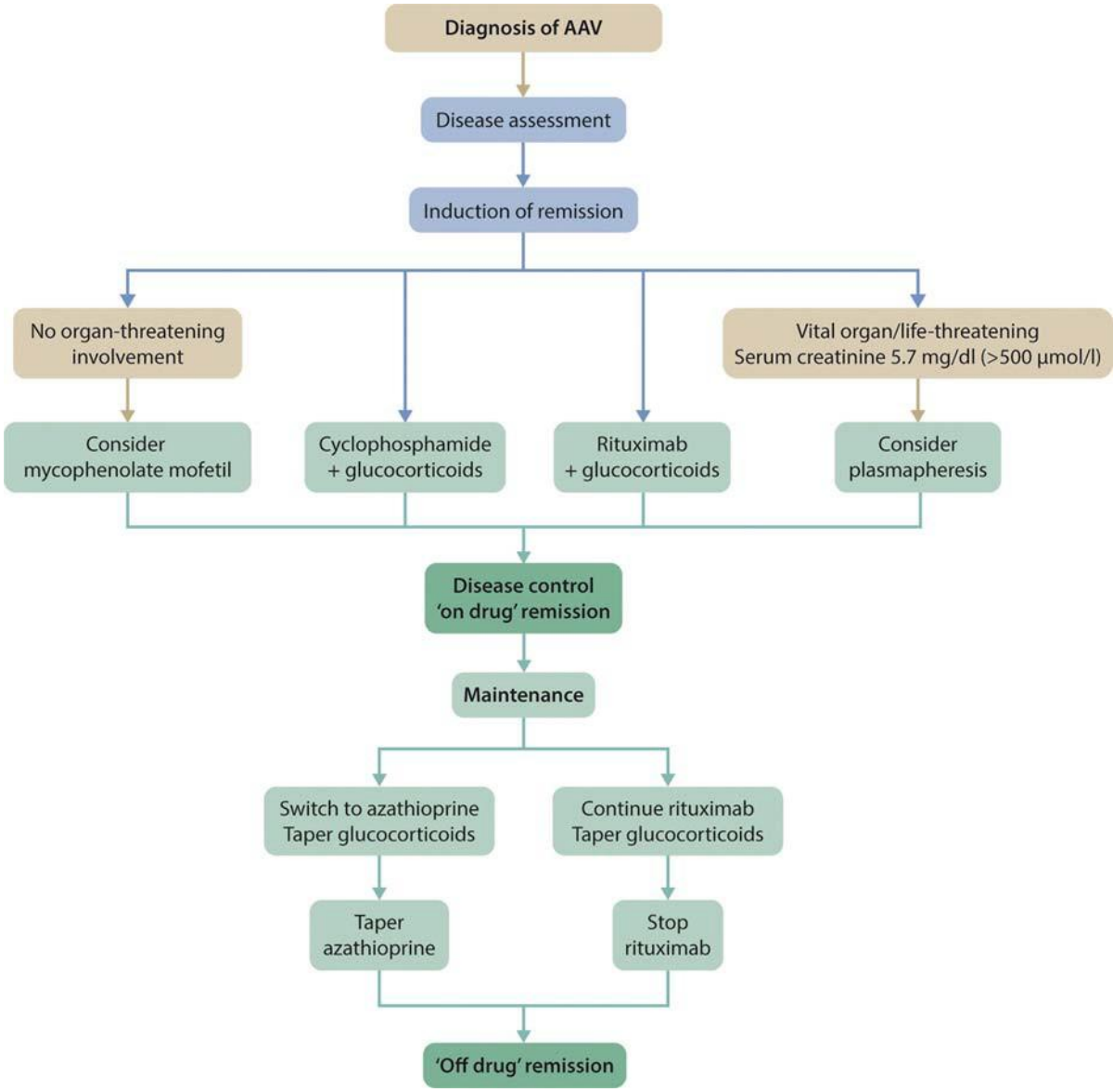

Figure 76 | Recommended treatment regimen for AAV. AAV, ANCA-associated vasculitis.

Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining GFR (SCr >4 mg/dl [>354 mmol/ l]), there are limited data to support rituximab and glucocor-
ticoids. Cyclophosphamide and glucocorticoids are preferred for induction therapy. The combination of rituximab and cyclophosphamide can also be considered in this setting.

No patients with a SCr >4 mg/dl (>354 mmol/l) were
included in the RAVE trial, and therefore in severe kidney disease, limited data for induction therapy with rituximab in combina- tion with glucocorticoids are available, and cyclophosphamide is

still the preferred agent for induction of remission. In severe kidney disease, combining 4 weekly infusions of rituximab and 2 i.v. cyclophosphamide pulses with glucocorticoids might be an alternative to i.v. cyclophosphamide for 3–6 months. In the RITUXVAS trial, this regimen resulted in a similar rate of remission and adverse events as cyclophosphamide.[566]

Practice Point 9.3.1.3: Considerations for choosing between rituximab and cyclophosphamide for induction therapy are given in Figure 77.

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 μmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered

Figure 77 | Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; SCr, serum creatinine.

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Figure 78 | Considerations for the route of administration of cyclophosphamide for AAV. AAV, ANCA-associated vasculitis.

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in Figure 78.

Practice Point 9.3.1.5: Discontinue immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease.

Practice Point 9.3.1.6: Recommendations for oral gluco- corticoid tapering are given in Figure 79.

Following cyclophosphamide induction, oral prednisolone should be reduced to a dose of 5 mg/d by 6 months.

Week	'Reduced-corticosteroid dose' in PEXIVAS trial		
	<50 kg	50–75 kg	>75 kg
1	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–16	5	5	7.5
17–18	5	5	7.5
19–20	5	5	5
21–22	5	5	5
23–52	5	5	5
>52	Investigators' local practice		

Figure 79 | Prednisolone tapering regimen for AAV. AAV, ANCA- associated vasculitis.

Following rituximab induction, prednisolone can be with- drawn by 6 months.

The dose of oral prednisolone is 1 mg/kg/d for the first week, and then a programmed reduction is followed (Figure 79). Intravenous methylprednisolone is widely used initially for patients with more severe presentations, at a dose of 1–3 g in total. This approach is not evidence-based and is likely to contribute to glucocorticoid toxicity.

Practice Point 9.3.1.7: Recommendations for immunosup- pressive dosing are given in Figure 80.

Practice Point 9.3.1.8: Consider plasma exchange for pa- tients with SCr >5.7 mg/dl (500 mmol/l) requiring dialysis or with rapidly increasing SCr, and in patients with diffuse alveolar hemorrhage who have hypoxemia.

The Methylprednisolone Versus Plasma Exchange for Renal Vasculitis (MEPEX) trial showed improved kidney outcomes in patients with severe kidney disease (SCr >5.7 mg/dl [>500 mmol/l]) who were treated with plasma exchange.[592] Also, a meta-analysis that looked at the addition of plasma exchange showed a reduction in the occurrence of ESKD at 3 and 12 months after diagnosis (Supplementary Table S37[566,569,592– 598]). The PEXIVAS trial failed to demonstrate that plasma ex- change delayed the time to ESKD or death for patients with AAV presenting with GFR <50 ml/min per 1.73 m^2 or alveolar hemorrhage over a median follow-up of 2.9 years.[579] *Post hoc* studies of the PEXIVAS dataset and meta-analysis may generate results relevant to future recommendations. However, no meta-analysis on the effect of plasma exchange in patients with severe kidney disease (SCr >5.7 mg/dl [>500 mmol/l]), including the PEXIVAS study, is yet available. For now, the routine use of plasma exchange is not recommended for

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m^2/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m^2/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m^2	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m^2			

Figure 80 | Immunosuppressive drug dosing for AAV. AAV, ANCA-associated vasculitis; GFR, glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil.

patients presenting with a GFR <50 ml/min per 1.73 m^2, but plasma exchange can be considered in those with more severe presentations (SCr >5.7 mg/dl [>500 mmol/l], especially if oliguric) or in those with alveolar hemorrhage and hypoxemia in whom early mortality is high.

Practice Point 9.3.1.9: Add plasma exchange for patients with an overlap syndrome of ANCA vasculitis and anti- GBM.

In a single-center study, 5% of patients who were ANCA- positive were also positive for anti-GBM antibodies, and 32% of patients who were anti-GBM-positive patients had detectable ANCA.[599] Thus, double-positivity for both ANCA and anti- GBM antibodies is common. These patients behave more like those with anti-GBM disease than like those with AAV, sup- porting the initiation of plasma exchange (Figure 81). However, unlike those with pure anti-GBM disease, these patients have a tendency to relapse and should receive maintenance therapy.

9.3.2 Maintenance therapy

Recommendation 9.3.2.1: We recommend mainte- nance therapy with either rituximab or azathioprine and low-dose glucocorticoids after induction of remission *(1C)*.

This recommendation places a higher value on prevention of relapses and a relatively lower value on adverse events related to immunosuppressive drugs.

Key information

Balance of benefits and harms. To date, most maintenance studies have been done after induction of remission with

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-GBM antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-GBM antibodies are undetectable

Figure 81 | Plasma exchange dosing and frequency for AAV. If a patient is at risk of bleeding, volume replacement should be with fresh, frozen plasma. ANCA, antineutrophil cytoplasmic antibody.

cyclophosphamide plus glucocorticoids. Maintenance regi- mens have evolved over time, and several immunosuppressive medications have been evaluated. Azathioprine, given after $3 months of cyclophosphamide induction, was found to be equally effective for relapse prevention with less leukopenia than extending cyclophosphamide for 12 months (Supplementary Table S38[569,600]). Compared to azathioprine, MMF maintenance was less effective in relapse prevention and did not have a superior infection profile (Supplementary Table S39[569,601]). In contrast, methotrexate and azathioprine were found to be equally effective in relapse prevention with similar toxicity and long-term outcomes (Supplementary Table S40[569,602]). Overall, azathioprine has been the stan- dard immunosuppressive used for maintenance of remission in AAV over the past several years.

The duration of azathioprine maintenance has been examined. Compared to tapering maintenance azathioprine after 12 months of treatment, tapering after 4 years of therapy decreased relapse rate and the incidence of kidney failure.[577,603] The benefits of longer- duration azathioprine maintenance therapy did not differ between PR3- or MPO-ANCA, or in patients who remained ANCA-positive or became ANCA- negative after 12 months. In these studies, there were no dif- ferences in all-cause mortality, infection, or serious adverse events between treatment arms, but the quality of the evidence was very low (Supplementary Table S41[569,577,603]).

After rituximab was found to be effective for induction of remission in AAV, it was tested as a maintenance medication. In new-onset disease, after cyclophosphamide induction, maintenance with rituximab decreased major, but not minor, relapses compared to azathioprine (MAINtenance of Remis- sion Using RITuximab in Systemic ANCA-associated Vascu- litis [MAINRITSAN]; Supplementary Table S42[569,604]). However, after rituximab induction for relapsing AAV, rit- uximab maintenance decreased major and minor disease re- lapses compared to azathioprine (Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis [RITAZAREM]).[605] No difference in infection rate was found between azathioprine and rituximab (Supplementary Table S43[569,606]).

As a maintenance drug, rituximab can be dosed on a fixed schedule or upon reappearance of CD19þ B cells and/or ANCA. Although both regimens prevented relapse equally well, dosing based on reappearance of B cells required fewer rituximab infusions. No differences in adverse events were reported (MAINRITSAN2; Supplementary Table S42[569,604]).

Addition of TMP-SMX (160/800 mg) compared with placebo in maintenance therapy may have little or no differ- ence on complete remission at 1 or 2 years (Supplementary Table S44[569,607,608]).

Quality of evidence. The overall quality of the evidence was rated as low due to the lower quality of the evidence for rit- uximab as maintenance therapy, which is based on fewer RCTs compared with that for azathioprine. All comparisons, apart

from azathioprine duration, included data from single studies with relatively low numbers of patients and limited follow-up, resulting in wide CIs and serious imprecision, in particular for the critical outcomes of all-cause mortality and kidney failure. The quality of the evidence for azathioprine as maintenance therapy was moderate for relapse in RCTs that compared azathioprine with cyclophosphamide (Supplementary Table S38[569,600]), methotrexate (Supplementary Table S40[569,602]), MMF (Supplementary Table S39[569,601]), and RCTs that compared extended with standard azathioprine therapy (Supplementary Table S41[569,577,603]).The quality of the evidence was downgraded because of imprecision, as there was only 1 study for each comparison. However, the comparison of MMF with azathioprine exhibited low quality of evidence for infection because of very wide CIs that indicated less certainty in the effect.

There is currently limited evidence available for mainte- nance therapy after induction therapy with rituximab and glucocorticoids. There was low-quality evidence from RCTs that compared rituximab with azathioprine for major relapse because of a lack of blinding of outcome assessors, and serious imprecision, as there are 2 RCTs that examined this comparison (Supplementary Table S42[569,604] and Supplementary Table S43[569,606]). The RCT, which compared tailored rituximab therapy based on the reappearance of $CD19^{b}$ B cells and ANCA-levels, exhibited low quality of evidence for major relapse and adverse events, including all- cause mortality, infection, and malignancy (Supplementary Table S42[569,604]). The quality of the evidence was down- graded from this RCT because of very serious imprecision, as there was only 1 study, and outcomes exhibited very wide CIs, indicating less certainty regarding the treatment effect.

Data are also limited regarding the continuation of glu- cocorticoids during maintenance. In most RCTs, glucocorti- coids were withdrawn within or shortly after the induction window. However, in the Randomised controlled trial of prolonged treatment in the remission phase of ANCA-asso- ciated vasculitis (REMAIN) trial, low-dose glucocorticoids were combined with azathioprine maintenance.[577] In a meta- analysis of observational studies and RCTs, a longer course of glucocorticoids in AAV was associated with fewer relapses.[609] *Values and preferences.* This Work Group places a relatively high value on the prevention of relapses of disease, which are associated with morbidity, and advises that maintenance therapy be given to all patients after induction of remission. However, extended immunosuppressive therapy should be associated with a minimum of adverse events, and relapse risk may influence maintenance initiation, choice of medication, and duration.

Several AAV relapse risk factors have been identified, including a prior history of relapse and having a PR3-ANCA rather than an MPO-ANCA.[562,610] In the RAVE study, pa- tients did not receive maintenance therapy after induction with rituximab, and a high relapse rate was seen in both the rituximab and cyclophosphamide–azathioprine groups, but glucocorticoids were withdrawn before 6 months.[570] Current

practice, and therefore expert opinion, varies on whether maintenance therapy can be avoided in patients with MPO- AAV after induction of remission with rituximab. It also varies on the use and duration of glucocorticoids in mainte- nance regimens. In the REMAIN trial, which studied patients with a history of renal vasculitis, no difference in relapse risk with ANCA serotype was seen. If maintenance therapy is not used, such patients should be considered at higher risk of relapse, and monitored accordingly.[577]

In the subgroup of patients with MPO-AAV presenting with kidney failure without extrarenal disease manifestations, the risk of relapses is low, so the risk of adverse infectious events from immunosuppression might outweigh the benefits of relapse prevention.[611] Therefore, in patients with MPO- ANCA who are treated with dialysis and have no extrarenal manifestations of disease, despite thorough review including chest computed tomography (CT) scanning, the risks of maintenance therapy could outweigh the benefit. Further, when a complete clinical remission is achieved in the sub- group of patients with MPO-ANCA disease and abnormal kidney function, these patients may not need maintenance immunosuppression, but instead could be closely monitored with regular ANCA serologies.

In summary, the best evidence for effective relapse pre- vention is available for rituximab maintenance or prolonged azathioprine in combination with low-dose glucocorticoids. However, there may be an advantage in favor of rituximab. In the MAINRITSAN study, health-related quality of life was compared between patients treated with rituximab and azathioprine. Mean improvements of Health Assessment Questionnaire (HAQ) scores from baseline to 24 months were significantly better for the rituximab group as compared to the azathioprine group.[612]

Therefore, this Work Group prefers rituximab for main- tenance therapy, particularly for patients with known re- lapsing disease, PR3-AAV, and azathioprine allergy, and after rituximab induction (RITAZAREM). However, some caution should be exercised, as there is a paucity of data on the long- term effects of rituximab maintenance treatment. Although significant falls in IgG were not seen after rituximab in the RCTs, longer-term observational data suggest an increasing risk of secondary immunodeficiency in this population.

Resource use and costs. Rituximab is relatively expensive and is not available worldwide; however, biosimilars will potentially generate global access to this drug. Additionally, prevention of relapses reduces the costs of hospitalization, and induction therapy with its frequent hospital visits. Rit- uximab also permits the withdrawal of glucocorticoids.

Rationale

This Work Group advises maintenance therapy be given to all patients with AAV after induction of remission with either cyclophosphamide or rituximab. The aim of this maintenance therapy is to prevent relapse of disease after induction of remission. Remission is defined as the absence of manifesta- tions of vasculitis. To score the absence of clinical features of

active disease, a validated scoring system such as the Bir- mingham Vasculitis Activity Score (BVAS) can be used.[613] During follow-up, a structured clinical assessment in com- bination with inflammatory markers and kidney function should be conducted in all patients.

Rituximab maintenance after cyclophosphamide induction has been shown to be superior to azathioprine for preventing relapses in 1 RCT. It probably decreases major relapses; no difference in adverse events was reported (MAINRITSAN).[604] Azathioprine maintenance up to 18 months after induction of remission with cyclophosphamide has been shown to be equally effective as continuing cyclophosphamide (Cyclo- phosphamide versus Azathioprine for Early Remission Phase of Vasculitis [CYCAZAREM]) for 1 year and then switching to azathioprine.[600] MMF has not been shown to be more effective than azathioprine.[601]

The evidence for the minimum duration of maintenance is weak; longer maintenance reduces relapse rate but could be associated with more adverse events. Azathioprine prolongation (REMAIN trial; Extended versus standard azathioprine main- tenance therapy in newly diagnosed proteinase 3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial [AZA-ANCA]) limits relapse rate after 4 versus 2 years.[577,603]

As the aim of maintenance therapy is the prevention of relapses, the risk of relapse should be considered for both the choice of the immunosuppressive agent and the duration of maintenance therapy.

Reported risk factors for relapse are PR3-ANCA versus MPO-ANCA, and CV or lung involvement.[562,610] Persistent ANCA-positivity after induction of remission has also been reported.[577,614] The RCT that tested extended azathioprine for 4 years versus azathioprine for 2 years in patients with PR3-AAV who remained ANCA-positive showed a nonsig- nificant difference (at 4 years, 48% standard vs. 24% extended relapses) but was underpowered.[603]

Comparison with other guidelines. Considering other guide- lines, the European League Against Rheumatism/ European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) prefers azathioprine and glucocorticoids over rituximab for remission maintenance.[578] According to the evidence reviewed by the ERT, rituximab was found to be superior to azathioprine, due to lower rates of major relapse. Therefore, this panel prefers rituximab over azathioprine for maintenance therapy in AAV. The EULAR/ERA-EDTA guideline advises maintenance therapy for at least 24 months following induction. This panel has not advised a fixed duration of maintenance but an interval of 18 months to 4 years following induction of remission, tailored according to an individual's risk of relapse and the drug used for maintenance. Additionally, in MPO-AAV after induction of remission with rituximab, maintenance therapy may sometimes be avoided if the patient can be monitored intensively. However, this point is based on expert opinion; little evidence is available, and no consensus was reached, even among experts.

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Lower serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

Figure 82 | Factors that increase relapse risk for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3.

Practice Point 9.3.2.1: Following cyclophosphamide induction, either azathioprine plus low-dose glucocorticoids or rituximab without glucocorticoids should be used to prevent relapse.

Practice Point 9.3.2.2: Following rituximab induction, maintenance immunosuppressive therapy should be given to most patients.

The preference of this Work Group, based upon observational reports and unpublished data from the RITAZAREM study, is for rituximab maintenance. The RITAZAREM study showed that also after rituximab induction for relapsing AAV, rituximab maintenance decreased major and minor disease relapses compared to azathioprine maintenance (RITAZAREM).[615] *However, azathioprine combined with glucocorticoids can be considered as an alternative.*

In the RAVE study, no maintenance was given following induction of remission in AAV. The relapse rate was lower in MPO-AAV compared to PR3-AAV. This finding led some experts to opine that patients with MPO-AAV in complete clinical remission after induction therapy with rituximab with a low relapse risk may not need maintenance therapy, but instead could be closely monitored with regular ANCA serologies and home urine checks. Consensus regarding no maintenance was, however, not reached within the KDIGO Work Group.

Practice Point 9.3.2.3: The optimal duration of azathioprine plus low-dose glucocorticoids is not known but should be between 18 months and 4 years after induction of remission.

Practice Point 9.3.2.4: The optimal duration of rituximab maintenance is not known, but studies to date have evaluated a duration of 18 months after remission. There is no role for the routine use of an oral glucocorticoid or oral immunosuppressive with rituximab maintenance.

Practice Point 9.3.2.5: When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur (Figure 82).

Practice Point 9.3.2.6: Consider methotrexate for maintenance therapy in patients, after induction with methotrexate or for those who are intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2.

Practice Point 9.3.2.7: Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Figure 83.

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Hepatitis B exposure (HBsAg positive) • Limited availability of rituximab

Figure 83 | Considerations for using rituximab or azathioprine for AAV maintenance therapy. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; HBsAg, hepatitis B surface antigen; IgG, immunoglobulin G; PR3, proteinase 3.

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at months 6, 12 and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at months 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until one yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yrs
	Extend azathioprine at complete remission until 4 yrs after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yrs after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yrs and then slowly reduced by 1 mg every 2 mo	

Figure 84 | Immunosuppressive dosing and duration of AAV maintenance therapy. *RITAZAREM was in relapsing AAV. MAINRITSAN, MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis; MMF, mycophenolate mofetil; RITAZAREM, Rituximab versus azathioprine as therapy for maintenance of remission for antineutrophil cytoplasm antibody-associated vasculitis (AAV).

Practice Point 9.3.2.8: Recommendations for dosing and duration of maintenance therapy are given in Figure 84.

9.3.3 Relapsing disease

Practice Point 9.3.3.1: Patients with relapsing disease (life- or organ-threatening) should be reinduced (Recommen- dation 9.3.1.1.), preferably with rituximab.

Relapses respond to immunosuppression with a similar response rate as the initial presentation, and severe relapses should be treated by reintroducing induction therapy. When deciding whether to use cyclophosphamide again, the cu- mulative dose of cyclophosphamide already given should be taken into account. Cumulative dosages above 36 g have been associated with the occurrence of malignancies.[616] In a post hoc analysis of the RAVE trial, higher remission rates were seen in relapsing patients treated with rituximab compared to cyclophosphamide, especially for patients with PR3-AAV.[570] Rituximab is therefore preferred for relapsing AAV. The RITAZAREM trial studied the effect of rituximab induction in 187 patients with relapsing GPA/microscopic polyangiitis—there was a high rate of remission, >90% by 4 months.[605]

In patients with non-severe relapses, immunosuppression should be increased while avoiding cyclophosphamide. Apart from MMF, which has been tested in combination with glu- cocorticoids in RCTs for induction therapy in relapsing pa- tients, there is no strong evidence to support other regimens.[574,575] However, if non-severe relapses are treated with MMF, there is an increased rate of future relapse, and glucocorticoid exposure will be increased accordingly; there- fore, in the current guideline, rituximab is preferred.

9.4 Special situations

9.4.1 Refractory disease

Practice Point 9.4.1.1: Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered.

The causes of refractory disease include drug intolerance, nonadherence, concomitant morbidities complicating treat- ment, a secondary drive for vasculitis such as malignancy, drugs or infection, and true treatment failure. Progression of kidney failure can reflect chronic damage and does not necessarily imply active disease; a kidney biopsy can be considered to assess ongoing kidney disease activity. Several small series suggest a role for rituximab in resistant ANCA vasculitis.

Practice Point 9.4.1.2: In the setting of diffuse alveolar bleeding with hypoxemia, plasma exchange should be considered in addition to glucocorticoids with either cyclophosphamide or rituximab.

In the absence of hypoxemia, diffuse alveolar hemorrhage has a benign prognosis and responds as extrapulmonary disease is controlled. Alveolar hemorrhage with hypoxemia has a high early mortality risk, and plasma exchange should be considered in addition to glucocorticoids with either cyclophosphamide or rituximab. Patients in the intensive care unit, such as those receiving assisted ventilation, have a particularly high risk of infection and death. Leukopenia should be avoided, with glucocorticoid use minimized. Plasma exchange and high-dose i.v. immunoglobulins can be considered in this setting.

9.4.2 Transplantation

Practice Point 9.4.2.1: Delay transplantation until patients are in complete clinical remission for ‡6 months. Persis- tence of ANCA should not delay transplantation.

AAV can recur after kidney transplantation. The frequency of disease recurrence in AAV has been assessed in several retrospective studies and is about 0.02–0.03 per patient-year.[617,618] This relapse rate was not influenced by remission duration or ANCA status before transplantation.[617]

Research recommendations

- *RCTs to incorporate patient-reported outcomes, to assess long-term outcomes, to define the use of rituximab in se- vere AAV, and to assess therapies in ethnically diverse populations*
- *Biomarker studies to identify early markers of disease relapse, markers to guide the choice of therapy, including plasma exchange, markers to predict optimal dosing and dosing interval for rituximab, and surrogate markers of response*

Chapter 10: Lupus nephritis

The reported lifetime incidence of lupus nephritis (LN) in patients with SLE is 20%–60%, depending on the de- mographics of the population studied.[619–622] Kidney involvement in SLE has been associated with higher mortality, especially for patients progressing to kidney failure.[623–625] The ultimate goal of treating LN is to preserve kidney function and reduce the morbidity and mortality associated with CKD and kidney failure, while minimizing medication-associated toxicities.

This chapter makes management recommendations for adults who have SLE with kidney involvement. The focus is on immune complex–mediated GN in the setting of SLE, commonly referred to as LN, but other types of kidney injury in patients with SLE are also discussed. Information for pe- diatric populations is limited, but an approach to the man- agement of children with LN is outlined in Practice Point 10.3.3.

10.1 Diagnosis

Practice Point 10.1.1: Approach to the diagnosis of kidney involvement in systemic lupus erythematosus (SLE) (Figure 85)

Patients with SLE should be actively and regularly moni- tored, as the clinical presentation of kidney involvement can remain silent or asymptomatic for a significant period of time. As the incidence of LN varies by race/ethnicity and age, a high index of suspicion should be maintained for patients of Asian, African/Caribbean, and Hispanic descent.[619–622] There is a higher incidence of LN and more-severe disease in childhood-onset SLE compared to adult-onset SLE.[626] Although a proteinuria level of 500 mg/d is suggested as a threshold for further investigations, taking into consideration physiological causes of low-level proteinuria and to avoid unnecessary kidney biopsies, it is important to note that the severity of proteinuria varies considerably in severe active nephritis and can appear relatively "insignificant" at times. A holistic assessment including clinical, urinary, and laboratory parameters, and also repeated investigations to note the progression of abnormal findings over time, are important in informing clinical management decisions. Because clinical findings do not always correlate with the extent or severity of kidney involvement,[627,628] a kidney biopsy is useful to confirm the diagnosis and for the assessment of activity and chronicity features that inform treatment decisions and prognosis.[627–637] Kidney biopsies should be read by an experienced kidney pathologist and classified according to the ISN/RPS scheme.[638–640] Electron microscopy, where available, is helpful in ascertaining ultrastructural details of histopa- thology such as the extent and severity of podocyte injury and

the loci of immune deposits. Clinicians should pay attention to the detailed description of both active and chronic histo- pathologic features affecting different elements of the kidney parenchyma, especially regarding potentially reversible active lesions versus chronic damage not reversible by immuno- suppressive medications (Figure 86).

10.2 Treatment

10.2.1 General management of patients with lupus nephritis

This recommendation places a relatively higher value on the various benefits associated with hydroxychloroquine use reported in observational studies (including lower rates of disease flares, progressive kidney damage, and vascular complications) and on the generally favorable safety profile of hydroxychloroquine treatment. It places a relatively lower value on the lack of large- scale prospective RCT data.

Key information

Balance of benefits and harms. The reported benefits of antimalarial use in SLE include lower flare (including kidney) rates,[641,642] higher response rates to therapy,[641–644] lower incidence of CV and thrombotic events in patients with antiphospholipid antibodies,[645–648] less organ damage,[649–654] improved lipid profile,[655,656] and better preservation of bone mass.[657]

Hydroxychloroquine use in pregnancy has been associated with a decrease in lupus activity and a satisfactory safety profile in both the mother and the fetus.[658–660] Significant side effects are uncommon but include skin rash, increase in skin pigmentation, muscle weakness, and visual change or loss of vision. Hydroxychloroquine may accumulate in lyso- somes and cause a form of phospholipidosis with accumu- lation of multilamellar zebra bodies in podocytes that can mimic the appearance of Fabry disease.[661,662]

Quality of evidence. Moderate-quality data support the benefit of hydroxychloroquine use in patients with SLE, but in LN, the available evidence is predominantly from observational studies and *post hoc* analyses. In a 24-week RCT that included 47 patients, the Canadian Hydroxychloroquine Study Group reported a higher incidence of SLE flares in patients who stopped hydroxychloroquine compared to those who continued treatment, with a hazard ratio (HR) of 2.50 (95%

Recommendation 10.2.1.1: We recommend that patients with SLE, including those with lupus nephritis (LN), be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated *(1C)*.

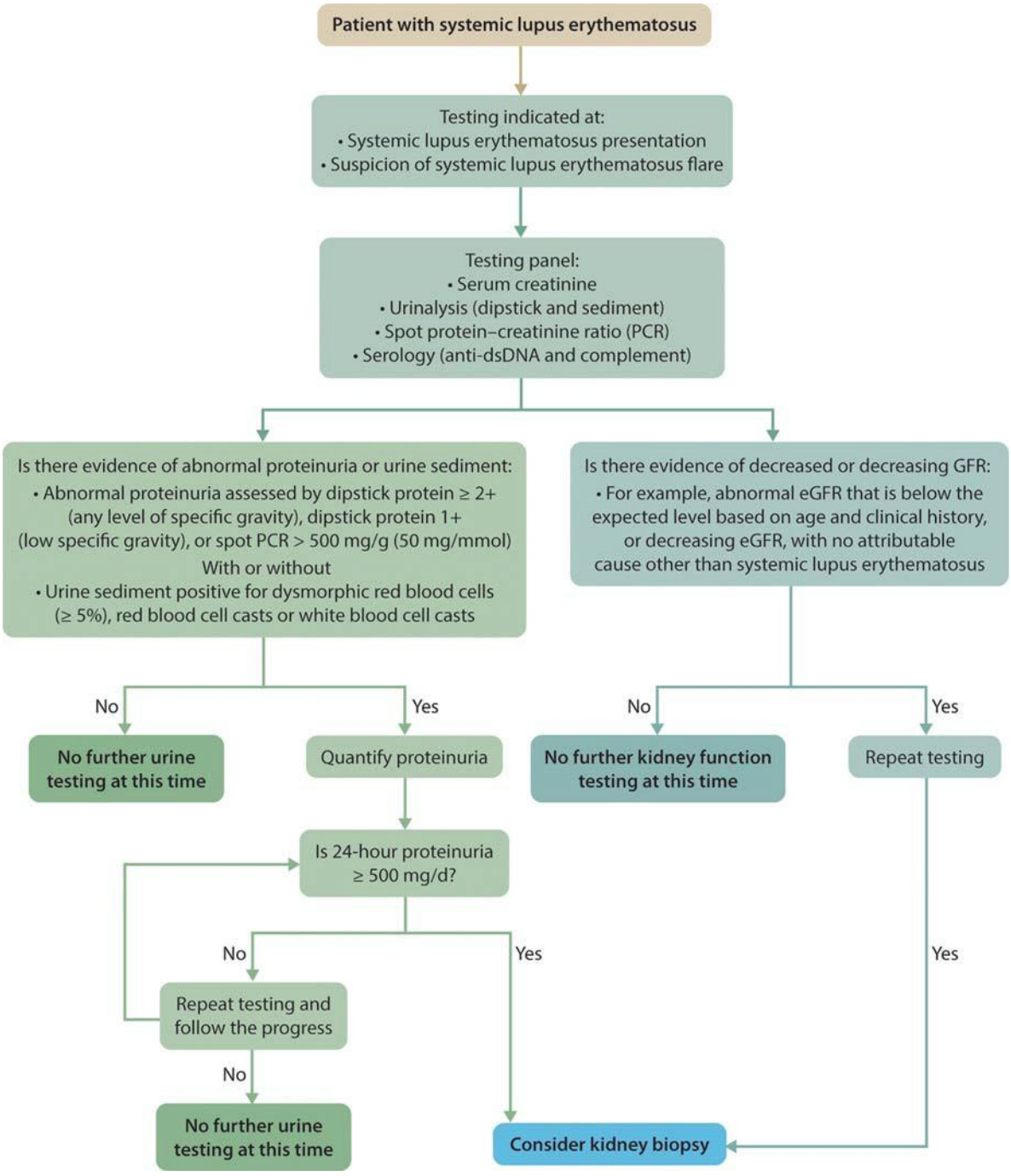

Figure 85 | Diagnosis of kidney involvement in SLE. eGFR, estimated glomerular filtration rate.

CI: 1.08–5.58). The frequency of severe LN flares was also increased but did not reach statistical significance.[663] A systematic review that included 95 reports published between 1982 and 2007, 5 of which were RCTs, concluded that hydroxychloroquine use could prevent SLE flares and increase long-term patient survival, while toxicity was infrequent, mild, and usually reversible; and hydroxychloroquine use in pregnancy was associated with a decrease in lupus activity without harm to the fetus.[664] Low-quality observational studies have indicated that hydroxychloroquine may have

kidney benefits, protective effects against infection, and may increase complete remission rate in patients with LN. The quality of the evidence is low because of study limitations, indirectness, or imprecision, but it has been upgraded because of the large reported effect sizes (Supplementary Table S45[643,644,651–666]). Two observational studies reported an association between hydroxychloroquine treatment and reduced mortality in patients with LN, but the quality of evidence for this outcome is very low (Supplementary Table S45[654,666]).

Components of the activity index	Score	Calculating the activity score Extent of lesion	Points
• Endocapillary hypercellularity	0–3	Not present	0
• Neutrophils and/or karyorrhexis	0–3	Present in <25%	1
• Fibrinoid necrosis	(0–3) × 2	Present in 25%–50%	2
• Hyaline deposits (wire loop and/or hyaline thrombi)	0–3	Present in >50%	3
• Cellular/fibrocellular crescents	(0–3) × 2		
• Interstitial inflammation (interstitial leukocytes)	0–3		
	Total: 0–24		
Items included into the NIH chronicity score	**Score**	**Calculating the chronicity score** **Extent of lesion**	**Points**
• Total glomerulosclerosis (global + segmental)	0–3	Present in <10%	0
• Fibrous crescents	0–3	Present in 10%–25%	1
• Interstitial fibrosis	0–3	Present in 25%–50%	2
• Tubular atrophy	0–3	Present in >50%	3
	Total: 0–12		
Other histologic findings not included in the activity or chronicity score			
• Foot process effacement (lupus podocytopathy) • Collapsing lupus glomerulopathy • Vascular lesions (arteriosclerosis, non-inflammatory vascular immune complex deposits, thrombotic microangiopathy, non-inflammatory necrotizing vasculitis, true renal vasculitis)			

Figure 86 | Activity and chronicity items included in LN kidney biopsy report. NIH, National Institutes of Health, USA.

Values and preferences. The potential benefits of preventing organ damage and vascular complications were judged as being important to patients. The Work Group also judged that the relatively low risk of adverse events associated with hydroxy- chloroquine would also be important to patients. Therefore, the Work Group felt that nearly all well-informed patients in the target population would choose to receive hydroxychloro- quine treatment in comparison to no treatment.

Resource use and costs. Hydroxychloroquine can be an expensive drug in some countries. Therefore, in low-resource settings, it may be acceptable to substitute structurally similar drugs such as chloroquine that have a similar mechanism of action but are less expensive.

Considerations for implementation. Because of the risk of hemolysis in patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency, measurement of G6PD levels is preferred in men, especially those of African, Asian, or Middle Eastern origin, before starting hydroxychloroquine. However, this risk appeared low, according to the findings of a recent report.[667] All patients should have a baseline retinal examination and then annual eye testing, especially after 5 years of use. Clinicians should be aware that antimalarials may be cardiotoxic (e.g., congestive heart failure, conduction abnormalities) after long-duration therapy or high cumulative exposure. The dosing of hydroxychloroquine is 6.5 mg/kg ideal weight/ d or 400 mg/d, and during the maintenance phase, this should be lowered to 4 to 5 mg/kg/d. In patients with

eGFR <30 ml/min per 1.73 m^2, the dose of hydroxychloro- quine should be reduced by $25%.

Rationale

Data from multiple observational cohort studies show various benefits of hydroxychloroquine treatment in SLE, notably a reduced incidence of flare and organ damage accrual, and a relatively low rate of drug-related adverse effects, including ocular toxicity. Despite the relatively low-quality evidence, the overall balance between benefits and potential risks provides the basis for recommending its use as part of general man- agement in patients with SLE.

Practice Point 10.2.1.1: Adjunctive therapies to manage LN and attenuate complications of the disease or its treatments should be considered for all patients, as outlined in Figure 87.

Although many of the above recommendations also apply to patients with proteinuric kidney diseases treated with immunosuppression in general (Chapter 1), some risks are especially relevant to patients with SLE and LN. Patients with SLE show increased mortality rates when compared to age- and sex-matched controls in the general population.[668,669] Infections, CV complications, and CKD, especially kidney failure, are major causes of death.[623–625,670] Early deaths are related to infections or lupus activity, while CV and malignant complications and deaths related to kidney failure account for late mortalities.[671]

Risk	Risk attenuation
Cardiovascular risk	• Lifestyle modifications – smoking cessation, body weight optimization, exercise • Dyslipidemia management • Low-dose aspirin during pregnancy
Proteinuria (Chapter 1)	• Avoidance of high-sodium diet • Blood pressure control • RAS blockade
Infection risk	• Assess medical history of herpes zoster and tuberculosis • Screening for HBV, HCV, HIV, and HBV vaccination • *Pneumocystis jirovecii* prophylaxis (issue of potential adverse drug reaction discussed below) • Influenza and pneumococcal vaccination • Individualized consideration for recombinant zoster vaccine • Individualized consideration for other infectious organisms as dictated by public health concerns at the time of treatment
Bone injury	• Bone mineral density and fracture risk assessment • Calcium and vitamin D supplementation • Bisphosphonates when appropriate
Ultraviolet light exposure	• Broad-spectrum sunscreen • Limit ultraviolet light exposure
Premature ovarian failure	• Gonadotropin-releasing hormone agonists (i.e., leuprolide) • Sperm/oocyte cryopreservation
Unplanned pregnancy	• Individual evaluation and counselling for contraception type (preference, thrombosis risk, age)
Cancer	• Evaluate individual risk factors for malignancies • Age-specific malignancy screening • Limit lifetime cyclophosphamide exposure to <36 g

Figure 87 | Measures to minimize the risk of complications related to LN or its treatment. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LN, lupus nephritis; RAS, renin–angiotensin system.

Cardiovascular complications in patients with LN. Patients with SLE have both traditional (dyslipidemia, smoking, obesity, etc.) and non-traditional (proteinuria, inflammation, etc.) CV risk factors. A patient often has multiple risk factors, which can be secondary to disease-related organ damage (especially CKD, hypertension, proteinuria) or treatment (such as glucocorticoids and CNIs). Regular evaluation of various risk factors and timely treatment are essential to prevent premature CV complications.[672]

Infections in patients with LN. Infection is a leading cause of death in patients with LN, and infection-related deaths are more common during the initial phase of management following exposure to intensive immunosuppressive therapy.[665,668,673] There are data to suggest a higher incidence of adverse outcomes related to infections in Asia, which may be related to delayed presentation and the access to care.[673] Avoidance of overimmunosuppression is an important measure to reduce the risk of infections and adverse outcomes. Prophylaxis for *Pneumocystis* is standard practice in organ transplant recipients, but its role in patients on high-dose glucocorticoid therapy without HIV infection remains controversial, and there are few data from patients with SLE.[618,619] Antibiotic-related adverse drug

reactions are not infrequent in patients with lupus, and in an early survey, 31% reported allergy to sulfonamide, with one-fifth of these patients also reporting worsening of SLE with the drug intolerance.[674] In a retrospective study from Thailand that included 132 patients with various connective tissue diseases, TMP-SMX was effective in preventing pneumocystis pneumonia, and adverse drug reaction occurred in only 9.4% of patients with SLE given prophylaxis.[675] However, a recent retrospective study from Japan reported a drug allergy rate of 41.9% in patients with lupus given TMP-SMX prophylaxis with conventional dosing, but only 10.7% in those with gradual introduction of the drug over a 9-day period.[676] Pneumocystis pneumonia is a severe complication in patient who are immunosuppressed and can result in fatality. Prophylaxis should be actively considered, taking into consideration a patient's allergic diathesis. The rate of *Herpes zoster* is 2–10 times higher in patients with SLE than in healthy controls, but the role of antiviral prophylaxis is uncertain. Available zoster vaccine preparations include the live-attenuated vaccine Zostavax and the adjuvanted recombinant vaccine Shingrix. In general, live vaccines should be avoided in immunosuppressed subjects. There are no data on the

efficacy of the recombinant zoster vaccine in patients with lupus, and there is concern about whether the adjuvant might affect disease activity. There is also concern that the polio vaccination has been associated with lupus flares, whereas the data on influenza vaccination are conflicting. Response to vaccination is reduced following exposure to high-dose immunosuppression.[677]

Contraception and pregnancy. Pregnancy in patients with LN is associated with increased maternal complications and inferior fetal outcomes compared with the occurrence in healthy individuals, and the risks are higher when LN is active. Some of the frequently used medications in patients with lupus are contraindicated during pregnancy, such as MMF, cyclophosphamide, and warfarin. Counseling with regard to contraception and pregnancy should be done early in patients of childbearing age. Patients should be seen by a gynecologist to discuss the choice of methods for contraception. For patients who prefer oral hormonal contraception, estrogen–progestin contraceptives with ethinyl estradiol dose at not higher than 30 mg may be used in patients who are negative for antiphospholipid antibodies and with stable low disease activity, whereas progestin-only contraceptives are preferable in patients with a moderate or high level of disease activity. Estrogen-containing contraceptives should be avoided in patients with antiphospholipid antibodies or a history of thrombosis, in view of the risk of thromboembolism.[678] Data from women exposed to chemotherapy showed efficacy of gonadotrophin-releasing hormone (GnRH) analogues in reducing the rate of premature ovarian failure, whereas the putative gonadal protective effect of oral contraceptive pills appeared variable.[679] Fertility protection with GnRH agonists, or sperm and oocyte cryopreservation, should be considered in patients treated with cyclophosphamide, especially in patients with high cumulative exposure.

Bone health. Glucocorticoid therapy, especially when high doses are used for long durations, increases bone loss.[680,681] In children, glucocorticoid cumulative dose affects peak bone mass and growth.[682] Individual evaluation of fracture risk can be estimated using patient demographics and clinical history, glucocorticoid dose, and the Fracture Risk Assessment Tool (FRAX) score.[683] Calcium (optimal intake 1000–1200 mg/d) and vitamin D supplementation are recommended for patients with LN, as well as consideration for oral bisphosphonates according to individual risk assessment.[684,685]

Malignancies in patients with LN. Patients with SLE have increased risk of malignant tumors, including non-Hodgkin's lymphoma, lung, liver, vulvar/vaginal, thyroid, nonmelanoma skin cancer, and the risk (especially with bladder cancer) is increased in patients with a history of exposure to cyclophos- phamide.[686,687] In general, the surveillance for malignancies in patients with LN follows the cancer-screening policies for the general population in the local community, and specific ma- lignancy screening guidelines for patients with SLE are either lacking or largely opinion-based.[688] Although there is pre- liminary evidence showing efficacy and safety of human papillomavirus vaccines in patients with SLE, there is also controversy about whether the vaccine may cause predisposi- tion to the development of SLE or lupus-like disease.[689,690]

10.2.2 Class I or Class II lupus nephritis

Practice Point 10.2.2.1: Approach to immunosuppressive treatment for patients with Class I or Class II LN (Figure 88)

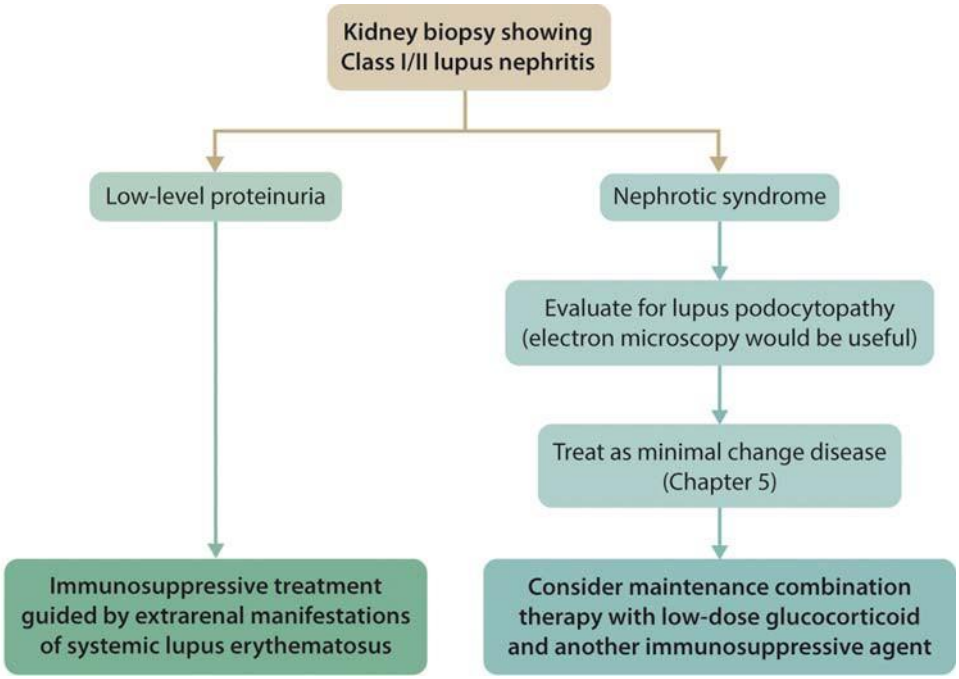

Figure 88 | Immunosuppressive treatment for patients with Class I or Class II LN. LN, lupus nephritis.

Patients with Class I or Class II LN generally have normal kidney function, or at most, low-grade proteinuria that is well below the nephrotic-range, and sometimes microscopic he- maturia. For these patients, no specific immunosuppressive therapy beyond what is being given for nonrenal lupus is needed.[691]

Patients with Class I or II histology but with nephrotic- range proteinuria or NS are considered to have lupus podo- cytopathy. This diagnosis may be confirmed by demonstrating diffuse podocyte effacement on electron microscopy. Clinically and histologically, these patients are similar to those with MCD or FSGS, often showing a good response to glucocorticoid treatment.[692–694] Although there have been no RCTs, obser- vational data showed that over 90% of patients given gluco- corticoid monotherapy achieved remission within a median time of 4 weeks.[692,695–699] Data on relapse are even more limited, but there appears to be a significant risk of relapse after glucocorticoids are tapered.[700] Although optimal duration is not known, maintenance with low-dose glucocorticoid plus an additional agent such as an MPAA, azathioprine, or a CNI is suggested, especially in patients with a history of relapse.

10.2.3 Class III or Class IV lupus nephritis

10.2.3.1 Initial therapy of active Class III/IV lupus nephritis

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus either low-dose intravenous cyclophosphamide or MPAA (1B)

This recommendation places a high value on the data demon- strating that glucocorticoids, in combination with MPAA or standard-dose cyclophosphamide, will improve kidney outcomes in active severe LN. It also places a high value on the data demonstrating comparable efficacy between MMF and cyclo- phosphamide in active severe LN. The Work Group recognizes that 2 new therapies have been approved for LN by the US FDA recently. The data leading to the approvals have recently been published.[701,702] This evidence has not yet been systematically reviewed in the context of current therapies, and it has not been graded for quality. Nevertheless, these therapies are promising and are discussed in subsequent practice points. All potential approaches to initial treatment of proliferative LN are shown in Figure 89.

Key information

Balance of benefits and harms. The short-term prognosis of patients with proliferative LN improved dramatically when treatment with high-dose glucocorticoids was started in the 1960s.[703] However, the long-term kidney prognosis continued to be poor as many patients progressed to kidney failure despite treatment. In landmark studies during the 1980s, the addition of cyclophosphamide to glucocorticoids was shown to be superior to treatment with glucocorticoids

alone in preserving long-term kidney survival in active severe LN.[630,704–707]

For decades, the accepted standard of care for prolifera- tive LN was high-dose glucocorticoids plus cyclophospha- mide, but the risk of severe side effects prompted investigation of alternative induction regimens. This led to several trials comparing other agents to cyclophosphamide for initial treatment of LN, including azathioprine and MPAA.

MPAAs received considerable attention and were shown to have efficacy similar to that of cyclophosphamide for initial treatment of LN.[708,709] Although some studies sug- gested that MPAAs were associated with fewer adverse ef- fects than cyclophosphamide, several investigations demonstrated a similar prevalence but different profile of adverse events.

However, all studies used concomitant high- dose gluco- corticoids, and these likely accounted for many treatment- associated adverse events.[629,631,708–710] The dose of MPAA also differed between the studies. Nonetheless, based on relatively favorable "real-world" clinical experience, MPAA- based regimens have mostly replaced cyclophosphamide- based regimens for the initial treatment of proliferative LN. The dose of MMF is typically 2–3 g/d. Figure 91 shows the details of cyclophosphamide-dosing regimens.

Based on the hypothesis that the risk–benefit ratio of initial LN treatment could be improved further, a reduced-dose cyclophosphamide regimen was compared to standard high- dose cyclophosphamide in a study of 90 patients of Euro- pean descent with active nephritis. The results showed no statistically significant difference in efficacy both short- and long- term and an improved side-effect profile.[634,711] This regimen was also tested in a short-term trial that included 100 Indian patients and showed similar remission rates compared to MPAA.[709] In view of the scarcity of data on reduced-dose cyclophosphamide in patients of African or Hispanic descent, there is concern as to whether this regimen is effective in these patient groups.

It is important to note that of all these treatment options, only initial treatment with cyclophosphamide has long-term data from controlled trials showing its higher efficacy in preserving kidney function compared to treatment with glucocorticoids alone.[705,706] All the other regimens have shown comparable or superior short-term efficacy, but trials have not been carried out to compare long-term efficacy on kidney survival. There is increasing evidence, based on data from observational studies,[632,711–715] that effective induction of renal response after initial therapy, especially a complete renal response, is associated with more-favorable long-term kidney outcomes.

In summary, Class III and Class IV LN are often very severe, and without treatment, they are associated with significant patient morbidity and mortality and a very high risk of kidney loss. Four distinct approaches have evolved to achieve renal response and prevent loss of kidney function. The attempt to reduce medication side effects

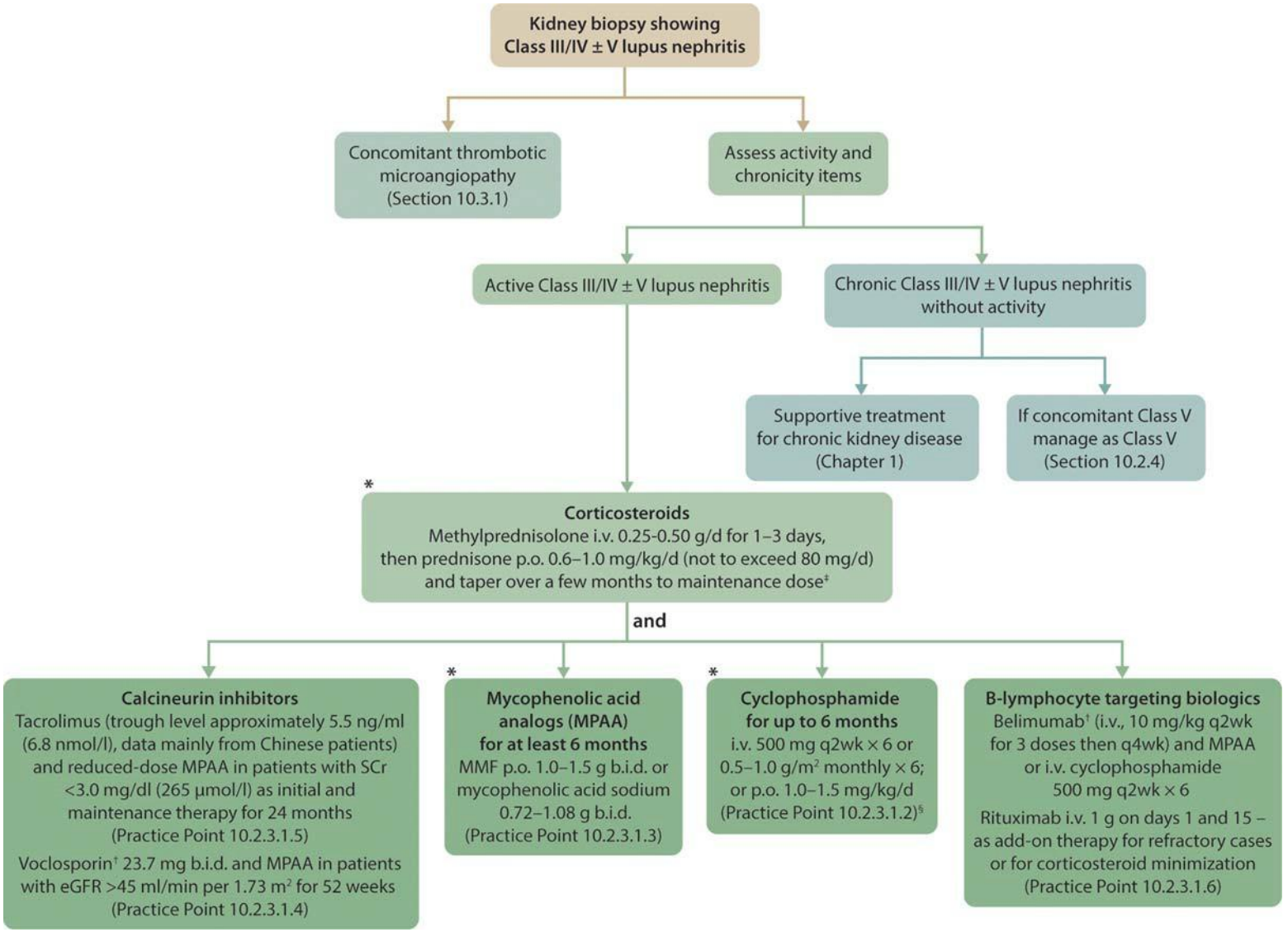

Figure 89 | Recommended approach for initial therapy of active Class III/IV LN. *Treatments in Recommendation 10.2.3.1.1. ‡Refer to Figure 90 for examples of corticosteroid treatment regimen. §Refer to Figure 91 for comments on cyclophosphamide regimens. †Denotes treatments approved by the U.S. Food and Drug Administration. b.i.d., twice daily; eGFR, estimated glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil; MPAA, mycophenolate acid analogs; p.o., oral; q2wk, every 2 weeks; q4wk, every 4 weeks; s.c., subcutaneous; SCr, serum creatinine.

has been modestly successful, shifting side-effect profiles away from the leukopenia, infertility, and future cancers associated with high cyclophosphamide exposure. Despite the potential of important treatment-associated toxicities, the benefits of treating proliferative LN outweigh the harms.

Quality of evidence. In the 6 RCTs that compared i.v. cyclophosphamide with glucocorticoids, there was moderate quality of evidence for a kidney benefit and decrease in kidney relapse. The quality of the evidence from these RCTs was downgraded to moderate because of study limitations (unclear blinding of participants and personnel, unclear allocation concealment; Supplementary Table S46[630,704,705,707,716–718]).

High-dose versus low-dose cyclophosphamide has been compared in a few RCTs (Supplementary Table S47[634,718–721]). The results from these trials indicate that low-dose cyclophosphamide is associated with fewer adverse events (such as infection, malignancy, leukopenia, and bone toxicity[718]; although in some studies, the efficacy also appeared lower than that of the high-dose regimen), with moderate quality of the evidence because of serious impre- cision (only a few events, resulting in wide CIs indicating appreciable benefit and harm).

From the RCTs, there is moderate quality in the evidence that MMF exhibits a similar efficacy, and a different side- effect profile compared with i.v. cyclophosphamide. The quality of the evidence was downgraded to moderate because of unclear reporting of allocation concealment in trials (Supplementary Table S48[629,708–710,718,722–725]).

Values and preferences. Without treatment, the prognosis for kidney survival in patients with proliferative LN is poor, so the Work Group judged that most well-informed patients with Class III and IV LN would choose to be treated with one of the immunosuppression regimens outlined previously. Given the risks of infertility associated with cyclophosphamide and the spectra of future malignancy, most patients of childbearing age who anticipate conceiving in the future, and most patients, in general, will likely opt for initial treatment with MPAA over standard-dose cyclophosphamide. Low-dose i.v. cyclophosphamide has less risk than standard-dose and is a reasonable alternative to MPAA, but because the data favoring low-dose cyclophosphamide have largely come from White patients with mild to moderately severe LN, this alternative may not be appropriate for the treatment of severe LN in patients of African or Hispanic ancestry.

Resource use and costs. Management of active LN with immunosuppression is resource and labor intensive because the medications and the surveillance for potential complica- tions are costly. Intravenous administration requires an infusion center with supervision, and patients must be monitored frequently for treatment- or disease-related complications, and require frequent clinical laboratory testing. However, it is likely that these costs are less over time than those associated with managing CKD and kidney failure resulting from no treatment, although a direct

economic analysis has not been done. Furthermore, there have been no comparisons of quality of life between patients with CKD, patients with kidney failure receiving kidney replacement therapy, and patients receiving immunosuppression, especially with high-dose or prolonged administration of glucocorticoids. MPAA regimens were associated with higher medication costs but lower facility costs and a superior quality of life compared to i.v. cyclophosphamide regimens.[726–728]

Considerations for implementation. In view of the significant treatment costs,[728–730] the choice of therapy is often region- specific and depends on drug availability, reimbursement policies, and the financial means of individual patients. Other considerations when choosing initial therapy for LN include likelihood of adherence, age, prior immunosuppressive exposure, disease tempo and severity, and race and ethnicity.

Physicians may choose an i.v. regimen if suboptimal adherence is anticipated. Age is an important factor with respect to preservation of fertility, as susceptibility to gonadal failure after cyclophosphamide use increases with age. Sus- ceptibility to future malignancies increases with higher life- time cyclophosphamide exposure, so a detailed knowledge of prior therapies is important. Despite these considerations for cyclophosphamide, many physicians would initially choose standard-dose cyclophosphamide for patients in whom kid- ney function is rapidly deteriorating and whose biopsy shows severe activity (e.g., capillary necrosis, an abundance of crescents). It should be noted that there are sparse data on this group of patients who present with aggressive disease, as their clinical characteristics precluded them from inclusion in clinical trials. Physicians caring for patients of mixed ethnic background or Hispanic ethnicity may choose MPAA over cyclophosphamide as there are some *post hoc* analysis data suggesting it has higher efficacy,[731,732] whereas physicians caring for Chinese patients may want to choose MPAA and glucocorticoids, or triple immunosuppression with gluco- corticoids plus low-dose MPAA plus low-dose CNI, as opposed to a cyclophosphamide-based regimen.[636,733]

Rationale

Class III or IV LN is an aggressive disease that requires prompt and effective therapy to abate ongoing injury and destruction of normal nephrons. Immunosuppressive treat- ment targets the active inflammatory lesions in kidney his- topathology, in contrast to the chronic lesions, the extent of which portend CKD and long-term kidney prognosis.

The choice of initial treatment for Class III or IV LN entails personalized consideration of the balance between benefit and risk and is informed by data on short-term response and long- term efficacy and safety, potential adverse effects including infections and cumulative toxicities, quality of life, and factors relevant to patient experience and adherence.

Patient and kidney survival rates in Class III or Class IV LN have improved since the 1970s, first with the use of glu- cocorticoids, and subsequently following the adoption of

combined immunosuppressive regimens with cyclophospha- mide or MPAA as standard therapy.

Glucocorticoids remain an integral component in initial therapy for Class III or IV LN based on their anti- inflammatory and immunosuppressive actions. The addition of cyclophosphamide or MPAA was associated with lower relapse rates and improved long-term kidney survival compared with glucocorticoid treatment alone. Combined immunosuppressive regimens also facilitate glucocorticoid minimization, thereby reducing their adverse effects (Figure 90).

Practice Point 10.2.3.1.1: A regimen of reduced-dose glu- cocorticoids following a short course of methylpredniso- lone pulses may be considered during the initial treatment of active LN when both the kidney and extrarenal disease manifestations show satisfactory improvement (Figure 90).

Glucocorticoids are used in all current treatment regimens of LN. These drugs have both immunosuppressive and anti-inflammatory effects and provide immediate treatment for the often extensive intrarenal inflammation that is seen in patients with Class III and Class IV LN. This regimen is necessary because there is a lag before the immunosuppressive effects of cyclophosphamide, MPAA, CNIs, or B cell–directed therapies are seen. The dose, tapering regimen, and duration of glucocorticoid schemes vary considerably among clinicians and are largely opinion-based. Examples are given in Figure 90.

The role of i.v. methylprednisolone pulses at the start of treatment is not well-studied but is commonly given as up to 3 daily doses of 500 mg each (range 250–1000 mg/d), espe- cially in patients who present with a clinical syndrome of RPGN—acute and severe deterioration of kidney function often accompanied by a high proportion of crescents or vascular lesions in the kidney biopsy, or when there are severe

extrarenal manifestations, such as central nervous system or lung involvement.

To minimize the side effects due to high cumulative exposure to glucocorticoids, there is increasing use of initial
i.v. glucocorticoid pulses followed by a lower starting dose and/or more-rapid taper of oral glucocorticoid in recent clinical trials.[734] Results from a retrospective propensity analysis of data from 63 patients enrolled in the Aspreva Lupus Management Study (ALMS) and the phase 2 Aurinia Urinary Protein Reduction Active-Lupus with Voclosporin (AURA-LV) trial suggested that doses of glucocorticoids and MPAA lower than those adopted in ALMS may result in better long-term safety, including a reduction in lympho- proliferative disorders, skin cancers, and glucocorticoid- related side effects.[735] In children, the avoidance of excessive glucocorticoid exposure also has implications for growth, psychosocial issues, and drug adherence.[736] With accumulating data on the efficacy and glucocorticoid-sparing role of immunosuppressive medications such as cyclophosphamide and MMF, there is a move toward reducing exposure to glu- cocorticoids (Supplementary Table S49[718,737]). Examples of dosing and tapering regimens in initial treatment of LN, based on published literature and recent clinical trials that investigate the efficacy and safety of new therapeutic agents, are shown in Figure 90. They serve to illustrate variations in exposure to glucocorticoids, but it is premature to recommend one over the other, as the regimens have not been formally compared to one another in prospective clinical trials.

Practice Point 10.2.3.1.2: Intravenous cyclophosphamide should be used as the initial therapy for active Class III and Class IV LN in patients who may have difficulty adhering to an oral regimen.

Cyclophosphamide may be given orally or intravenously, and in a standard-dose (also known as the modified National

	Standard-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

Figure 90 | Example of glucocorticoid regimens for LN. LN, lupus nephritis.

	Intravenous cyclophosphamide – modified (NIH regimen)	Intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	i.v. 0.5–1 g/m^2 monthly for 6 months	i.v. 500 mg every 2 weeks for 3 months	p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months
Comments	Efficacy data included patients of different races/ethnicities	Efficacy data mainly in Caucasian patients, with some data from patients of Afro/Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

Figure 91 | Cyclophosphamide dosing regimens, combined with glucocorticoids, in initial treatment for active Class III/IV LN. i.v., intravenous; LN, lupus nephritis; max, maximum; NIH, National Institutes of Health, USA.; p.o., oral.

Institutes of Health (NIH) regimen or high-dose regimen) or low-dose (also known as the Euro-Lupus regimen). The dosing and duration for these regimens are given in Figure 91.

The choice of which regimen to use depends on several factors and can be individualized:

- *Efficacy:* Oral and standard-dose i.v. cyclophosphamide regimens have been used in diverse ethnic populations and for all levels of disease severity, and show equivalent efficacy.[635,738–741] Reduced-dose cyclophosphamide (Euro- Lupus regimen) shows equivalent efficacy to standard-dose cyclophosphamide but was tested mainly in White pa- tients.[634,711] Emerging data suggest low-dose cyclophos- phamide is effective in Asians, Hispanics, and Black patients, but these studies did not make direct comparisons to standard-dose i.v. cyclophosphamide (Supplementary Table S47[634,718–721,742]).
- *Cost:* Intravenous cyclophosphamide is more expensive than oral and requires the availability of an infusion suite and experienced staff.
- *Convenience:* Oral cyclophosphamide does not require pa- tients to stop work or family activities.
- *Toxicity:* The toxicities of cyclophosphamide may be consid- ered immediate (e.g., gastrointestinal, susceptibility to infec- tion) or delayed (e.g., loss of fertility, future malignancies).
  - Standard-dose i.v. cyclophosphamide was shown to be less toxic than oral cyclophosphamide, but the dose and dura- tion of oral treatment in these reports were substantially higher and longer than those currently recommended (Supplementary Table S50[630,718,741]). The incidence of bladder toxicity is also felt to be lower with i.v. cyclo- phosphamide. Reduced-dose i.v. cyclophosphamide has the most favorable immediate toxicity profile among the 3 cyclophosphamide regimens.
  - The risk of future hematologic malignancy is related to total lifetime exposure (>36 g), as is myelofibrosis (>80 g). Total lifetime exposure plus age constitutes a signif- icant risk factor for premature ovarian failure (>7.5–15 g/m^2 for young to older pediatric patients, respectively; 300 mg/kg for adults).

Practice Point 10.2.3.1.3: An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, patients who have a moderate to high prior cyclophosphamide exposure, and patients of Asian, Hispanic, or African ancestry.

Trials of MMF for initial treatment of proliferative LN have targeted dosing of 2–3 g/d. Several studies have shown that MMF has comparable short-term efficacy to oral or i.v. cyclophosphamide for induction of complete and partial renal responses (Supplementary Table S48[629,631,632,710,718,722–725]). MMF has significant gastrointestinal toxicity, and at moderate-to-high doses, some patients may not tolerate it. In patients with gastrointestinal intolerance, a trial of enteric- coated MPA in a dose range of 1440–2160 mg is warranted, in view of its greater gastrointestinal tolerance.[737]

Although MPAA does not predispose patients to gonadal failure or hematologic malignancies as does cyclophospha- mide, the ALMS trial (target dose 3 g/d) showed a similar incidence of side effects between patients treated with MMF plus glucocorticoids and patients treated with cyclophos- phamide plus glucocorticoids.[629] In this trial, 9 deaths occurred in the MMF group, and 5 in the cyclophosphamide group. Seven of the 9 deaths in the MMF group were due to infections, and 7 of the 9 deaths in MMF-treated patients occurred in Asia. Concomitant high-dose glucocorticoids and the relatively high MPA exposure have been proposed as contributory factors to the higher-than-expected infection-related adverse outcomes in this trial. In this regard, data from kidney transplant clinical trials showed that, compared with an MMF dose of 2 g/d, an increased MMF dose of 3 g/d did not result in a higher efficacy in the non-Black patient population, but was associated with more adverse events.[743] Therefore, consideration of the race or ethnicity of a patient, or the geographic locality, may also be relevant when deciding on the dose of MPAA to be used, in view of the potential differences in risk profiles among patients.

MPA pharmacokinetics varies considerably among pa- tients, especially in the context of hypoalbuminemia and impaired kidney function. Data from small-scale studies

suggested that an MPA area under the concentration-versus- time curve of 35–45 mg/hr/l or a trough level of 3.0–4.5 mg/l may serve to ensure adequate exposure during initial therapy, but the role of therapeutic drug-level monitoring remains to be established.[744–748]

MMF has been tested successfully in diverse ethnic groups. A more granular look at the efficacy of MMF in specific ethnic groups was done through a *post hoc* analysis of data from the ALMS study, the largest trial comparing MMF to i.v. cyclo- phosphamide to date.[629,731] The analysis showed higher treatment response rates for MMF compared to cyclophos- phamide in Hispanic patients (60.9% vs. 38.8%, $P = 0.011$) and patients from Latin America (60.7% vs. 32%, $P = 0.003$), whereas the response to MMF was numerically higher but not statistically different than that to cyclophosphamide in Black patients (53.9% vs. 40.0%, $P = 0.39$). A higher response rate to MMF than to cyclophosphamide in Hispanic patients was also reported in cohort studies.[732] In contrast, the response rate to cyclophosphamide was numerically higher but not statistically different than that to MMF in Asian patients (63.9% vs. 53.2%, $P = 0.24$).[629,731]

Cyclophosphamide has historically been the first-choice treatment for very severe proliferative LN. An analysis of pooled data from various clinical trials of patients with Class III/IV LN, crescents in >15% of glomeruli, and abnormal SCr level at presentation showed a comparable early response to glucocorticoids plus either cyclophosphamide or MMF.[749] However, the analysis also suggested that initial treatment with cyclophosphamide might be associated with a more sustained response and more favorable long-term kidney outcome than initial treatment with MMF. In the mainte- nance phase of ALMS,[633] although not statistically different, patients initially treated with cyclophosphamide had numer- ically lower rates of disease flare compared with those initially treated with MMF.

Practice Point 10.2.3.1.4: Initial therapy with a triple immunosuppressive regimen that includes a CNI (tacroli- mus or cyclosporine) with reduced-dose MPAA and glu- cocorticoids is reserved for patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.

Calcineurin inhibitors (CNI) are potent immunosuppres- sive medications due to their inhibition of T lymphocyte activation and release of interleukin-2. They also modulate the podocyte cytoskeleton, leading to reduction of proteinuria in various glomerular diseases. The use of a CNI in the treatment of LN may therefore lead to more effective or more rapid reduction of proteinuria.

Data from short-term studies with follow-up of 6–12 months suggest that a regimen of glucocorticoids combined with cyclosporine or tacrolimus, with or without reduced- dose MPAA, as initial LN therapy has comparable efficacy to glucocorticoids combined with cyclophospha- mide.[636,750,751] Until recently, most of these trials had been done in Asia (see Practice Point 10.2.3.1.5). The largest trial,

conducted in China, combined a fixed, relatively low-dose of tacrolimus (4 mg/d, achieved trough levels of 5.2–5.5 ng/ml [6.4–6.8 nmol/l]) with low-dose MMF (1 g/d) in patients with a baseline serum creatinine level #3.0 mg/dl (265 mmol/l), and reported earlier attainment of renal response than in controls treated with NIH-cyclophosphamide regimen with a higher complete renal response rate (46% vs. 26%) after 24 weeks of treatment.[636] Extended follow-up, however, showed comparable renal response rates in both groups during the second year of treatment.[733] Similarly, a study from Japan reported a complete response rate of 80% after 6 months of treatment with a triple immunosuppres- sive regimen that included glucocorticoids, reduced-dose cyclophosphamide, and tacrolimus.[750]

The evidence from the few RCTs that compared triple- therapy to cyclophosphamide is judged as low quality because of study limitations and indirectness (Supplementary Table S51[636,718,752]). As these early trials mainly included pa- tients of Asian ethnicity, and some excluded patients with se- vere disease, the generalizability of this therapy to the broader LN population is unclear (see also Practice Point 10.2.3.1.5).

Of importance, in the large Chinese study, the number of infections was higher in patients who received triple therapy than in those who were treated with cyclophosphamide, although this difference did not reach statistical significance. More data are also required on the incidence of acute and chronic CNI nephrotoxicity, the metabolic side effects of CNIs and their effect on blood pressure control, as well as the optimal duration of treatment and whether there may be a rebound of proteinuria after stopping CNI.[751]

Practice Point 10.2.3.1.5: In patients with baseline eGFR of at least 45 ml/min per 1.73 m^2, voclosporin can be added to MPAA and glucocorticoids as initial therapy for 1 year.

Voclosporin is an analogue of cyclosporine that exhibits enhanced potency in calcineurin inhibition. Voclosporin was noninferior to tacrolimus in the prevention of biopsy-proven acute rejection in a 6-month multicenter open-label phase 2b trial that involved 334 low-risk kidney transplant re- cipients.[753] Voclosporin for the treatment of active biopsy-proven Class III, IV, or V lupus nephritis was investigated in Aurinia Urinary Protein Reduction Active - Lupus With Voclosporin (AURA-LV),[734] a phase 2 RCT of 265 subjects and Aurinia Renal Response in Active Lupus With Voclo- sporin (AURORA),[702,754] a phase 3 RCT of 357 subjects. Both trials included patients of diverse ancestry. Voclosporin was compared to placebo, and all patients received glucocorticoids and MMF (target dose: 2 g/d) as background therapy. The rapidly tapered corticosteroid regimen used was novel. All patients received 2 doses of intravenous methylprednisolone (500 mg/dose) followed by 20–25 mg prednisone that was rapidly tapered to 2.5 mg/d by 16 weeks. The primary endpoint of these trials was renal response (RR), defined as urine PCR #0.5 mg/mg, eGFR $60 ml/min per 1.73$m^2$, or no decline of >20% from baseline, and prednisone dose of <10 mg/d for the 8 weeks prior to endpoint measurement.

In AURA-LV, 33% of patients treated with voclosporin 23.7 mg twice per day reached an RR at 24 weeks compared to 19% of placebo-treated patients (OR 2.03, $P < 0.05$).[734] Similarly, in AURORA, 41% of voclosporin-treated patients achieved RR at 52 weeks, compared to 23% of placebo-treated patients (OR 2.65, $P < 0.001$).[702,754] A pooled analysis of the 2 trials showed that patients treated with voclosporin added to standard ther- apy had an RR rate of 44% at 1 year, compared to 23% in placebo patients ($P < 0.0001$).[755] Adverse events were similar between the placebo and voclosporin arms.

Compared to other CNIs, such as cyclosporine and tacrolimus, voclosporin has a more consistent pharmacokinetic–pharmacodynamic relationship due to enhanced binding of the voclosporin–cyclophilin complex to calcineurin and reduced drug and metabolite load. Pre- liminary evidence, based on data from the AURA-LV and AURORA trials, suggests that therapeutic drug monitoring may not be necessary in patients.[756]

Results from these 2 pivotal trials led to the US FDA approval of voclosporin to treat adult patients with LN in January 2021. Of note, voclosporin is not recommended for patients with a baseline eGFR #45 ml/min per 1.73 m^2, as these patients were excluded from the trials. Also, voclosporin has not been studied with cyclophosphamide.

The positive results of AURA-LN and AURORA coupled with the Asian studies of tacrolimus and cyclosporine suggest triple immunosuppressive therapy incorporating a CNI can be an effective treatment regimen for LN. An advantage of a CNI-based regimen is the more rapid reduction of protein- uria. However, more data on long-term efficacy and safety of CNI use in LN are required.

Practice Point 10.2.3.1.6: There is an emerging role for B- lymphocyte targeting biologics in the treatment of LN. Belimumab can be added to standard therapy in the treatment of active LN. Rituximab may be considered for patients with persistent disease activity or repeated flares.

Results from phase 2 and phase 3 clinical trials did not demonstrate superiority in efficacy when B cell–targeting therapies (rituximab, ocrelizumab), costimulatory blockade (abatacept), or anti-interleukin-6 monoclonal antibody were added to standard initial therapy of glucocorticoids and either MMF or cyclophosphamide.[757–762] The negative outcomes contrast with reports of case series that suggested efficacy when patients with suboptimal response to standard therapy were treated with rituximab.[763–766] Interestingly, patients treated with rituximab and abatacept in the RCTs showed more effective suppression of anti-double-stranded deoxy- ribonucleic acid (dsDNA) levels and complement activation, but this biological efficacy did not translate to conventional clinical indicators of treatment response.[757,759] Reasons for the apparent discrepancy between biological efficacy versus clinical observations, and between the case series versus RCT results, include the different populations of patients studied, the outcome parameters used in the trials, and the relatively short

duration of observation in the trials. Some trials using biologics have yielded encouraging results. For example, in a prospective single-center pilot study to investigate whether rituximab could facilitate corticosteroid avoidance, 50 patients with active LN (22 Class V, 28 Class III/IV V) were treated with rituximab 1 g and methylprednisolone 500 mg i.v. on day 1 and day 15 and were maintained on MMF (maximum dose 1.5 g twice per day, target trough blood level of mycophenolic acid 1.2–2.4 mg/ml [3.7–7.5 mmol/l]) without glucocorticoids, and by 52 weeks, 52% of patients achieved complete remission and 34% achieved partial remission.[767]

The negative outcomes in previous clinical trials do not preclude a therapeutic role for some of these novel agents in selected patients, including those who have not responded well to or who do not tolerate standard therapy, or when steroid-sparing is attempted (Supplementary Tables S56–S59[718,742,757–759,764]).[767]

Ongoing clinical trials continue to investigate the role of biologics for the treatment of LN. A recent phase 2 study showed that in adult patients with active proliferative LN treated with MPAA and glucocorticoids, the addition of obinutuzumab resulted in higher complete renal response rates at week 76 (40% vs. 18%, $P = 0.007$), and at week 104 compared to placebo (54% vs. 29%, $P = 0.005$). The rate of serious adverse events and serious infections did not differ between the 2 groups.[760]

A phase 3 RCT of belimumab (10 mg/kg i.v. on days 1, 15, and 29, then every 28 days to week 100) added to standard-of-care therapy resulted in approval of belimumab for LN by the U.S. FDA in December 2020.[701] This trial, Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis (BLISS-LN), examined the 2-year primary efficacy renal response (PERR) after belimumab or placebo was added to standard-of-care therapy, which was either MMF or the Euro-Lupus reduced-dose cyclophosphamide regimen chosen by the site investigator. PERR was defined as a ratio of PCR of <0.7, an eGFR that was no worse than 20% below baseline or at least 60 ml/min per 1.73 m^2, and no use of rescue therapy for treatment failure. At week 104, significantly more patients who received belimumab achieved a PERR compared to the number of those who received placebo (43% vs. 32%; OR 1.60; $P = 0.03$; Supplementary Table S60[701]). Key secondary endpoints included complete renal response and the risk of renal event or death. These also favored belimumab. Subgroup analysis showed that the overall PERR response was driven by the results in the larger subgroup (73.5%) of patients who received MMF as background therapy. Belimumab treatment was not associated with excess adverse events.

In summary, there are accumulating data on the biological and clinical efficacy of various biologics. Although long-term results are awaited, results on these biologics have expanded the armamentarium of therapeutic options and potential combinations of treatments. The favorable safety profile associated with some of the new biologics presents a distinct advantage. Further investigations are necessary to define the profiles and characteristics of

patients who would benefit most from each of the various novel therapies.

Practice Point 10.2.3.1.7: Other therapies, such as azathioprine or leflunomide combined with glucocorticoids, may be considered in lieu of the recommended initial drugs for proliferative LN in situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs, but these alternatives may be associated with inferior efficacy, including increased rate of disease flares and/or increased incidence of drug toxicities.

Azathioprine combined with methylprednisolone pulses showed a comparable short-term renal response rate to that for prednisolone combined with standard-dose i.v. cyclophospha- mide in a study that included 87 patients in the Netherlands, but the azathioprine and pulse methylprednisolone group had more infections, and their extended follow-up data showed a higher relapse rate and greater progression of CKD (Supplementary Table S52[630,718,768,769]). Nonetheless, some patients may not tolerate MPAA, cyclophosphamide, or CNIs, or these drugs may be unavailable, too costly in some regions of the world, or contraindicated, as in pregnant patients.

Short-term studies in Chinese patients compared lefluno- mide against i.v. cyclophosphamide, in both cases com- bined with glucocorticoids, and reported comparable renal response rates of approximately 70% after 6 months.[770,771]

Other therapies that have not shown significant benefit when added to standard therapy include plasmapheresis (Supplementary Table S53[618,635,772–774]), and the anti-interleukin-6 antibody sirukumab (Supplementary Table S54[618,775]). In a phase 2a trial, laquinimod was associ- ated with a higher renal response rate (62.5% compared with 33.3% in the placebo group) when added to standard-of-care treatment with glucocorticoids and MMF in patients with active LN (Supplementary Table S55[618,776]).

10.2.3.2 Maintenance therapy for Class III and Class IV lupus nephritis

This recommendation places a high value on the data demon- strating that long-term, reduced-dose MPAA decrease the risk of LN relapse compared to azathioprine or no treatment and that MPAA have effectiveness comparable to that of cyclophospha- mide but with a lower risk of adverse events. The recommen- dation places a lower value on the risk of adverse events associated with long-term MPAA treatment as compared to no treatment (Figure 92).

Key information

Balance of benefits and harms. High-intensity immuno- suppression for the initial treatment of LN is given for 3–6 months, depending on the regimen (Section 10.2.3.1). At the end of initial therapy, only about 10% to 40% of patients achieve complete response as defined by clinical parame- ters,[2,628,634,636] and approximately 20% achieve complete histologic remission, defined as an activity index of zero on repeat kidney biopsy.[627] Also, LN relapses frequently, and relapses predispose to additional kidney damage and pro- gression to kidney failure. Ongoing treatment is therefore needed to consolidate initial responses into more complete and sustained responses, and to prevent disease flares. After initial therapy, ongoing immunosuppression is designated as maintenance therapy.

Recommendation 10.2.3.2.1: We recommend that after completion of initial therapy, patients should be placed on MPAA for maintenance *(1B)*.

The evolution of current maintenance therapy for prolif- erative LN is an example of how investigators have tried to balance preservation of kidney function against the toxicities of long-term immunosuppressive therapy. After it became

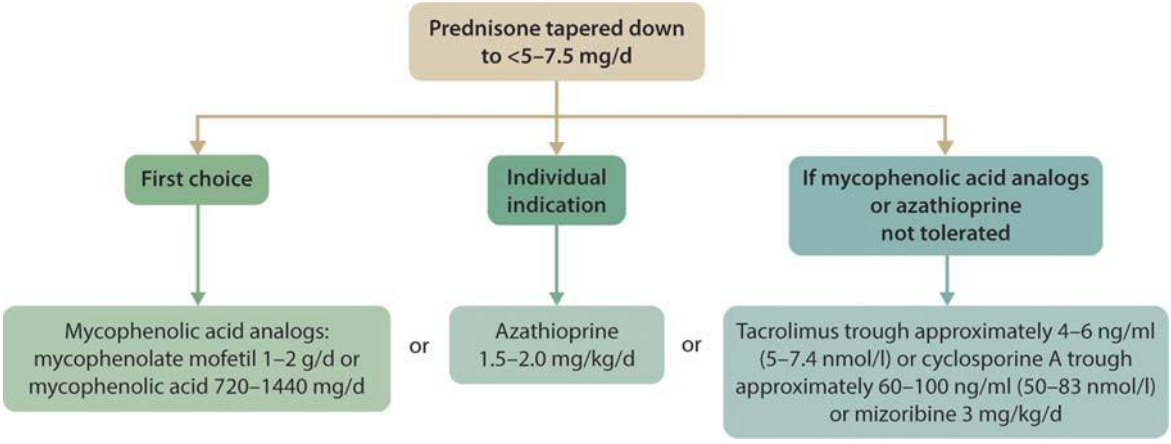

Figure 92 | Maintenance therapy for Class III and Class IV LN. The target ranges for CNIs have been based on the transplant literature. The KDIGO Work Group acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against serum creatinine level, reducing the dose if serum creatinine level increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. CNI, calcineurin inhibitor; LN, lupus nephritis.

clear that the addition of a cytotoxic agent to glucocorticoids during the initial treatment of LN improved long-term kidney survival, patients were kept on oral, or in later studies i.v., cyclophosphamide for months or years.[716] This led to considerable lifetime cyclophosphamide exposure and toxicity.[777,778] A study reported in 2004 compared quarterly i.v. cyclophosphamide against oral MMF or azathioprine for LN maintenance, and the results showed not only a significant reduction in side effects in those treated with MMF or azathioprine but also improved kidney and patient outcomes compared to the cyclophosphamide group.[779] This led to a decrease in the use of quarterly cyclophosphamide as main- tenance treatment. Favorable long-term results with sequen- tial immunosuppressive regimen have been published by others,[712,713] and together, they ushered in the current era of intense, high-dose immunosuppression for the initial treat- ment of proliferative LN, followed by prolonged immuno- suppression with a less intense regimen to reduce adverse events while ensuring the continued suppression of immune-mediated pathogenic processes so that the response following initial therapy is consolidated, the disease remains quiescent, flares are prevented, and further damage to the kidney or other organs is avoided.

MMF and azathioprine were directly compared as main- tenance agents in 2 major clinical trials (Supplementary Table S61[629,718,779–781]).[633,711] In an LN cohort of 227 ethni- cally diverse patients, the maintenance phase of ALMS showed that over 3 years of follow-up, the composite treat- ment failure endpoint of death, ESKD, LN flare, sustained doubling of SCr, or requirement for rescue therapy was observed in 16% of MMF-treated patients and in 32% of azathioprine-treated patients (P ¼ 0.003).[633] LN flares occurred in 12.9% of MMF-treated patients and 23.4% of azathioprine-treated patients. In contrast, the Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis (MAINTAIN) trial randomized 105 pre- dominantly White patients to MMF or azathioprine and glucocorticoid maintenance therapy after initial therapy with the low-dose cyclophosphamide regimen and showed no difference in time to kidney flare between the 2 groups, with a cumulative kidney flare rate of around 20% in both groups after 36 months.[711] A higher proportion of patients in the azathioprine group had adverse events leading to withdrawal of therapy in the ALMS maintenance trial (39.6% vs. 25.2%), and there was a higher incidence of cytopenia in the azathi- oprine group in the MAINTAIN trial. Thus, in most LN populations, MMF (MPAA) is the maintenance drug of choice.

An RCT compared maintenance treatment with triple immunosuppression that included low-dose MPAA, low-dose tacrolimus, and low-dose glucocorticoids ("multitarget" regimen) against azathioprine in responders following "multitarget" regimen or NIH i.v. cyclophosphamide as initial treatment for 6 months in the 2 groups respectively, and the results showed similar efficacy in preventing flares in the 2 groups and a higher incidence of adverse events due to

transaminitis in the azathioprine group.[733] However, the follow-up duration of 18 months was relatively short, and the generalizability of data needs further investigation. Also, although the response rate was significantly higher in the "multitarget" group after 6 months of initial treatment, the cumulative response rate was similar between the 2 groups during the second year of therapy, increasing to approximately 90% by the end of 24 months. Other investigators have reported relatively favorable results with various "mul- titarget" triple immunosuppressive maintenance treatment regimens that comprised glucocorticoids with MPAA and either cyclosporine[782,783] or tacrolimus.[784]

Based on these considerations collectively, the Work Group concluded that the benefits of maintenance immunosup- pression far outweigh its potential harms, and MPAA is the preferred drug based on the data to date (Practice Point 10.2.3.2.1).

Quality of evidence. Only 1 RCT compared long duration (18 months) of cyclophosphamide therapy encompassing both the initial treatment period and the maintenance phase with short duration (6 months) of cyclophosphamide therapy as initial treatment followed by maintenance treatment with variable immunosuppressive regimens. Due to study limita- tions and very serious imprecision (only 1 study, and very wide CIs, indicating appreciable benefit and harm), the quality of the evidence for this trial is very low (Supplementary Table S62[716]).

Similarly, only 1 RCT (n ¼ 39) compared azathioprine with quarterly pulse cyclophosphamide as maintenance treatment, indicating very low quality of the evidence because of study limitations and very serious imprecision (only 1 study, wide CIs) (Supplementary Table S63[779]).

The ALMS trial compared azathioprine with MMF as maintenance therapy in patients with proliferative LN and showed an increased rate of composite "treatment failure" endpoint and adverse effects (e.g., leukopenia) in patients who received azathioprine.[633] Despite the large sample size and the fact that this was an RCT, the quality of the evidence was downgraded to moderate because of imprecision (few events) or study limitations (unclear allocation concealment). Data on the use of CNIs or mizoribine as maintenance treatment are generally of low quality (Practice Point 10.2.3.2.4[785–788]).

Values and preferences. In the judgment of the Work Group, most well-informed patients who have undergone aggressive immunosuppression to control their LN would choose maintenance therapy to try to attain complete remission if it had not yet been achieved, and in all cases to avoid disease relapses needing reinstitution of high-dose immunosuppression. In the judgment of the Work Group, the better efficacy of MPAA with its generally favorable tolerability profile, compared to azathioprine, attests that most well- informed patients would choose MPAA as the first-line treatment. However, patients who have had severe adverse effects while on MPAA, or who place a high value on becoming pregnant, may choose azathioprine (or a CNI) over MPAA, as

may patients for whom MPAAs are unavailable or unaffordable.

Resource use and costs. In general, it is reasonable to as- sume that the personal and societal cost of not using main- tenance therapy and risking disease relapse after investing in initial therapy would be higher than the cost of maintenance medications. Compared with initial therapy, facility costs are often lower, as maintenance regimens are oral, and outside of medication expense, with major resource implications arising from laboratory monitoring of lupus activity and immuno- suppression and managing complications of treatment. Although the drug cost of MPAA is considerably higher than that of azathioprine, there are few cost-effectiveness analyses of maintenance treatment for LN.[789] Also, some drugs may have limited accessibility in certain regions, and this may influence choices. Drug-level monitoring is required in patients treated with CNIs, but not when azathioprine or MPAA is used, and this also has implications for affordability and accessibility.

Considerations for implementation. Apart from availability and cost of MPAA, the major consideration for implementation of maintenance therapy is safety during pregnancy. Although it is not advisable to attempt pregnancy until LN and SLE have been well-controlled for some time, which would give ample opportunity to switch patients over to a "pregnancy-friendly" regimen, pregnancy decisions are complex, and maintenance therapy often needs to be individualized on this basis (Section 10.3.2.). MPAA is contraindicated during pregnancy and should be discontinued well in advance of trying to conceive. In contrast, low-dose azathioprine and CNIs can be used during pregnancy.

Rationale

The use of maintenance combined immunosuppressive therapy in Class III/IV LN to consolidate response to initial immunosuppressive treatment and prevent disease flares is supported by evidence of at least moderate quality. There are more robust data supporting the superiority of MPAA over azathioprine as maintenance therapy, from clinical trials that included patients of different races and ethnicities.

Practice Point 10.2.3.2.1: Azathioprine is an alternative to MPAA after completion of initial therapy in patients who do not tolerate MPAA, who do not have access to MPAA, or who are considering pregnancy.

As discussed under Recommendation 10.2.3.2.1, the direct comparison between MPAA and azathioprine as maintenance treatment in LN, both combined with low-dose glucocorti- coids, is mainly based on data from ALMS and the MAIN- TAIN trial.[633,780] Although the results from the latter showed no statistically significant difference in time to disease flare or long-term clinical outcomes in Caucasian patients, data from ALMS based on a large sample size from different countries with different ancestry demonstrated superior efficacy of MPAA compared with azathioprine, and in both trials, azathioprine was associated with more adverse effects, such as

leukopenia and abnormal liver-enzyme levels. However, azathioprine is much cheaper than MPAA, and financial barriers may limit access to MPAA in many countries. Under such circumstances, or in patients who do not tolerate MPAA because of side effects, low-dose glucocorticoids combined with azathioprine are an effective maintenance immunosuppressive treatment. Observational cohort data from Chinese patients showed that in patients who received MPAA as initial therapy, the disease flare rate was increased when the total duration of MPAA was <2 years,[632,715] and that long-term maintenance treatment with MPAA was associated with a low disease flare rate.[790] Overall, although the efficacy and safety data to date favor MPAA as maintenance treatment, azathioprine is an acceptable alternative, especially in the later phase of long- term management.

Practice Point 10.2.3.2.2: Glucocorticoids should be tapered to the lowest possible dose during maintenance, except when glucocorticoids are required for extrarenal lupus manifestations; discontinuation of glucocorticoids can be considered after patients have maintained a complete clinical renal response for ‡12 months.

Prolonged glucocorticoid exposure is associated with continued and significant organ damage accrual and morbidity.[737,791] At the end of the initial phase of treatment, the goal is to have reduced most patients to a daily dose of prednisone (or equivalent) that is #7.5 mg, and preferably as low as possible. The tapering regimen and duration of gluco- corticoid maintenance therapy vary considerably among cli- nicians and are largely opinion-based, informed by individualized considerations of a patient's risk of developing disease flare, and the risk–benefit balance of the prevailing dose of immunosuppressive medications. A recent open-label controlled trial (Evaluation of the Discontinuation of Main- tenance Corticosteroid Treatment in Quiescent Systemic Lupus [CORTICOLUP] trial) compared continuation of prednisone 5 mg daily against discontinuation in 124 multiethnic patients in Paris with stable and quiescent SLE (history of LN in 34% and 41%, respectively).[792] The results showed a significantly increased flare rate over 52 weeks of follow-up in patients who discontinued prednisone (HR: 0.2 in those who continued prednisone 5 mg daily, $P = 0.002$), and 45 of 63 patients in the discontinuation group remained glucocorticoid-free. Gluco- corticoid discontinuation in patients with stable quiescent disease can be considered, but it should be undertaken with caution and careful monitoring for disease flare. Glucocorti- coid avoidance in maintenance therapy has been attempted with the use of rituximab, but the evidence to support this approach remains limited to one cohort.[767]

Practice Point 10.2.3.2.3: The dose of MMF in the early maintenance phase is approximately 750–1000 mg twice daily, and for MPA, approximately 540–720 mg twice daily. The suggested dosages are largely based on data from the ALMS and MAINTAIN trial.[633,780] As mentioned before, the

Work Group recommends maintenance of these doses until achievement of complete response and then tapering (Figure 93). Due to pharmacogenetic differences, the level of MPA exposure varies considerably among patients receiving the same dose of MPAA. Although there are insufficient data to date to provide recommendations on therapeutic drug monitoring, measurement of MPA exposure may be helpful in patients with unsatisfactory treatment response or who manifest drug toxicities. There are preliminary data associating disease flares with low MPA exposure, but optimal drug level at different phases of clinical management remains to be determined.[793]

Practice Point 10.2.3.2.4: If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine should be considered.

Experience in Japanese patients suggested that low-dose tacrolimus at 3 mg/d was safe and effective when given as long-term maintenance therapy together with low-dose glucocorticoids.[785,794] In a study of 70 Chinese patients who achieved remission after initial therapy with glucocor- ticoids and either i.v. cyclophosphamide or tacrolimus, maintenance therapy with tacrolimus (trough blood level target of 4–6 ng/ml [5–7.4 nmol/l]) was compared with azathioprine 2 mg/kg/d, both in combination with predni- sone 10 mg/d. Over 6 months of follow-up, kidney relapse occurred in 2 azathioprine-treated patients and in none in the tacrolimus group (Figure 93).[795]

Adding tacrolimus or cyclosporine to maintenance therapy was reported in case series as effective in reducing proteinuria in patients with unsatisfactory suppression of proteinuria following initial therapy with glucocorticoids and MMF, especially in patients who showed features of MN in their baseline kidney biopsies.[783,786,796–798] Caution is required when considering adding CNI for the purpose of decreasing proteinuria. It is desirable that there be his- tologic evidence of podocyte injury so that the CNI is likely to be effective. Also, it is prudent to avoid over- immunosuppression and chronic CNI nephrotoxicity, especially in patients with CKD.

Although most studies were done in patients of Asian origin, it is reasonable to consider a CNI for maintenance therapy in any patients who cannot take MPAA or azathioprine. CNIs can also be used safely during pregnancy (Figure 93).

The experience with mizoribine as maintenance therapy in LN is largely limited to Japanese patients.[787,799] Results from a post-marketing surveillance study that included 559 mizoribine-treated patients showed that nearly all were receiving glucocorticoids, and 43.8% were receiving tacrolimus as concomitant treatment. Overall, 63.3% of patients achieved complete or partial remission, and only 3.6% of patients experienced serious adverse drug reactions within 2 years of mizoribine treatment, and the authors concluded that mizoribine was safe and effective (Figure 93).[800]

Practice Point 10.2.3.2.5: The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should not be <36 months.

The optimal duration of maintenance immunosuppression in patients with proliferative LN is not known. If withdrawn too early, patients may relapse even after having had a good response to treatment. Prolonged maintenance increases exposure to immunosuppression and may not provide sufficient continued benefits to outweigh toxicity risk. The Work Group recommends that the total duration of immunosuppression (initial therapy plus maintenance) for patients with proliferative LN who have achieved a complete renal response and have no ongoing extrarenal manifestations be $36 months, based on considering the following evidence collectively:

- In Chinese patients who received MMF as initial therapy, discontinuation of MMF before 2 years was associated with an increased risk of disease flare.[632,715]
- During the third to fourth year of MMF maintenance therapy, kidney flare was associated with low 12-hour trough MPA blood levels, whereas patients with trough levels of approximately 2 mg/l remained in remission.[801]

Maintenance immunosuppressive regimens	Low-dose glucocorticoid AND				
	Mycophenolic acid analogs	AZA	CNI	Mizoribine	Mycophenolic acid analogs and CNI
Comments	Preferred treatment based on high-quality evidence Lower flare rate than alternative regimens such as AZA	Safe in pregnancy Low medication cost	Tacrolimus or cyclosporine Safe in pregnancy	Data mostly from Japanese patients	Data predominantly from Chinese and Japanese patients Long-term safety data of triple immunosuppression required

Figure 93 | Maintenance immunosuppressive regimens in patients with LN. AZA, azathioprine; CNI, calcineurin inhibitor; LN, lupus nephritis.

- The ALMS maintenance phase data reported a relatively high incidence of treatment failure (16%–32%) and kidney flares (13%–23%) despite 36 months of immunosuppres- sion and maintenance with low-dose glucocorticoids and either MMF or azathioprine.[633]
- In an Italian cohort, immunosuppression was tapered in patients who were in complete remission for >12 months, and 27% relapsed. One of the predictors of successful treatment discontinuation was a longer duration (median of 4 years) of prior immunosuppressive therapy.[802]
- Despite $36 months of immunosuppression and $12 months of sustained complete clinical renal response, 28%– 50% of patients continue to show inflammatory histologic activity on repeat kidney biopsy.[803–805] Patients with persistent histologic activity have an increased risk of LN flare after maintenance immunosuppression is dis- continued, compared to patients who have no residual in- flammatory activity in their kidneys.[804,805]
- Patients who have achieved a partial remission tend to be left on maintenance immunosuppression indefinitely. Kidney biopsy studies of such patients have shown that many have resolution of histologic activity[803–805] but are clinically only in partial remission due to residual proteinuria. In such patients, proteinuria may reflect CKD as opposed to active disease, and immunosuppression may be able to be dis- continued in the absence of ongoing kidney inflammation.

In summary, despite not knowing the optimal duration of maintenance immunosuppression for proliferative LN, most patients will require $3 years of therapy. Clinical response findings do not correlate completely with ongoing kidney inflammation. A repeat kidney biopsy could be considered to inform the decision to continue or withdraw maintenance immunosuppression.

10.2.4 Class V lupus nephritis

Practice Point 10.2.4.1: A suggested approach to the man- agement of patients with pure Class V LN is described in Figure 94.

Class V LN accounts for 5%–10% of all LN cases. Data on clinical management are based on very few RCTs with small sample sizes, analyses of pooled data, and observational studies. Because 10%–30% of patients with Class V LN and nephrotic proteinuria progress to kidney failure during long- term follow-up, heavy proteinuria does not usually sponta- neously remit, as it may in primary MN, and as heavy pro- teinuria increases CV morbidity and predisposes patients to thrombosis, treatment of Class V patients who have nephrotic-range proteinuria or NS is warranted.[806–809]

A small RCT demonstrated that remission was significantly more likely with prednisone plus cyclophosphamide (60%) or prednisone plus cyclosporine (84%) than prednisone alone (27%), but cyclophosphamide maintained remission longer (no relapses within a year) than CNI treatment (40% relapsed within a year of discontinuing the CNI).[738] Pooled data from 2 studies showed that prednisone plus either cyclophospha- mide or MMF had similar efficacy in lowering proteinuria after 6 months of treatment.[810] Other studies with relatively

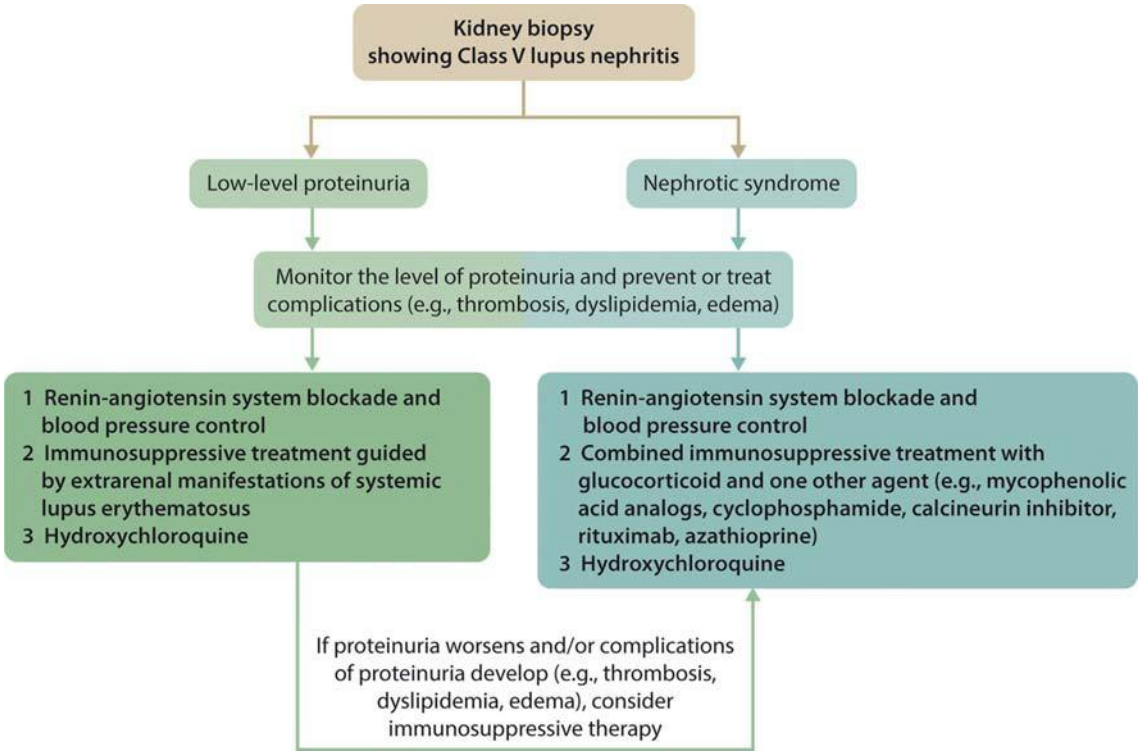

Figure 94 | Management of patients with pure Class V LN. LN, lupus nephritis.

small sample sizes reported the efficacy of glucocorticoids combined with azathioprine,[644,809] oral cyclophosphamide,[811] i.v. cyclophosphamide,[738,812] MMF,[643,644,812–815] CNIs,[738,797,814,816–818] and rituximab,[767,819] with response rates of 40%–60%. Tacrolimus was reported as effective when given together with glucocorticoids as initial therapy to pa- tients with Class V LN who presented with NS, or when given as add-on therapy to patients with mixed Class V and Class III/IV LN whose proteinuria response was judged suboptimal after initial treatment with prednisolone and MMF.[786] In the phase 3 voclosporin trial (AURORA; see Practice Point 10.2.3.1.5), 14% of the patients had pure Class V LN.[754] Although adding voclosporin to background therapy was more effective than background immunosuppression alone in achieving renal response, the details on the patients with Class V have not been presented. There is a lack of robust data in the management of Class V LN, especially in patients who present with NS. The data to date are more in favor of combining glucocorticoids with MPAA, a CNI, or short-term cyclophosphamide than with other options.

In addition to general methods to reduce urine protein, such as RASi and meticulous BP control, MMF is a reasonable first choice for treating patients with Class V and nephrotic- range proteinuria. If ineffective, we suggest cyclophospha- mide for #6 months next in an effort to induce long-term remission, but long-term CNI or rituximab may also be tried if the patient has had prior significant exposure to cyclophosphamide or is reluctant to take the medication in view of the associated toxicities. Appropriate measures to prevent venous thrombosis should be considered in patients whose proteinuria persists despite treatments (Chapter 1).

10.2.4.1 Assessing treatment response in LN.

Practice Point 10.2.4.1.1: Definitions of response to therapy in LN are provided in Figure 95.

All response criteria currently used in clinical trials of LN require improvement in proteinuria and stabilization or improvement in kidney function. Several observational studies suggest that long-term kidney health is considerably more favorable in patients who respond to treatment.[712,820–822]

However, there are no universally accepted criteria for the level of improvement required, which makes direct compari- sons of different clinical trials more difficult.

The definitions in Figure 95 are commonly used with "baseline" kidney function referring to the level before disease flare, which is not known in patients with no previous medical record. Long-term data from 2 large European LN trials showed that favorable kidney outcomes were predicted by achieving a proteinuria level of 0.7–0.8 g/d after 12 months of therapy, a conclusion supported by other reports.[714,823–825] In this regard, renal response at week 104 or week 52 have been used as study endpoints in recent clinical trials such as the phase 3 BLISS-LN study.[701]

Another caveat is the lack of consensus on the appropriate time when response should be assessed. For logistic and economic reasons, large clinical trials often evaluate response at 6–12 months, but improvement of proteinuria and eGFR is continuous over time, and the rate of improvement varies considerably among patients. Also, there are marked differ- ences in baseline kidney abnormalities at disease presentation. Therefore, the time to reach prespecified proteinuria and eGFR cutoffs, either absolute or relative to baseline, varies considerably among patients.[629,631,632,739,797,826,827]

Outside of a formal clinical trial setting, the Work Group suggests that if patients are improving, allowing 18–24 months to achieve a complete response is reasonable in pa- tients who show continuous improvement. A potential tool to predict kidney outcomes was derived from a *post hoc* analysis of the large ALMS trial. This analysis suggested favorable kidney outcomes are predicted by normalization of comple- ment levels and $25% reduction of proteinuria after 8 weeks of treatment.[828]

SLE is a systemic disease, and the kidney should not be examined in isolation from other clinical manifestations. Several other clinical parameters have not been evaluated in detail in clinical studies but are relevant at individual levels such as systemic activity of SLE (e.g., SLEDAI score), BP control, edema resolution, urine sediment, hemoglobin and albumin improvements, and serologic parameters, including dsDNA antibodies and serum complements. If

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

Figure 95 | Commonly used definitions of response to therapy in LN. *For children <18 years old, complete response is defined as proteinuria <0.5 g/1.73 m^2/d or <300 mg/m^2/d based on a 24-h urine specimen. LN, lupus nephritis; PCR, protein–creatinine ratio.

lupus serologies are abnormal, it is reasonable to expect improvement with therapy for LN, although many patients remain positive for anti-dsDNA and/or have low comple- ment levels despite resolution of proteinuria. Extrarenal lupus activity requiring continuation or a change in ther- apy could remain even if the kidney improves. Finally, response is currently only assessed clinically. Considerable data suggest that persistent intrarenal lupus activity may remain, despite resolution of proteinuria and eGFR.[803–805] A repeat kidney biopsy may, therefore, be useful in con- firming renal response, especially before important major treatment decisions such as discontinuation of immuno- suppression.[627]

10.2.4.2 Management of unsatisfactory response to treatment Practice Point 10.2.4.2.1: An algorithmic approach to pa- tients whose response to therapy is deemed unsatisfactory is provided in Figure 96.

Judging the response to therapy as unsatisfactory is difficult because there are no robust data with which to compare an individual's response trajectory, and there needs to be a balance between giving a patient sufficient time to respond and the likelihood of ongoing nephron loss. Nonetheless, patients are expected to show improvement over time after treatment. So, no improvement or worsening despite treatment for 3–4 weeks is clearly unsatisfactory and warrants early appraisal of potential causes for nonresponse and early intervention, whereas patients who show response to treatment can be closely observed, and investigated when the level of improvement after 3–4 months of therapy is suboptimal or below expectation. A 2-month time frame to see improvement was suggested based on post hoc analysis of data from the ALMS trial,[828] but deterioration needs to be evaluated on an individual basis in terms of rapidity and severity.

The role of nonadherence in unsatisfactory treatment response cannot be over-emphasized. The prevalence of nonadherence in patients with SLE could be >60%.[829–832] Switching from oral immunosuppression to i.v. cyclophos- phamide should be considered when nonadherence is sus- pected or proven.

The quality of evidence on the management of LN "re- fractory" to standard initial therapy is marred by variable definitions of treatment response or refractoriness, the disparity between kidney histology and clinical outcome pa- rameters, the legacy effect of prior therapy, and the impact of factors other than disease activity on outcome parameters such as proteinuria and kidney function. Available data on the management of refractory disease are largely from uncon- trolled observational cohort studies, with varied inclusion criteria and based on relatively small sample size.

The role of switching between therapeutic regimens has not been formally investigated. In a US study that compared mycophenolate with i.v. cyclophosphamide, patients who did not show response, defined as improvement by $30%, after 12 weeks of treatment were switched to the other treatment arm.[710] Another study reported efficacy of MMF in patients refractory to or who had relapsed after cyclophosphamide treatment.[833] However, a legacy effect of prior therapy could not be excluded. Unequivocal evidence on the efficacy of switching therapies is lacking.

Evidence supporting the use of rituximab for refractory LN is from open-label observational studies that have re- ported response rates of 50%–80%[762,790,834–845] and a meta-analysis of 31 studies with 1112 patients that showed complete and partial response rates of 46% and 32%, respectively, after rituximab was added.[846] The role of other biologics with demonstrated efficacy in recent clinical trials, such as obinutuzumab or belimumab, warrants further investigation.

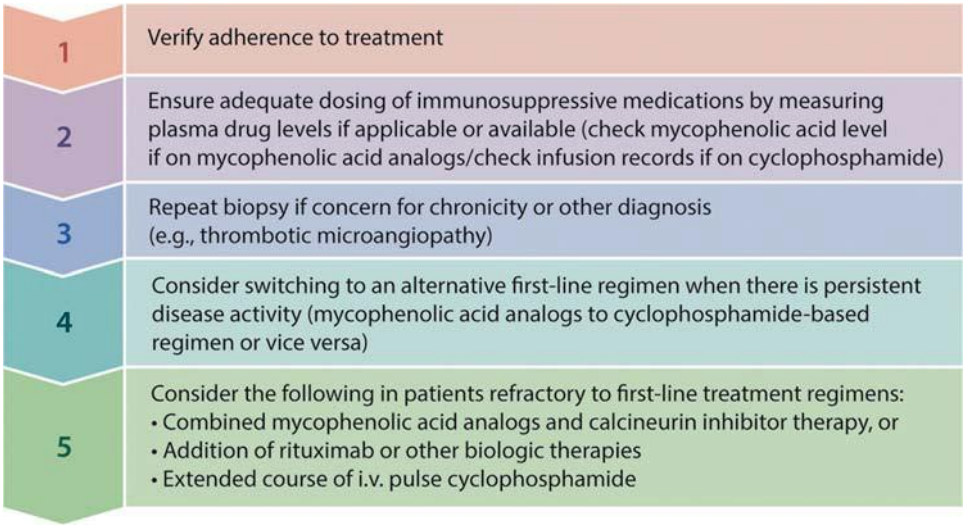

Figure 96 | Management of patients who show unsatisfactory response to initial therapy for active LN. i.v., intravenous; LN, lupus nephritis.

Similarly, data from observational cohorts suggested efficacy of CNIs, combined with either glucocorticoids and/or MMF, in patients with refractory or relapsing LN.[783,784,847–851]

10.2.4.3 Treatment of LN relapse

Relapses of LN are common, and LN flare is an important predictor of poor long-term kidney survival.[852–855] LN flare rates of 10%–50% have been reported, and relapses occur over time.[856] Failure to achieve complete remission increases the risk of subsequent relapse.[706,712,857] Relapse rates of 39% and 64% were found in patients who achieved complete remission or partial remission, respectively, and time-to-relapse after complete response was 36 months, compared to 18 months after partial response.[706] Similarly, an HR of 6.2 for relapse was reported in Chinese patients who did not achieve complete remission after initial therapy.[712]

Practice Point 10.2.4.3.1: After a complete or partial remission has been achieved, LN relapse should be treated with the same initial therapy used to achieve the original response, or an alternative recommended first-line therapy.

There are no data that focus on the treatment of LN flares alone. However, it is generally agreed that there is no major difference between management of an LN flare and that of *de novo* active LN, and initial therapies are the same as outlined above. Although not yet ready for clinical management, emerging data from a recent transcriptomic study of paired serial kidney biopsies showed slight differences in intrarenal inflammatory gene expression between the initial presentation and LN relapse.[858] All LN clinical trials testing initial, induction therapies for LN include both types of patients. Although these considerations form the basis for Practice Point 10.2.4.3.1, there are several caveats in choosing an approach:

1. If patients had been treated with cyclophosphamide in the past, it is important to calculate lifetime exposure. Ovarian failure has been associated with age (and oocyte reserve) and cumulative dose, with sustained amenorrhea occurring in up to 50% of patients aged >32 years with a cumulative exposure of 8 g/m^2.[859,860] The chance of future malignancy increases after a total exposure of 36 g, so if a patient is approaching this level, cyclophosphamide is better avoided.
2. If patients relapse during pregnancy, treatment choices are more limited. These are discussed in Section 10.3.2.
3. Patient preference and/or tolerance of the initial regimen should be considered. Also, patient adherence should be considered in the choice of treatment.
4. Disease activity should be verified, as proteinuria may be secondary to CKD.

The last point is critical but complex. The same clinical criteria used to diagnose *de novo* LN are used to diagnose LN flares absent a kidney biopsy. That is, flares are generally considered when proteinuria increases beyond a certain threshold, with or without an active urinary sediment or deterioration of kidney function. Without histology, it is sometimes difficult to determine whether changes in

proteinuria are due to active inflammatory kidney injury or reflect progression of chronic damage incurred during pre- ceding episodes of active LN, because there is often discordance between clinical findings and histologic findings.[627,628] The tempo and magnitude of change in proteinuria may help with rapid increases, and large changes often reflect active disease. SLE serologies (e.g., complement, anti-dsDNA) may support a flare diagnosis but need to be evaluated in the context of prior serologic trends. A change from normal to abnormal is more useful than serologic studies that are always normal or always abnormal. Given the risks of immunosup- pression, if the diagnosis of flare remains uncertain, a repeat kidney biopsy to assess disease activity versus chronic damage is important to inform treatment decisions.[861]

In lieu of waiting until LN flares before treating it, some investigators have examined preemptive treatment to prevent flare. A trial in the Netherlands compared "early treatment" of 16 patients to conventional management of 23 patients who increased their anti-dsDNA levels by 25%.[862] Prednisone was increased by 30 mg/d in the early treatment group and was tapered back to baseline over 18 weeks. After a mean follow- up of <2 years, 2 major relapses (12.5%, both with LN relapse) occurred in the early treatment group, compared to 20 relapses (87%), 7 of which were major (1 kidney relapse), in the conventionally managed patients. A prospective trial in the US randomized 41 patients who showed an increase in both anti-dsDNA and C3a to prednisone (30 mg/d tapered >4 weeks) or placebo. During a short follow-up (90 days), no patients given prednisone had a severe flare, but 6 placebo patients did, and 3 of the flares were kidney-related.[863] A recently published retrospective study of Chinese patients with LN suggested that a moderate increase in immunosup- pressive treatment dose was effective in preventing kidney and nonrenal flares without excessive treatment-related adverse effects.[793] Taken together, all of these data suggest that impending LN flares may be preventable, at least for some patients, but larger RCTs of sufficient duration are needed before this approach can be endorsed.

10.3 Special situations

10.3.1 Lupus nephritis and thrombotic microangiopathy

Practice Point 10.3.1.1: Patients with LN and thrombotic microangiopathy (TMA) should be managed according to the underlying etiology of TMA, as shown in Figure 97[864]. TMA is a pathologic description of vascular endothelial injury secondary to various etiologies.[865] The causes of TMA most relevant to patients with LN are thrombotic thrombo- cytopenic purpura (TTP), antiphospholipid syndrome (APS), and complement-mediated TMA. However, patients with lupus can also develop TMA due to Shiga-toxin-hemolytic uremic syndrome, infections, drugs, or malignancies.[454,866] The key to a good outcome for TMA in LN is rapid diag- nosis and prompt treatment. When appropriate expertise is available, it is preferable that patients with LN and TMA be comanaged with an experienced hematologist. However,

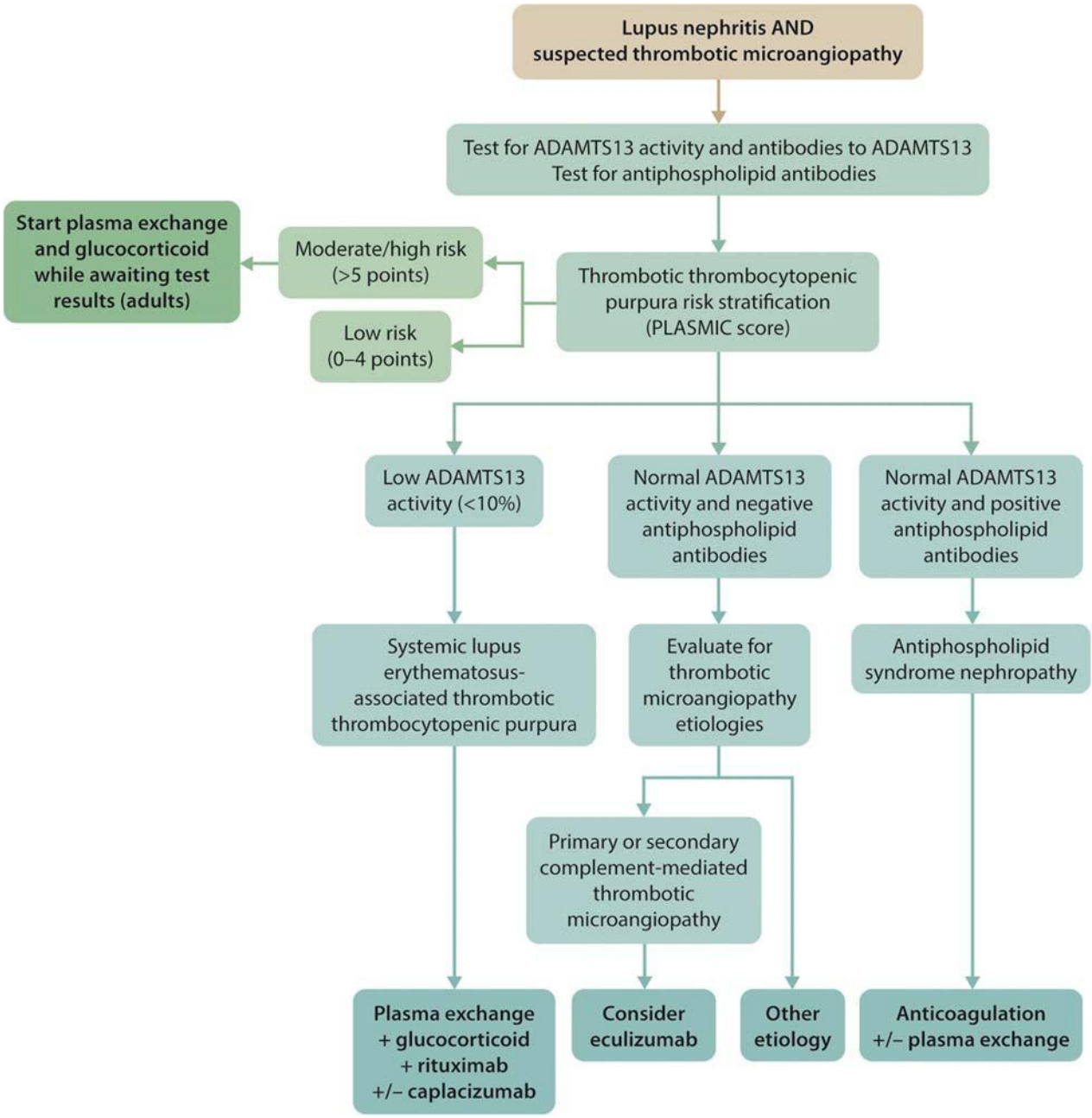

Figure 97 | Management of patients with LN and TMA. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol.* 2017;4:e157–e164.[864] ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PLASMIC, Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem-cell or solid-organ transplant, MCV, INR, Creatinine.

some of the serologic and genetic testing needed for a specific diagnosis, such as ADAMTS13 activity or the presence of anti- ADAMTS13 antibodies in the case of TTP, antiphospholipid antibodies, and complement studies may not be available, and even when they are available, they often take considerable time to complete (Figure 97). If TTP is suspected, one may consider using the PLASMIC score,[864] and if the score defines

an intermediate-to-high risk of TTP, adults should be started on plasma exchange and glucocorticoids while waiting for the investigation results. In children, TTP is less common, and plasma exchange has been associated with considerable morbidity,[867] so it is acceptable to defer plasma exchange for 24–48 hours until the ADAMTS13 result is available to confirm that the procedure is indicated.[868]

TMA due to lupus-associated TTP. The diagnosis of TTP is mainly reserved for patients with TMA and low ADAMST13 activity (#10%).[865,869] The treatment of confirmed TTP in LN is extrapolated from that of acquired TTP and includes plasma exchange,[870,871] high-dose glucocorticoids,[872,873] rit- uximab,[874–877] and/or caplacizumab (von Willebrand factor inhibitor; Figure 97).[878,879]

TMA due to APS. Antiphospholipid antibodies (aPLA) are found in about 30% of patients with SLE and may be asso- ciated with venous and/or arterial macro- or microvascular thrombosis, thrombocytopenia, adverse pregnancy outcomes, and neurologic abnormalities. Kidney damage is a well-recognized complication of APS, presenting as renal artery thrombosis or stenosis, RVT, or injury to the kidney microvasculature, also known as APS nephropathy.[880] There are few data on the management of APS nephropathy. In a retrospective study of 97 patients with kidney TMA, 62.9% tested positive for aPLA, 38.1% for lupus anticoagulant, and 13.4% had APS.[881] Complete and partial response rates were 38.1% and 22.6%, respectively, after 12 months of immunosuppressive treatment. Thirty-seven of 61 patients who were aPLA-positive also received anticoagulation therapy, and anticoagulated patients showed a higher complete response rate (59.5% vs. 30.8%), and the partial response rate was 18.9% and 26.9% in patients who had or had not received anticoagulant therapy, respectively. Therefore, it is reasonable to treat APS nephropathy with long-term anticoagulation with warfarin. Direct oral anticoagulants are not recommended, as they were inferior to warfarin in preventing thromboembolic events in this setting.[882,883]

Catastrophic APS is characterized by thrombosis, often of rapid onset, affecting multiple organs, and it is associated with high mortality. Treatment includes both total anti- coagulation and high-dose glucocorticoids.[884] Plasma ex- change is often used in catastrophic APS[152] and has been associated with improved patient survival in retrospective studies.[885] There are recent anecdotal reports on the potential efficacy of rituximab in catastrophic APS.[886,887] It has been shown that complement activation is involved in the patho- genesis of tissue injury induced by aPLA, and there is emerging evidence on the efficacy of eculizumab in the treatment of catastrophic APS.[888–890]

Complement-mediated TMA and atypical hemolytic uremic syndrome (aHUS). Many cases of kidney TMA with ADAMTS13 activity >10% and negative aPLA correspond to complement-mediated TMA, and these patients ideally should be evaluated with complement studies when they are available.[539,543] aHUS is a rare and severe form of TMA caused by dysregulation of the alternative complement pathway due to genetic or acquired functional defects in complement regulatory proteins, resulting in excessive production of the

terminal complement complex C5b-C9, triggering endothelial cell injury that predominantly affects the kidney vasculature in the arterioles and interlobular arteries.

Complement-mediated TMA in LN does not respond well to plasma exchange or immunosuppression with glucocorti- coids and cyclophosphamide, and it may be best treated with a complement inhibitor such as eculizumab, although the optimal dose and duration remain controversial.[891–893] The limited data to date show a high response rate, with resolution of TMA in 68% of patients with secondary aHUS.[894] Data from 31 adult patients (26 treated with plasma therapy and 5 plasma-resistant patients treated with eculizumab) showed complete kidney recovery in 4 of 5 eculizumab-treated pa- tients.[895] Efficacy of eculizumab treatment was also reported in a patients with lupus and heterozygous deletion in com- plement factor H CFHR1-CFHR3 gene presenting with TMA, and a review of 20 patients showed a kidney recovery rate of 85% in patients with SLE and/or APS after treatment with eculizumab.[896] A recent report on 9 patients with TMA associated with SLE and/or APS showed that kidney function improved by 25% in half of the patients after 4 weeks of eculizumab treatment, and 2 of 3 patients were able to dis- continue dialysis.[897]

Another recent report on 11 patients with TMA and LN showed complement regulatory protein mutations in 6 pa- tients, and response to eculizumab treatment in 10 patients.[889] Prior to the advent of eculizumab, plasma exchange and/or plasma infusion was the only treatment for aHUS, with effi- cacy in less than half of patients and little benefit in patients with membrane cofactor protein mutations.[873,898,899] As complement studies often take some time to return, initiation of plasma exchange is warranted during the waiting period, or if access to eculizumab is limited. The rationale and objectives of plasma infusion and plasma exchange include the replacement of absent or mutated circulating complement regulators such as CFH and the removal of antibodies directed to complement regulatory proteins or mutated fac- tors that play a permissive role in aberrant complement activation. In the absence of eculizumab, the efficacy of plasma exchange and plasma infusion varies, and the duration of therapy is dependent on the treatment response.[900–903] Data from 31 adult patients (26 treated with plasma therapy and 5 plasma-resistant patients treated with eculizumab) showed recovery of kidney function in approximately 40% of patients given plasma therapy.[895]

10.3.2 Pregnancy in patients with lupus nephritis

Practice Point 10.3.2.1: Patients with active LN should be counseled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for ‡6 months after LN becomes inactive.

Practice Point 10.3.2.2: To reduce the risk of pregnancy complications, hydroxychloroquine should be continued during pregnancy, and low-dose aspirin should be started before 16 weeks of gestation.

Practice Point 10.3.2.3: Only glucocorticoids, hydroxy- chloroquine, azathioprine, and CNIs are considered safe immunosuppressive treatments during pregnancy.

Adverse pregnancy outcomes, such as preeclampsia, preterm birth, and fetal loss, are higher in patients with active LN.[904,905] Commonly used medications for LN induction and mainte- nance therapy, particularly cyclophosphamide and MMF for- mulations, are toxic to the fetus or teratogenic, respectively. A discussion of acceptable methods of contraception should, therefore, take place as part of initiating treatment for LN. Because of the increased risk of clotting in patients with SLE and antiphospholipid antibodies, use of estrogen-containing birth control should be avoided or minimized. A risk-factor checklist has been proposed by some organizations to stratify, plan, and counsel pregnancy in patients with lupus.[906]

Hydroxychloroquine is considered safe in pregnancy and may decrease the rate of preterm birth and intrauterine growth retardation, whereas withdrawal of hydroxy- chloroquine has been associated with LN flare, so it should be continued when an LN patient becomes preg- nant.[659,664,907] Low-dose aspirin (#100 mg/d) may also reduce the risk of preeclampsia and intrauterine growth retardation and can be started at conception or as soon as pregnancy is recognized.[908,909] The incidence of LN flare in pregnancy has been reported to be 11%–28% and is higher if patients have low serum complement levels or high anti- dsDNA antibody titers.[904] Active LN during pregnancy can be treated with glucocorticoids plus azathioprine and/or a CNI, although in the first trimester, the use of glucocorti- coids is associated with an increased risk of gestational diabetes and cleft palate. For patients on maintenance therapy, if they are on azathioprine, this can be continued, but if they are on MPAA, this must be discontinued or changed to azathioprine.

10.3.3 Treatment of lupus nephritis in children

Practice Point 10.3.3.1: Treat pediatric patients with LN using immunosuppression regimens similar to those used in adults, but consider issues relevant to this population, such as dose adjustment, growth, fertility, and psychosocial factors, when devising the therapy plan.

Approximately 20% of SLE is diagnosed before the age of 18 years, and genetic components are more common in childhood- onset SLE.[910–912] There is suggestive evidence that disease is often more severe in the pediatric population. In adolescent patients with SLE and isolated proteinuria, orthostatic or postural proteinuria should be excluded, as this phenomenon has been observed frequently in this population.[913,914]

There are few large-scale RCTs to guide treatment of chil- dren with LN, and much of the current literature reports the

results of adult regimens applied to this population. The data are insufficient to confirm superiority of efficacy for any particular treatment regimen. Several issues must be addressed when treating pediatric lupus, including adherence concerns, which may favor i.v. medications; growth concerns, which may favor limiting glucocorticoid exposure; fertility concerns, especially as patients approach adolescence, which may favor limiting cyclophosphamide exposure; and psychosocial con- cerns relating to school and socialization with peers. Special considerations regarding glucocorticoid dosing in children are included under Practice Point 10.2.3.1.1. Children with LN should be comanaged by pediatric nephrologists and rheu- matologists with expertise in lupus, and the expertise of other professionals, such as clinical psychologists, psychiatrists, or social workers, can be helpful.

10.3.4 Management of lupus patients with kidney failure

Practice Point 10.3.4.1: Patients with LN who develop kidney failure may be treated with hemodialysis, peritoneal dialysis, or kidney transplantation; and kidney trans- plantation is preferred to long-term dialysis.

There are no data to favor one form of dialysis over another in kidney failure due to LN. Patients with lupus receiving hemodialysis display similar 3-year survival rates and mortality due to CV or infectious complications to those of patients receiving peritoneal dialysis.[915–917] Therefore, kidney replacement therapy should be individualized, taking into account patient characteristics and preferences.

Kidney transplantation is preferred to dialysis. Kidney transplant outcomes are similar to those in patients who developed kidney failure due to other types of kidney dis- ease,[918,919] and transplanted patients have lower mortality than patients with lupus who remain on dialysis.[920] As clinical outcomes are better in patients with shorter durations of dialysis,[921,922] transplantation may be carried out as soon as disease is quiescent. Although lupus activity tends to decrease after kidney failure develops, patients can still flare,[923] so pe- riodic monitoring is required. LN can recur in kidney allo- grafts, but the risk is low, and flares do not generally result in allograft loss.[924–926] One important consideration is that pa- tients who have antiphospholipid antibodies may experience dialysis vascular access clotting or allograft thrombosis and may require prophylactic anticoagulation.[927–929]

Research recommendations

- Identify and validate biomarkers of kidney histology that can be used to follow the tissue response to treatment in real-time to help in managing immunosuppression.
- Identify and validate biomarkers of impending LN flare that can be used to decide if preemptive immunosuppressive therapy is indicated.
- Classify LN on the basis of molecular pathogenesis and histology as opposed to histology alone. This classification ideally could be used in conjunction with novel, targeted

therapies for LN to select the most appropriate treatment, including biologic medications targeting specific pathogenic pathways.

- Establish renal response criteria that reflect resolution of disease activity at the tissue level and are also predictive of long-term kidney survival and patient survival without need of kidney replacement therapy.
- Establish criteria for duration of maintenance immuno- suppression and the safe withdrawal of therapy.
- RCTs are needed to test the following questions:
  - What is the optimal therapy for patients with severe Class III/IV LN (i.e., patients presenting with severe AKI and/or markedly abnormal SCr level or eGFR) who have been excluded from the majority of clinical trials to date?
  - What is the optimal therapy for pure Class V LN?
  - Do antimalarials improve the responsiveness of LN to treatment and/or help maintain disease quiescence and prevent flares?
  - Is there a role for complement inhibition in the man- agement of LN?
  - What are the optimal or prioritized therapies for child- hood LN?
  - What are the efficacy and safety profiles of CNIs, including the optimal drug exposure when used as initial or maintenance treatment of LN? What are the long- term implications of such treatment?
  - What are the optimal glucocorticoid- reduction protocols for LN management?

Chapter 11: Anti-glomerular basement membrane (Anti-GBM) antibody glomerulonephritis

Anti-glomerular basement membrane (GBM) antibody GN is a rare glomerular disease with an incidence of 0.5–1 per million population. It is caused by autoantibodies against the noncollagenous domain of the a3 chain of type IV collagen. Anti-GBM GN may present either as an isolated kidney dis- ease or as a pulmonary–renal syndrome (Goodpasture's syndrome). Anti-GBM is usually a rapidly progressive cres- centic GN, and about 80% of patients have crescents in half or more of their glomeruli.[930] Goodpasture's syndrome occurs in 40%–60% of patients, and kidney disease is accompanied by sometimes massive and fatal pulmonary hemorrhage.[931] Anti- GBM disease with pulmonary involvement is more frequent in men (about 80%) and typically occurs during the second decade.[932] Isolated anti-GBM nephritis does not have clear male preponderance and may also occur in older persons.[933] If untreated, anti-GBM disease has very high morbidity, with almost all patients going on to kidney failure, and it can have significant mortality. In patients with Goodpasture's syn- drome, the mortality rate was 96% before the introduction of immunosuppression, and 47% despite treatment with immunosuppression.[934] Most patients died of respiratory failure.[932] The cornerstone of the treatment is rapid removal of the pathogenic autoantibodies and suppression of their production to prevent further kidney and pulmonary injury. This chapter makes management recommendations for adults (≥18 years of age) who have anti-GBM GN with or without pulmonary involvement.

11.1 Diagnosis

Practice Point 11.1.1: Diagnosis of anti-glomerular base- ment membrane (GBM) disease should be made without delay in all patients with suspected RPGN (Figure 98).

In patients who present with a suspected RPGN, serologic testing for the presence of anti-GBM antibodies should be done urgently using commercially available enzyme-linked immunoassays. The immunoassays for anti-GBM antibodies may be negative in up to 10% of patients, and in these in- dividuals, diagnosis may be established only by kidney biopsy demonstrating linear IgG deposition along the GBM.[935,936]

Diagnosis of diffuse alveolar hemorrhage is usually done clinically and confirmed by high-resolution CT scan. Bron- choscopy and pulmonary functional testing may be useful, but they are often unnecessary and may be difficult to perform in critically ill and unstable patients. Diagnosis should be made without delay, and kidney biopsy findings should be reported to the clinician by the pathologist on the day of the biopsy (Figure 98).

11.2 Treatment

This recommendation places a relatively higher value on pre- venting mortality and further loss of kidney function and a relatively lower value on the potential adverse events that may occur with the intense immunosuppression regimen recommended. Given the uniformly poor prognosis of untreated dis- ease, almost every patient and physician would be expected to choose this treatment regimen.

Key information

Balance of benefits and harms. Untreated anti-GBM disease is associated with considerable morbidity and mortality. Observational studies have shown that early mortality of anti- GBM decreased from 47%[932] to 8.5% with plasma exchange and immunosuppression,[933] and 5-year patient survival is currently >90% with treatment.[937] In contrast, although kidney survival has improved with plasma exchange and immunosuppressive treatment, it still remains relatively poor, in part because of delayed diagnosis and initiation of treatment. Since 2007, the 5-year kidney survival rate of treated patients has improved from about 25% to 50%, probably because of both earlier diagnosis and a higher proportion of patients being treated with plasma exchange.[937,938]

Plasma exchange, in combination with immunosuppres- sion is, undoubtedly, life-saving and helps prevent kidney failure in patients with independent kidney function at presentation.

Potential harms include infections associated with immu- nosuppression and bleeding after plasma exchange. Admin- istration of fresh frozen plasma after plasma exchange may be indicated, especially in patients with alveolar hemorrhage and after kidney biopsy.

Quality of evidence. The evidence is based mostly on the comparison of treated patients with historical controls; there has been only one RCT, which is of very low quality. No systematic review of observational studies was undertaken by the ERT. However, the observational studies that were

Recommendation 11.2.1: We recommend initiating immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis in all patients with anti-GBM GN except those who are treated with dialysis at presentation, have 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hem-

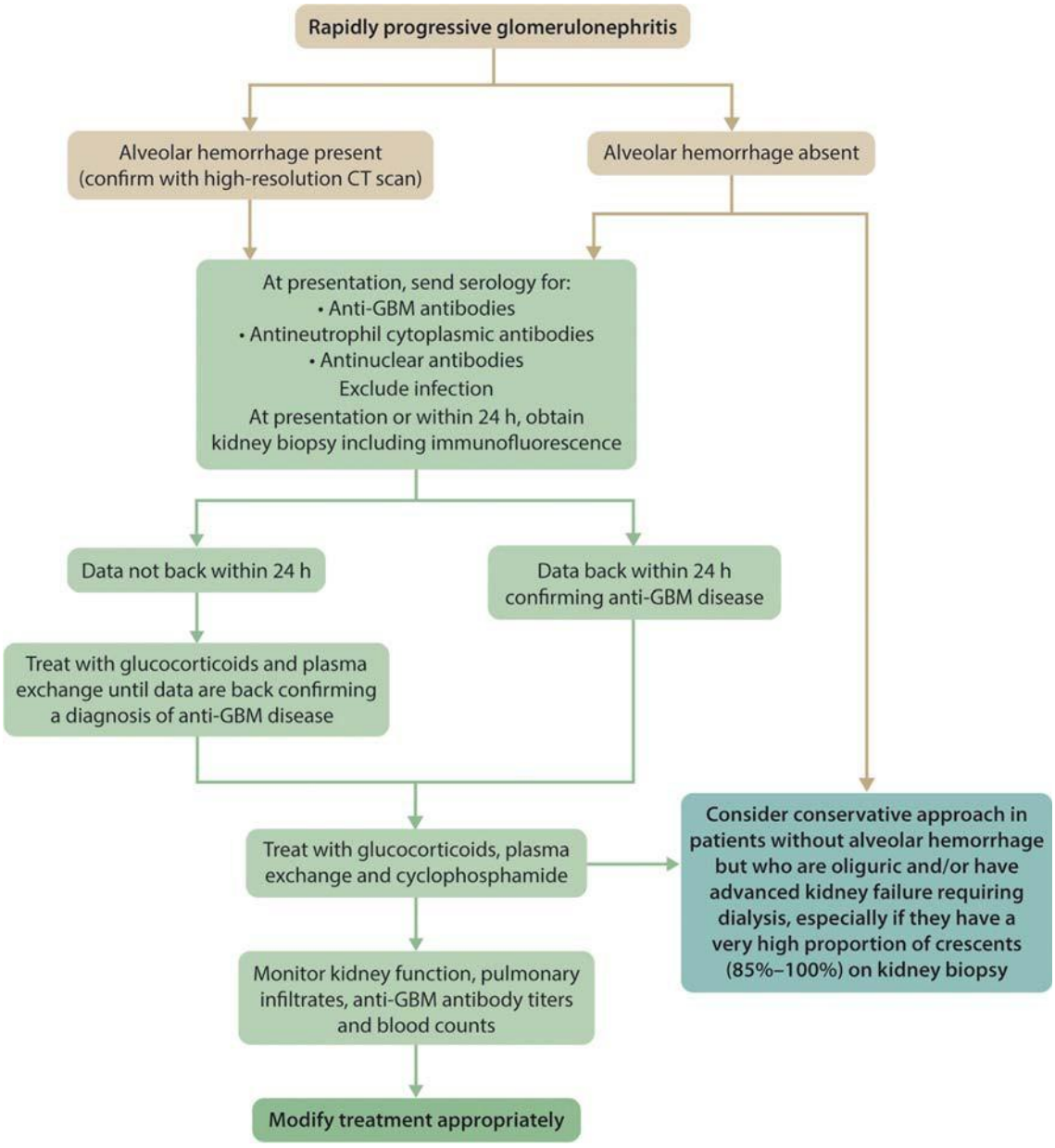

Figure 98 | Diagnosis and therapy in anti-GBM disease. CT, computed tomography; GBM, glomerular basement membrane.

identified by the Work Group exhibit strong mortality and kidney benefit for patients treated with immunosuppression and plasma exchange, compared with those receiving incomplete treatment or no treatment. Therefore, the overall quality of evidence was rated as low.

One small (n ¼ 17) RCT compared plasma exchange with standard of care in patients with anti-GBM disease (Supplementary Table S64[939]). The quality of the evidence for critical outcomes (all-cause mortality, kidney failure, and infection) was very low because of study limitations (unclear randomization and allocation concealment methods used) and very serious imprecision (only 1 study, with few patients and very wide CIs indicating less certainty in effect). Other outcomes, such as anti-GBM antibodies, were not considered to be critical and important outcomes for the guideline.

Values and preferences. Because untreated anti-GBM GN and Goodpasture's syndrome carry a high risk of mortality and morbidity (kidney failure), it is likely all patients and physicians would opt for treatment with aggressive immunosuppressive therapy.

Resource use and costs. The management of anti-GBM disease and Goodpasture's syndrome is expensive and resource-intensive. Patients with suspected anti-GBM disease optimally require a specialized center with available intensive care, plasma exchange, nephropathology, and acute hemodialysis capabilities, some or all of which may not be available in some regions. Costs are offset to some extent if treatment results in preservation of independent kidney function, and patients do not require long-term kidney replacement therapy.

Considerations for implementation. Treatment for anti-GBM disease should be started as soon as possible for most patients. However, the chance for recovery and preservation of independent kidney function is low in patients presenting with certain clinical and pathologic conditions. Recovery of kidney function is only about 5% in patients who have a high proportion of crescents (85%–100%) on kidney biopsy, oliguria, and/or advanced kidney failure requiring initiation of dialysis.[940] In such patients, the decision to initiate therapy should take into account this low chance of kidney recovery and the ability of the patients to withstand intense immunosuppression based on their other clinical characteristics. However, treatment is necessary in these patients if they have pulmonary hemorrhage.

Anti-GBM disease is more common in Caucasian patients. In Chinese patients, the disease occurs more frequently in older people.[941] Pulmonary disease is more frequent in smokers,[942] and presence of pulmonary disease may be associated with better kidney outcomes,[943] probably because of earlier diagnosis. Pulmonary–renal syndrome occurs more frequently in young men; isolated anti-GBM nephritis may occur in older persons and with less male preponderance.

Rationale

The aim of treatment is to suppress kidney inflammation, remove circulating pathogenic autoantibodies (with plasma exchange), and suppress the formation of the autoantibodies (with immunosuppression). This treatment is able to prevent ongoing kidney damage, but it is unable to reverse already established chronic kidney damage. Treatment usually results in recovery from alveolar hemorrhage.

Formation of anti-GBM antibodies ceases spontaneously after several months and within weeks in patients treated with plasma exchange and immunosuppression. Relapses are rare (mostly in smokers), and long-term maintenance immuno- suppression is not necessary. When anti-GBM antibodies are persistently negative, kidney transplantation is associated with a very low recurrence rate.

Practice Point 11.2.1: Treatment for anti-GBM disease should start without delay if this diagnosis is suspected, even before the diagnosis is confirmed.

As anti-GBM antibodies are pathogenic, they should be removed completely from the circulation as quickly as possible. Antibodies are cleared in most patients treated with plasma exchange combined with immunosuppression within 8 weeks.[933] Acceleration of the anti-GBM removal could improve the recovery of kidney function in anti-GBM disease. If there is a high index of suspicion of anti-GBM disease, treatment should start without delay (within 24 hours), even before the diagnosis is confirmed with a kidney biopsy.

Practice Point 11.2.2: Plasma exchange should be per- formed until anti-GBM titers are no longer detectable.

Plasma exchange gradually and relatively slowly (within several weeks) eliminates anti-GBM antibodies from the

circulation and usually needs to be performed for 2–3 weeks before anti-GBM antibodies disappear completely.[933,935,944] In patients with alveolar hemorrhage, or immediately after kidney biopsy, plasma exchange should be done with fresh frozen plasma. If albumin is used, administration of fresh frozen plasma at the end of plasma exchange is warranted.

Practice Point 11.2.3: Cyclophosphamide should be administered for 2–3 months and glucocorticoids for about 6 months (Figure 99[931,945,946]).

Formation of anti-GBM antibody ceases spontaneously after 6–9 months.[947] However, based on available clinical experience, oral cyclophosphamide daily for 3 months and gradually tapered glucocorticoids completely withdrawn within 6 months seem to be appropriate in most patients to prevent new antibody production.[933,948] In patients with persistent anti-GBM antibody after 3 months of cyclophosphamide, continuation of treatment with either azathioprine or mycophenolate (in combination with glucocorticoids) is suggested.[945]

As the risk of infection in patients with kidney failure treated with cyclophosphamide is high,[949] prophylaxis of *Pneumocystis* pneumonia with cotrimoxazole can be considered.[945] In patients with serious infection during treatment with plasma exchange, adding i.v. immunoglobulin therapy to antibiotics can be considered. Intravenous immunoglobulin should be given immediately after plasma exchange to limit its removal, but the real impact of this approach is uncertain.[950]

Practice Point 11.2.4: No maintenance therapy of anti-GBM disease is necessary.

Relapses of anti-GBM disease are uncommon (0%–6% of cases). None of 41 patients with anti-GBM disease had recurrent antibodies or relapsed beyond 6 months.[935] Individual patients with relapses many years after the first presentation of the disease were, however, reported,[951–954] and repeated relapses may occur in patients who do not stop smoking or who are exposed to lung irritants.[955,956] Treatment of patients who do not have detectable anti-GBM antibodies beyond 6 months is not recommended. Smoking should be strongly discouraged.

Practice Point 11.2.5: Patients with GN who are anti-GBM- and ANCA-positive should be treated with maintenance therapy as for patients with AAV.

Double positivity of anti-GBM and ANCA is frequent. About 5% of patients with AAV will also have anti-GBM antibodies, and up to one-third of patients with anti-GBM GN may be ANCA-positive.[599]

Double-positive patients also may have severe kidney disease and often have lung hemorrhage at presentation, but they have a greater chance of kidney recovery from dialysis-dependence than patients with only anti-GBM antibodies. In contrast to patients with only anti-GBM antibodies, double-positive patients have a similar relapse rate as that of patients with AAV and require aggressive early treatment as for anti-GBM disease followed by maintenance immunosuppression as for AAV (Chapter 9).[935]

Intervention	Dosing	Duration of treatment
Plasma exchange	• 40–50 ml/kg ideal body weight exchange daily against 5% albumin • Add fresh frozen plasma at the end of plasma exchange in patients with alveolar hemorrhage and/or after kidney biopsy	Until circulating anti-GBM antibodies can no longer be detected; usually 14 days
Cyclophosphamide	• 2–3 mg/kg orally (reduce to 2 mg/kg in patients >55 years); experience with pulse intravenous cyclophosphamide is limited and efficacy is uncertain • Cyclophosphamide dosing should be reduced (or treatment interrupted) in cases of leukopenia • In patients not tolerating (or not responding to) cyclophosphamide, rituximab or mycophenolate mofetil may be tried but experience is limited and efficacy uncertain	3 months
Glucocorticoids	• Pulse methylprednisolone may be given initially up to 1000 mg/d on 3 consecutive days • Prednisone 1 mg/kg orally • Reduce to 20 mg/d by 6 weeks	6 months

Figure 99 | Treatment of anti-GBM disease. Adapted from *Journal of the American Society of Nephrology*, volume 10, issue 11, Kluth DC, Rees AJ. Anti-glomerular basement membrane disease, pages 2446–2453, Copyright ª 1999, with permission from the American Society of Nephrology.[946] Adapted from *Clinical Journal of the American Society of Nephrology*, volume 12, issue 7, McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease, pages 1162–1172, Copyright ª 2017, with permission from the American Society of Nephrology.[931] Adapted from Kaplan AA, Appel GB, Pusey CE, et al. Anti-GBM (Goodpasture) disease: treatment and prognosis. UpToDate: Evidence-based Clinical Decision Support. Available at: www.uptodate.com. Accessed September 7, 2021.[945]

Practice Point 11.2.6: In refractory anti-GBM disease, rit- uximab may be tried.

Refractory anti-GBM disease is rare (<10%).[952] Experience with rituximab in anti-GBM disease is limited to case reports, along with 2 small case series of 8 patients who incompletely responded to standard treatment and were successfully rescued with rituximab,[957] and 4 patients treated with dialysis primarily treated with rituximab instead of cyclophosphamide as first-line therapy for pulmonary remissionwith no effect on the kidney.[958] There are several case reports of patients with anti-GBM disease who were successfully treated with mycophenolate or MPA instead of cyclophosphamide.[959–962] Mycophenolate could be used instead of cyclophosphamide in patients who refuse cyclophosphamide or are intolerant of cyclophospha- mide because of its toxicity.

Imlifidase is an IgG-degrading endopeptidase from Strep- tococcus pyogenes (IdeS) that cleaves human IgG into F(ab)2 and Fc fragments, and inhibits antibody- and complement- dependent cytotoxicity. IdeS treatment immediately cleared anti-GBM antibodies from the circulation of 3 patients with anti-GBM disease who were treated with dialysis, but none of these patients recovered independent kidney function.[963] A clinical trial testing the utility and safety of IdeS in anti-GBM disease is currently underway (NCT03157037).

Immune adsorption removes anti-GBM antibody effec- tively. Among 10 patients with anti-GBM disease treated with immunoadsorption, dialysis dependency was successfully reversed in 3 out of 6 patients.[964]

Practice Point 11.2.7: Kidney transplantation in patients with kidney failure due to anti-GBM disease should be postponed until anti-GBM antibodies remain undetectable for ‡6 months.

Survival of patients with anti-GBM disease after kidney transplantation is comparable to that in patients with other causes of kidney failure.[965] Recurrence of anti-GBM disease may be as high as 50% after transplantation in patients who have detectable anti-GBM antibodies at the time of trans- plantation,[966] but it is very rare (<3%) in patients who have no antibodies.[948]

Anti-GBM antibodies form in 5%–10% of patients with Alport syndrome after kidney transplantation, but overt anti- GBM disease is less frequent. If clinical anti-GBM GN occurs, it often does so early and results in graft loss.[967]

Research recommendations

- Compare:
  - Rituximab to cyclophosphamide plus glucocorticoids and plasma exchange for induction of remission in anti- GBM disease
  - MMF to cyclophosphamide plus glucocorticoids and plasma exchange for induction of remission in anti- GBM disease
  - Immune adsorption to plasma exchange plus back- ground immunosuppression for induction of remission in anti-GBM disease

Methods for guideline development

Aim

This is an update of the KDIGO Clinical Practice Guideline for Glomerulonephritis published in 2012.[968] In November 2017, KDIGO held a Controversies Conference to determine whether there was sufficient new evidence to support updating any of the guideline recommendations. It was decided that a guideline update was required.[1,2]

The objective of this project was to update the evidence-based clinical practice guideline for the management of glomerular dis- eases. The guideline development methods are described below.

Overview of the process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3).[969] This guideline has been developed and reported in accordance with the AGREE II reporting checklist.[970] The processes undertaken for the development of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases are described below.

- Appointing Work Group members and the ERT
- Finalizing guideline development methodology
- Defining scope and topics of the guideline
- Formulating clinical questions—identifying the Population, Intervention, Comparator, Outcome, Methods (PICOM)
- Selecting topics for systematic evidence review and linking to existing Cochrane Kidney and Transplant systematic reviews
- Developing and implementing literature search strategies
- Selecting studies according to predefined inclusion criteria
- Data extraction and critical appraisal of the literature
- Evidence synthesis and meta-analysis
- Grading the quality of the evidence for each outcome across studies
- Grading the strength of the recommendation, based on the quality of the evidence and other considerations
- Convening a public review in June 2020
- Updating the guideline
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT. The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult and pediatric nephrology, pathology, epidemiology, and public health. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of adult and pediatric nephrologists, and methodologists with expertise in evidence synthesis and guideline development. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data extraction, critical appraisal, evidence synthesis and meta-analysis, grading the quality of the evidence per outcome, and grading the quality of the evidence for recommendations. The Work Group was responsible for writing the recommendations and practice points and underlying rationale, as well as grading the strength of each recommendation.

The KDIGO Co-Chairs, KDIGO Methods Chair, Work Group Co-Chairs, and the ERT had a 1-day meeting in Houston, Texas, USA in February 2018 to discuss the previous guideline and the findings from the KDIGO Controversies Conference on Glomeru- lonephritis,[1,2] and finalize the guideline development process. Guideline topics from the previous guideline and new guideline topics were linked with appropriate clinical questions to underpin the systematic evidence review. The draft guideline topics and review topics were finalized with feedback from the Work Group.

Defining scope and topics and formulating key clinical questions. The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline[968] and the KDIGO Controversies Conference on Glomerular Diseases.[1,2] Analytical frameworks were developed to present a visual representation of the clinical question and facilitate discussion about the scope of the guideline. The majority of clinical questions for this guideline were based upon RCTs to avoid bias by design. Clinical questions adhered to the PICOM format (a list of critical and important outcomes was compiled after voting from the Work Group [Table 1]). The Work Group and the ERT further refined the clinical questions to finalize the inclusion and exclusion criteria to guide literature searching and data extraction. Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accord- ingly. For clinical questions that did not map to any Cochrane Kidney and Transplant systematic reviews, *de novo* systematic re- views were undertaken. The previous guideline was reviewed to ensure all identified studies were included in the evidence review.[968] Details of the PICOM questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2[95,112,146,192,218,253,294,317,385,475,569,718]. All evidence reviews were conducted in accordance with the Cochrane Handbook,[971] and guideline development adhered to the standards of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).[972]

Table 1 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	All-cause mortality • Kidney failure (formerly known as ESKD) • $50% loss of GFR • Infection • Glucocorticoid-related adverse events • Malignancy
Important outcomes	Complete remission/relapse • Annual GFR loss (minimum 3 years follow-up)

ESKD, end-stage kidney disease; GFR, glomerular filtration rate.
The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes were rated 7–9, and important outcomes were rated 4–6 on the 9-point scale.

Table 2 | Clinical questions and systematic review topics in PICOM format

Guideline Chapter 1	General principles in the management of glomerular diseases
Clinical question	In patients with glomerular diseases, what are patient preferences and values for immunosuppressive and non- immunosuppressive therapy?
Population	Patients with glomerular disease
Factor of interest	Values and preferences for immunosuppressive or non-immunosuppressive therapy
Outcomes	Values and preferences
Study design	All study types
SoF tables	Supplementary Tables S65–S67
Guideline Chapter 2	**IgAN/IgAV**
Clinical question	In patients with biopsy-proven IgAN, what non-immunosuppressive agents, compared to no treatment or placebo, improve efficacy outcomes and reduce adverse effects?
Population	Patients with IgAN
Intervention	Fish oil, anticoagulants or antiplatelets, antioxidants, tonsillectomy, statins, traditional Chinese medicine, vitamin D, vitamin E, allopurinol, etc.
Comparator	No treatment or placebo
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Reid SM, *et al.* Non-immunosuppressive agents for treating IgA nephropathy (Review). *Cochrane Database of Systematic Reviews.* 2011:3;CD003962[95]
SoF tables	Supplementary Tables S4, S5, S7, and S87–S104
Clinical question	In patients with biopsy-proven IgAN, what immunosuppressive agents, compared to no treatment or placebo, improve efficacy outcomes and reduce adverse effects?
Population	Patients with IgAN
Intervention	Immunosuppressive therapy
Comparator	No treatment or placebo
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Natale P, *et al.* Immunosuppressive agents for treating IgA nephropathy (Review). *Cochrane Database of Systematic Reviews.* 2020:3;CD003965[112]
SoF tables	Supplementary Tables S6 and S68–S86
Clinical question	In patients with biopsy-proven IgAV (Henoch-Schönlein purpura nephritis), what immunosuppressive agents, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?
Population	Patients with IgAV (Henoch-Schönlein purpura nephritis)
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1 Additional outcomes—BMI
Study design	RCTs
Cochrane systematic review	Hahn D, *et al.* Interventions for preventing and treating kidney disease in Henoch-Schönlein purpura (HSP) (Review). *Cochrane Database of Systematic Reviews.* 2015:8;CD005128[146]
SoF tables	Supplementary Tables S8 and S105–S109
Guideline Chapter 3	**MN**
Clinical question	In adults with biopsy-proven MN and NS, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects?
Population	Adults with primary MN and NS
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Chen Y, *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome (Review). *Cochrane Database of Systematic Reviews.* 2014:10;CD004293[192]
SoF tables	Supplementary Tables S9–S13 and S110–S131
Guideline Chapter 4	**NS in children**
Clinical question	In children (3–18 years of age) with SSNS, what glucocorticoid therapy regimens, compared with no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?
Population	Children (3–18 years of age) with SSNS
Intervention	Glucocorticoid therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Hahn D, *et al.* Corticosteroid therapy for nephrotic syndrome in children (Review). *Cochrane Database of Systematic Reviews.* 2020:8;CD001533[218]
SoF tables	Supplementary Tables S14–S15 and S132–S147

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Table 2 | (Continued) Clinical questions and systematic review topics in PICOM format

Guideline Chapter 4	NS in children
Clinical question	In children (3–18 years of age) with SSNS, what non-glucocorticoid immunosuppressive regimens, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?
Population	Children (3–18 years of age) with SSNS
Intervention	Non-glucocorticoid immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Larkins NG, *et al.* Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children (Review). *Cochrane Database of Systematic Reviews.* 2020:4;CD002290[253]
SoF tables	Supplementary Tables S16–S20 and S148–S163
Clinical question	In children (3–18 years of age) with SRNS, what immunosuppressive therapy, compared to no treatment, placebo, or other immunosuppressive medication, improves efficacy outcomes and reduces adverse effects?
Population	Children (3–18 years of age) with SRNS
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies (including glucocorticoids)
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Liu ID, *et al.* Interventions for idiopathic steroid-resistant nephrotic syndrome in children (Review). *Cochrane Database of Systematic Reviews.* 2019:11; CD003594[294]
SoF tables	Supplementary Tables S21–S24 and S164–S173
Guideline Chapter 5	**MCD in adults**
Clinical question	In adults with biopsy-proven MCD and NS, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapy, improve efficacy outcomes and reduce adverse effects?
Population	Adults with biopsy-proven MCD and NS
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Palmer SC, *et al.* Interventions for minimal change disease in adults with nephrotic syndrome (Review). *Cochrane Database of Systematic Reviews.* 2008:1;CD001537[317]
SoF tables	Supplementary Tables S25–S27 and S174
Guideline Chapter 6	**FSGS in adults**
Clinical question	In adults with biopsy-proven FSGS, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapy, improve efficacy outcomes and reduce adverse effects?
Population	Adults with biopsy-proven FSGS
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Braun N, *et al.* Immunosuppressive treatment of focal segmental glomerulosclerosis in adults. *Cochrane Database of Systematic Reviews.* 2008:3;CD003233[385]
SoF tables	Supplementary Tables S28–S30 and S175–S181
Guideline Chapter 7	**Infection-related glomerulonephritis**
Clinical question	In adult patients with HBV- or HCV-related GN, what antiviral treatment therapy, compared to no treatment, placebo, or standard of care, improves efficacy outcomes and reduces adverse effects?
Population	Adults with HBV- or HCV-related GN
Intervention	Antiviral treatment therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S182–S184
Clinical question	In patients with HIV-associated nephropathy, what antiretroviral treatment, compared to no treatment, placebo, or standard of care, improves efficacy outcomes and reduces adverse effects?
Population	HIV-associated nephropathy
Intervention	Highly active antiretroviral therapy (HAART; alone or combined with antihypertensive agents, glucocorticoids, and immunosuppressive therapies)
Comparator	No treatment, placebo, or standard of care

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Table 2 | (Continued) Clinical questions and systematic review topics in PICOM format

Guideline Chapter 7	Infection-related glomerulonephritis
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Yahaya I, *et al.* Interventions for HIV-associated nephropathy (Review). *Cochrane Database of Systematic Reviews.* 2013:1;CD007183[475]
SoF tables	Supplementary Table S185
Guideline Chapter 8	**Immunoglobulin- and complement-mediated glomerular diseases with an MPGN pattern of injury**
Clinical question	In patients with complement-mediated disease, what immunosuppressive agents, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?
Population	Patients with C3-mediated GN, C3 DDD, CFHR5 nephropathy, C4-mediated GN, idiopathic
MPGN Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs and observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S186 and S187
Clinical question	In adults with proliferative GN (monoclonal immunoglobulin deposits [monoclonal immunoglobulin deposition disease], immunotactoid GN, fibrillary GN, cryoglobulinemia-related kidney disease), compared to no treatment, placebo, or standard of care, does immunosuppressive therapy improve clinically relevant outcomes and decrease harms?
Population	Adults with proliferative GN kidney with monoclonal immunoglobulin deposits (monoclonal immunoglobulin deposition disease), immunotactoid GN, fibrillary GN, cryoglobulinemia-related kidney disease,
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Mortality, kidney failure, complete kidney remission, hematologic response, adverse events
Study design	RCTs and observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S188 and S189
Guideline Chapter 9	**ANCA-associated vasculitis**
Clinical question	In adults with AAV, what immunosuppressive agents compared to no treatment, placebo, or other immunosuppressive therapies improve clinical efficacy outcomes and reduce adverse effects?
Population	Adults with AAV
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Walters *et al.* Interventions for renal vasculitis in adults (Review). *Cochrane Database of Systematic Reviews.* 2020:1;CD003232[569]
SoF tables	Supplementary Tables S31–S44 and S190–S200
Guideline Chapter 10	**Lupus nephritis**
Clinical question	In patients with biopsy-proven LN, compared to no treatment, placebo, or standard of care, does antimalarial therapy improve clinical efficacy outcomes and reduce adverse effects?
Population	Patients with biopsy-proven LN
Intervention	Antimalarial therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs and observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S45
Clinical question	In patients with nonproliferative (Class I, II, V, or VI) LN, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects?
Population	Patients with biopsy-proven nonproliferative (Class I, II, V, or VI) LN
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S203, S204, and S205

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Table 2 | (Continued) Clinical questions and systematic review topics in PICOM format

Guideline Chapter 10	Lupus nephritis
Clinical question	In patients with biopsy-proven proliferative (Class III, IV, III/V, or IV/V) LN, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects?
Population	Patients with biopsy-proven proliferative (Class III, IV, III/V, or IV/V) LN
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Tunnicliffe DJ, *et al.* Immunosuppressive treatment for proliferative lupus nephritis. *Cochrane Database of Systematic Reviews.* 2018:6;CD002922[718]
SoF tables	Supplementary Tables S46–S63, S201–S204, and S207–S218
Guideline Chapter 11	**Anti-GBM antibody GN**
Clinical question	In patients with biopsy-proven anti-GBM, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects?
Population	Patients with biopsy-proven anti-GBM
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S64

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BMI, body mass index; CFHR5, Complement factor-H–related protein 5; DDD, dense deposit disease; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, immunoglobin A nephropathy; IgAV, immunoglobin A vasculitis; LN, lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; PICOM, Population, Intervention, Comparator, Outcomes, Methods; RCT, randomized controlled trial; SoF, summary of findings; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

Literature searches and article selection. Searches for RCTs utilized the Cochrane Kidney and Transplant Registry of studies in October 2018 and supplemented until September 2019. An updated search was undertaken in June 2020. The Cochrane Kidney and Transplant Registry of studies is a database of RCTs in kidney disease that is maintained by information specialists. The database is populated by monthly searches of the Cochrane Central Register of Controlled Trials, weekly searches of MEDLINE OVID, yearly searches of Embase OVID, hand-searching of major kidney and transplant conference proceedings, searches of trial registries, including clinicaltrials.gov and the International Clinical Trials Register search portal.

For review topics that matched existing Cochrane Kidney and Transplant systematic reviews, an updated search for the review using the Cochrane Kidney and Transplant Registry of studies was conducted. The Cochrane Kidney and Transplant Registry of studies was searched for clinical questions that included only RCTs and were not linked to any existing Cochrane systematic review. For clinical questions that included other study types, for example, observational studies, the medical literature databases MEDLINE and Embase were searched. The search strategies are provided in Supplementary Appendix A: Supplementary Table S1.

The titles and abstracts resulting from the searches were screened by 2 members of the ERT who independently assessed retrieved abstracts, and if necessary, the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third member of the ERT.

A total of 25,925 citations were screened. Of these, 479 RCTs and 102 observational studies were included in the evidence review (Figure 100).

Data extraction. Data extraction was performed independently by 2 members of the ERT. Unclear data were clarified by contacting the author of the study report, and any relevant data obtained in this

manner were included. The ERT designed data extraction forms to capture data on study design, study participant characteristics, intervention and comparator characteristics, and critical and important outcomes. Any differences in extraction between mem- bers of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies. The majority of reviews undertaken were intervention reviews that included RCTs. For these reviews, the Cochrane Risk of Bias tool was used to assess individual study limitations based on the following items[973]:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately pre- vented during the study (detection bias)?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudica- tions resolved by consultation with a third review author.

Evidence synthesis and meta-analysis. Measures of treatment effect. Dichotomous outcome (all-cause mortality, kid- ney failure, $50% loss of GFR, infection, malignancy, complete remission/relapse) results were expressed as RR with 95% CI. When continuous scales of measurement were used to assess the effects of treatment, such as annual GFR loss, the mean difference (MD) with 95% CI was used. Data synthesis. Data were pooled using the

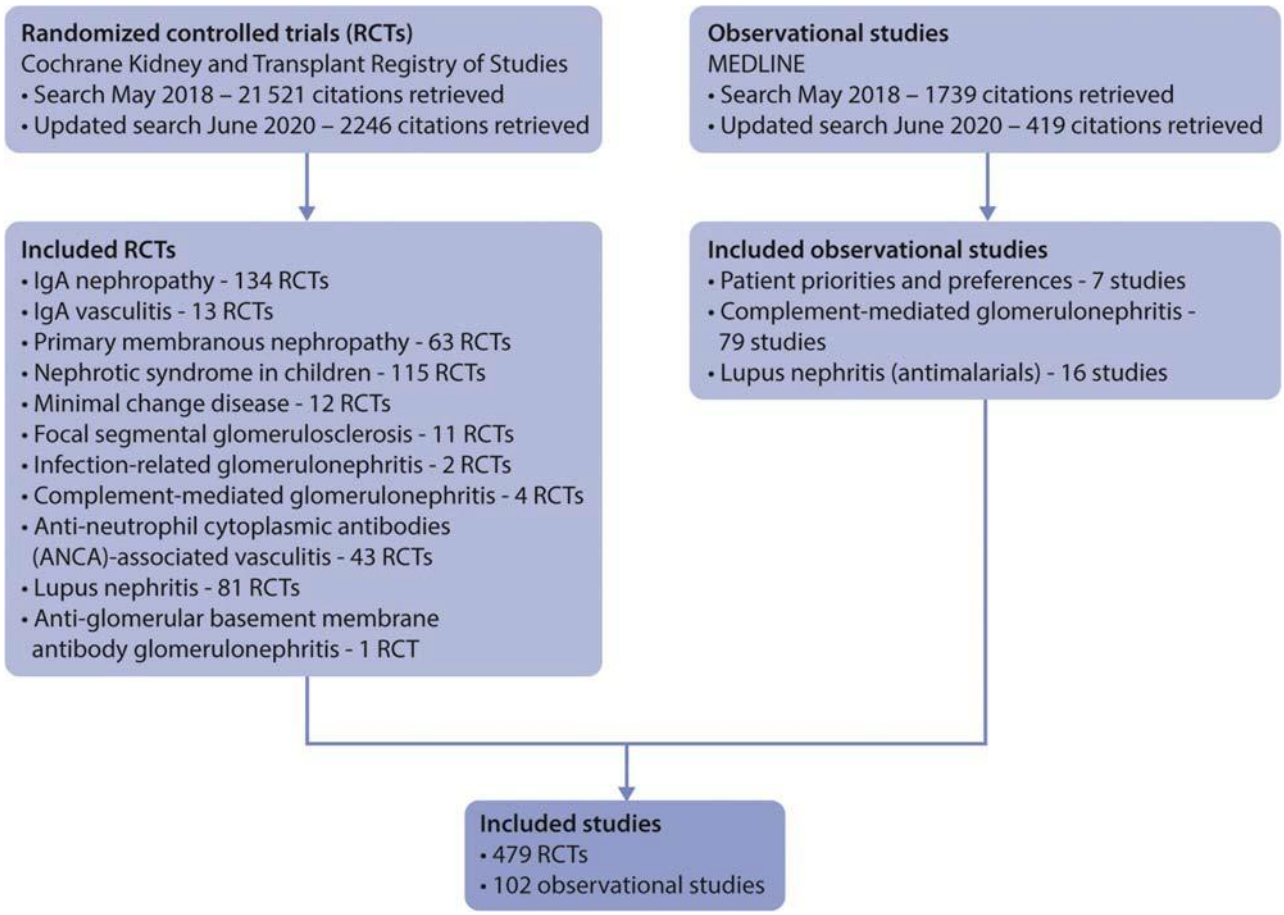


Figure 100 | Search yield and study flow diagram.

Mantel-Haenszel random-effects model for dichotomous outcomes and the inverse variance random-effects model for continuous out- comes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and un- known heterogeneity.[971]

Assessment of heterogeneity. Heterogeneity was assessed by vi- sual inspection of forest plots of standardized mean effect sizes, and of risk ratios, and by C^2 tests. A P value of <0.1 was used to denote statistical heterogeneity, and an I^2 was calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.[971] We used conventions of interpretation as defined by Higgins *et al.*[974]

Assessment of publication bias. We made every attempt to minimize publication bias by including unpublished studies (for example, by searching online trial registries). To assess publication bias, we used funnel plots of the log odds ratio (effect vs. standard error of the effect size) when a sufficient number of studies were available (i.e., >10 studies).[971] Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity. Subgroup analysis was undertaken to explore whether there were clinical dif- ferences among the studies that may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be interpreted with caution. The following subgroups were considered: baseline kidney

function (GFR, proteinuria, presence of albuminuria, presence of macroscopic hematuria), histopathologic class of disease, primary versus secondary forms of disease, sex, and adult versus pediatric. The test of subgroup differences used the I^2 statistic and a P value of 0.10 (noting that this is a weak test).[971]

Sensitivity analysis. The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis, taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies, to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted.

However, the available data were insufficient to determine the influence of these factors on the effect size of critical and important outcomes.

Grading the quality of the evidence and the strength of a guideline recommendation. *Grading the quality of the evidence for each outcome across studies.* The overall quality of the evidence related to each critical and important outcome was assessed using the GRADE approach,[972,975] which assesses the quality of the evidence for each outcome. For outcomes that are based on data from RCTs, the initial grade for the quality of the evidence is considered to be high. For observational studies, the initial quality of

Table 3 | Classification for quality and certainty of the evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect.

the evidence is low. The quality of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, and outcomes measured in trials and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, data were benchmarked against optimal information size, low event rates in either arm, CIs that indicate appreciable benefit and harm (25% decrease and 25% increase in the outcome of interest), and sparse data (only 1 study), all indicating concerns about the precision of the results.[9,72] The final grade for the quality of the evidence for an outcome could be high, moderate, low, or very low (Table 3). For observational studies and other study types, it is possible for the quality of the evidence to be upgraded from a rating of low quality, according to the specified criteria. For further details on the GRADE approach for rating quality of the evidence, see Table 4.

Summary of findings (SoF) tables. The SoF tables were developed to include a description of the population, intervention, and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the quality of evidence for each critical and important outcome is also provided in the SoF tables. The SoF tables were generated using MAGICapp, an online software application designed to support guideline development, and they are available in the Data Supplement: Appendix C and Appendix D (https://kdigo.org/guidelines/gd/).

Developing the recommendations. The recommendations were drafted by the Work Group Co-Chairs and Work Group members. Recommendations were revised in a multistep process during face-to-face meetings (Amsterdam, The Netherlands, August 2018 and Budapest, Hungary, June 2019) and by email communication. The final draft was sent for external public review, and reviewers provided open-ended responses. Based on the external stakeholder feedback, the draft was further revised by the Work Group. All Work Group members provided feedback on initial and final drafts of the guideline statements and text and approved the final version of the guideline. The ERT also provided a descriptive summary of the evidence quality in support of the recommendations.

Grading the strength of the recommendations. The strength of a recommendation is graded as strong or weak (Table 5). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall quality of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 6).

Balance of benefits and harms. The Work Group and ERT determined the anticipated net health benefit on the basis of ex- pected benefits and harms across all critical and important outcomes from the underlying evidence review.

Quality of evidence. The overall quality of the evidence was based on the certainty of the evidence for all critical and important out- comes, taking into account the relative importance of each outcome to the population of interest. The overall quality of the evidence was graded (A, B, C, or D—Table 3).

Patient values and preferences. No patients or caregivers were involved in the Work Group. The Work Group, from their experi- ence in managing patients with glomerular disease and their un- derstanding of the best available scientific literature, made judgments

Table 4 | GRADE system for grading quality of evidence

Study design	Starting grade for the quality of evidence	Step 2—Lower grade	Step 3—Raise grade for observational evidence

RCT	High	Study limitations: −1, serious −2, very serious	Strength of association þ1, large effect size (e.g., <0.5 or >2) þ2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: −1, serious −2, very serious	Evidence of a dose–response gradient
Observational	Low	Indirectness: −1, serious −2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: −1, serious −2, very serious	
		Publication bias: −1, serious −2, very serious	

RCT, randomized controlled trial; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Table 5 | KDIGO nomenclature and description for grading of recommendations

Grade	Implications		
	Patients	Clinicians	Policy
Level 1 'Strong' "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'Weak' "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Table 6 | Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low quality of the evidence will warrant a strong recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

on the values and preferences of patients. Formal qualitative evidence synthesis on patient priorities and preferences was undertaken, but there was limited evidence available to inform the formulation of guideline recommendations (Appendix D).

Resource use and costs. Healthcare and non-healthcare resources, including all inputs in the treatment management pathway,[976] were considered in grading the strength of a recommendation. The following resources were considered: direct healthcare costs; non-healthcare resources, such as transportation and social services; informal caregiver resources (e.g., time of family and caregivers); and changes in productivity. Economic evaluations, including cost-effectiveness analysis, were not conducted for any of the guideline topics.

Practice points

In addition to graded recommendations, KDIGO guidelines now include "practice points" to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they supplement recommendations for which a larger quantity of evidence was identified. These were used when no formal systematic evidence review was undertaken, or there was insufficient evidence to provide a graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they also may be based on limited evidence. For example, practice points were provided on monitoring, frequency of testing, dosing adjustments for the stage of CKD, and use of therapies in specific subgroup populations. Practice

points were sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Format for guideline recommendations

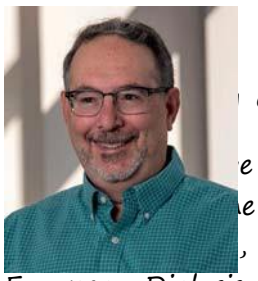
Each guideline recommendation provides an assessment of the strength of the recommendation (strong, level 1; or weak, level 2) and the quality of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Quality of evidence, Values and preferences, Resource use and costs, Considerations for implementation), and Rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale also may support a practice point.

Limitations of the guideline development process

The evidence review prioritized RCTs as the primary source of evi- dence. For a select number of clinical questions in this guideline, the ERT undertook a comprehensive evidence review beyond RCTs. However, these reviews were not exhaustive, as specialty or regional databases were not searched, and manual searching of journals was not performed for these reviews. In the development of these guidelines, no scoping exercise with patients, limited searches of the qualitative literature, or formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.

Biographic and disclosure information

Jürgen Floege, MD (Work Group Co-Chair), received his training at the Hannover Medical School, Hannover, Germany; the Albert Einstein College of Medicine, New York, NY, USA; and the University of Washington, Seattle, WA, USA. He was appointed as head of the Divi- sion of Nephrology and Immunology of Aachen, Aachen, Germany



e is a former executive council e International Society of , European Renal Association-European Dialysis and Transplant Associ- ation (ERA-EDTA), and KDIGO. He is a Distinguished Fellow of the ERA-EDTA and recipient of the 2018 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology, past-president of the German Society of Nephrology, as well as an honorary member of the Japanese, Polish, Portuguese, Serbian, and Slovakian Societies of Nephrology. Together with Professors Richard Johnson, Marcello Tonelli, and John Feehally, he edits the best-selling textbook *Comprehensive Clinical Nephrology*. He is associate editor of *Kidney International* and a member of the editorial board of *Journal of the American Society of Nephrology*, *Journal of Nephrology*, and other journals. Until 2017, he served as associate editor of *Nephrology Dialysis Transplantation*.

His research interests encompass progression of kidney disease, in particular kidney fibrosis, immune-mediated renal disease, in particular IgA nephropathy, as well as bone and mineral disorders (CKD-MBD) and cardiovascular disease in uremic patients.

His scientific work encompasses about 600 original papers, reviews, editorials, and 40 book chapters.

JF reports consultancy for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas, MorphoSys, Novo Nordisk, Omeros, and Travere (formerly Retrophin); and speaker bureau for Amgen and Fresenius-Vifor.

Brad H. Rovin, MD, FACP, FASN (Work Group Co-Chair), is the Lee A. Hebert Professor of Nephrology at The Ohio State University Wexner Medical Center, Columbus, OH, USA. He is the division director of nephrology and medical director of The Ohio State University Clinical Research Management Organization, Columbus, OH, USA. Dr. Rovin conducts translational research on autoimmune glomerular diseases and applies

these studies to clinical trial development and design for investigator-initiated and industry-sponsored trials of novel therapeutics.

BHR reports consultancy for AstraZeneca/MedImmune, Aurinia, Biogen Idec, Bristol Myers Squibb, Calliditas, Che- moCentryx, EMD Serono, Genentech/Hoffmann-La Roche, Omeros, Janssen, Lupus Foundation of America, MorphoSys, Novartis, Pfizer, RILITE Foundation, and Travere (formerly Retrophin); grant/research support from Lupus Clinical Investigators Network* and the National Institutes of Health**

**Monies paid to institution.*

Sharon G. Adler, MD, is Chief of Nephrology and Hypertension at Harbor-University of California Los Angeles (UCLA) Medical Center, Los Angeles, CA, USA, and a Professor of Medicine at the Geffen School of Medicine at UCLA, Los Angeles, CA, USA. Dr. Adler has made many contributions to our understanding of clinical and experimental diabetic kidney and glomerular diseases. She is a member of several active clinical consortia, including the Nephrotic Syndrome Study Network (NEPTUNE), Cure Glomerulonephropathy (CureGN), and the Kidney Research Network. With Karger Publishers, she founded a new journal to focus on the glomerulus, aptly called *Glomerular Diseases*, which is expected to launch in the first half of 2021. She has authored more than 100 publica- tions in peer-reviewed journals and over 50 chapters, reviews, and editorials.

SGAreports consultancy for Bayer and MorphoSys; and grants/research support from Bayer, Bristol Myers Squibb*, Omeros*, NIDDK (REBOOT), and Travere (formerly Retrophin).*

**Monies paid to institution.*

Jonathan Barratt, MBChB, PhD, is the Mayer Professor of Renal Medi- cine, Department of Cardiovascular Sciences at the University of Leicester, Leicesiter, UK. He leads the Renal Research Group within the College of Life Sciences, Uni- versity of Leicester. His research is focused on a bench-to-bedside

oroving our understanding of esis of IgA nephropathy, a cause of kidney failure. Dr. Nephropathy Rare

Disease Group lead for the United Kingdom (UK) National Registry of Rare Kidney Diseases (RaDaR), and a member of the steering committee for the International IgA Nephropathy Network. He works closely with pharmaceutical companies interested in new treatments for IgA nephrop- athy and is the chief investigator for several international randomized controlled Phase 2 and 3 clinical trials in IgA nephropathy. He was a Work Group member of the Food and Drug Administration (FDA) and American Society of Nephrology (ASN) Kidney Health Initiative "Identifying Surrogate Endpoints for Clinical Trials in IgA Nephropathy."

JB reports serving on Study Steering Committees for Alnylam, Calliditas, Chinook, Novartis, Omeros, and Travere (formerly Retrophin); consultancy for Alnylam, Argenx, Astellas, Bio- Cryst, Calliditas, Chinook, Dimerix, Galápagos, Novartis, Omeros, Syncona, Takeda, Travere (formerly Retrophin), UCB, Vera Therapeutics, and Visterra; grant/research sup- port for basic science work for 6 companies under confiden- tiality agreements; and he is named in a patent to be submitted by Calliditas, based on analysis of exploratory data generated from the NEFECON trial, conducted at the University of Leicester.*
**Monies paid to institution.*

Kelly A. Burdge, MD, received her BA in Art History and Chemistry from Northwestern University, Evanston, IL, USA. She completed her medical degree in 1999 at the Wright State University Boonshoft School of Medicine, Dayton, OH, USA. She trained in internal medicine and pediatrics and completed a fellowship in adult nephrology at The Ohio State University, Columbus, OH, USA.

Dr. Burdge has held clinical associate professorships at the University of South Dakota, Vermillion, SD, USA and Tufts University School of Medicine, Boston, MA, USA. She currently practices general nephrology in Boston, MA, USA in private practice as part of the Mass General Brigham-Salem Hospital. She is passionate about patient care, efficiency, and reducing waste in medicine. In addition to her interest in clinical nephrology and patient management, Dr. Burdge is a participant in the Chronic Kidney Disease Outcomes and Practice Patterns (CKDopps) Trial. She is a fellow of the ASN, a member of the National Kidney Foundation (NKF), and a member of Women in Nephrology.

KAB declared no competing interests.

Frank Bridoux, MD, PhD, is pro- fessor of nephrology and head of the Nephrology, Dialysis and Renal Transplantation Department at Poit- iers University Hospital, Poitiers, France. After completing his nephrology residency at Lille Uni- versity, Lille, France in 1999, he was a clinical assistant and senior consultant at the Poitiers University Hospital. He completed his PhD thesis in immunology at the French National Centre for Scientific Research (CNRS) Unit 7276 in Limoges, France, in 2003.

Dr. Bridoux's main area of work is clinical nephrology. His research interests are mostly focused on the patho- physiology and treatment of monoclonal immunoglobulin- associated kidney disorders, covering basic research on experimental animal models and clinical studies, including randomized controlled trials. Dr.

Bridoux has co-authored more than 170 peer-reviewed publications and several book chapters. He is one of the co-founders and a past president of the International Kidney and Monoclonal Gammopathy Research Group, and the current associate coordinator of amyloid light-chain (AL) amyloidosis and other disorders associated with monoclonal immunoglob- ulin deposits at the CNRS.

FB reports consultancy for AstraZeneca, Baxter, and Pro-
thena; grants/research support from Amgen; and speaker bureaus for Amgen, AstraZeneca, Celgene, and Janssen.

Tak Mao Chan, MBBS, MD, DSc, FHKCP, FHKAM, MD, FRCP, FASN, obtained his MBBS, MD, and DSc from the University of Hong Kong (HKU), Hong Kong, China. He became Personal Chair Professor at HKU in 2005, Yu Pro- fessor in Nephrology in 2008, and Yu Chiu Kwong Professor in Medicine in 2011. Dr. Chan has been chief of nephrology since 2010. He has served as associate dean, senate member, and Uni- versity Selection & Promotion Committee member at HKU, president of the Asian Pacific Society of Nephrology (APSN), and council member of the ISN. Since 2016, he has served as vice-president and chairman of the Education and Accredi- tation Committee of the Hong Kong College of Physicians, Hong Kong, China.

Dr. Chan's research focuses on lupus nephritis and viral hepatitis in patients with kidney diseases. His work has helped establish mycophenolate as the standard-of-care for lupus nephritis and preventive antiviral therapy for hepatitis B in kidney transplant recipients, contributing to significant im- provements in clinical management and patient outcomes. Translational studies from his laboratory have increased the understanding of pathogenic mechanisms in kidney inflam- mation and fibrosis. Dr. Chan's publications have appeared in the *New England Journal of Medicine, Kidney International, Journal of the American Society of Nephrology, Arthritis & Rheumatology, Nature Reviews of Nephrology, Hepatology,* and *UpToDate.* He received the Asian-Pacific Society of

Nephrology (APSN) Kenzo Oshima Award in 2014. He is also the author of the chapter on "The Far East" in *Brenner and Rector's The Kidney*, 11th Edition.

TMC reports consultancy for Novartis; and grant/research support from Astellas, AstraZeneca, and Baxter.

H. Terence Cook, MBBS, MRCP, MRCPath, FRCPath, FMedSci, is a professor of renal pathology at Imperial College, London, UK, and a consultant renal pathologist at Hammersmith Hospital, London, UK. He qualified at St Mary's Hospital Medical School, London, UK in 1980 and became a lecturer in Experimental Pathology in 1983. Since then, he has pursued research in experimental glomerulonephritis and human glomerular disease at Imperial College, London, UK. He has major interests in the role of complement activation in glomerular disease and in how histologic features in human kidney biopsies can be used to predict outcomes and responses to treatment. He has organized international collaborative studies to develop consensus classifications of lupus glomerulonephritis, IgA nephropathy, and C3 glomerulopathy. He is a past president of the Renal Pathology Society. He has over 370 peer-reviewed publications.

HTC reports consultancy for Alexion, Apellis, Aurinia, and Novartis; grant/research support from Achillion and Ra Pharmaceuticals*; and speaker bureau for Alexion.*

**Monies paid to institution.*

Fernando C. Fervenza, MD, PhD, is a professor of medicine at the Mayo Graduate School of Medicine, Rochester, MN, USA. He received his medical degree at the Pontificia Universidade Catolica do Rio Grande do Sul, Porto Alegre, Brazil. Dr. Fervenza underwent his clinical nephrology and research training at Oxford University, Oxford, UK, and the Oxford Renal Unit from 1985 to 1991. Subsequent training included a post-doctoral fellowship at Stanford University, Stanford, CA, USA (1993–1997). Dr. Fervenza is a fellow of the ASN and the American College of Physicians, a past member of the American Board of Internal Medicine nephrology section, and an *UpToDate* section editor for glomerular disease. His area of interest is pursuing patient-oriented research projects aiming to bring new bench research discoveries to the bedside treatment of patients with glomerular diseases.

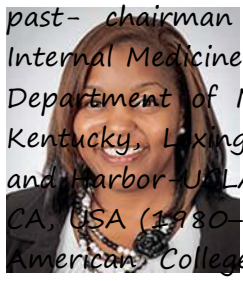
FCF reports serving as a board member of UpToDate—Associate Editor; consultancy for Alexion, Alnylam, BioCryst, and Takeda; grant/research support from Achillion, Gen-entech, Janssen, MorphoSys, and Travere (formerly Retrophin).

Keisha L. Gibson, MD, MPH, received her medical degree and Master of Public Health degree in epidemiology from the University of North Carolina (UNC) Chapel Hill, NC, USA. She completed a residency in general pediatrics at the Medical University of South Carolina, Charleston, SC, USA and a clinical fellowship in pediatric nephrology from UNC Chapel Hill. She is currently an associate professor of medicine and pe- diatrics, the chief of pediatric nephrology in the Division of Nephrology and Hypertension, and the Vice-Chair of Di- versity and Inclusion for the Department of Medicine at UNC Chapel Hill.

Dr. Gibson's research and clinical interests focus on lupus nephritis and other glomerular diseases. In the area of epide- miology, she is interested in ethnic and socioeconomic disparities and their effect on patient outcomes. She has been involved as a co-investigator with large consortium studies such as the Nephrotic Syndrome Network Study (NEPTUNE Study) and the Cure Glomerulonephropathy Network (CureGN Study).

KLG reports serving as an advisory board member for Reata and Travere (formerly Retrophin); and consultancy for Aurinia.

Richard J. Glassock, MD, MACP, graduated from the UCLA School of Medicine, Los Angeles, CA, USA, in 1960 and received post-graduate training at UCLA, Los Angeles, CA, USA; Harvard University, Cambridge, MA, USA; and the Scripps Research Institute, La Jolla, CA, USA.



His main interests are in glomerular disease and clinical nephrology. He has published over 750 original papers, books, book chapters, and reviews. He is the past-president of the ASN and the NKF (USA), and past- chairman of the American Board of Internal Medicine. He is the former chair of the Department of Medicine at the University of Kentucky, Lexington, KY, USA (1992–1999) and Harbor-UCLA Medical Center, Los Angeles, CA, USA (1980–1992). He is a Master of The American College of Physicians, Philadelphia, PA, USA and a fellow of The Royal College of Physicians, London, UK.

Dr. Glassock was the founding editor-in-chief of the *Nephrology Self-Assessment Program (NephSAP) Journal of the American Society of Nephrology* (2002). He is an editor of the nephrology section of *UpToDate*, an associate editor of the *American Journal of Nephrology*, and a founding moderatorof the ASN Communities website. He received the David Hume Me- morial Award of the NKF, the Robert Narins Award of the ASN, and Distinguished Achievement Awards from UCLA and the Association of Professors of Medicine. He is currently Professor Emeritus at the David Geffen School of Medicine at UCLA, Los Angeles, CA, USA and an independent medical consultant.

RJG reports consultancy for Apellis, Aurinia, BioCryst, Bristol Myers Squibb, Calliditas, ChemoCentryx, Equillium Bio, Horizon, Ionis, Natera (Renasight), Novartis, Omeros, Tra- vere (formerly Retrophin), and Walden Biosciences; providing expert testimony for legal firms in the USA; speaker bureau for Aurinia; providing manuscript preparation for Neph- SAP—Associate Editor, Karger, and Wolters Kluwer (UpTo- Date); owning stock/stock options in

ceiving travel expenses from ic centers in the USA, Europe, th America.

David R.W. Jayne, MD, FMedSci, is a professor of clinical autoimmunity at the University of Cambridge, Cambridge, UK, and director of the Vasculitis and Lupus Service at Addenbrooke's Hospital, Cambridge, UK. He trained at the Universities of Cambridge and London, Cam- bridge and London, UK, and in nephrology at Harvard Medical School, Boston, MA, USA. Dr. Jayne was a research fellow at Imperial College, London, UK and the University of Cambridge and was appointed as a senior lecturer in Nephrology at St George's Hospital, London, UK. He is a co-founder and the current president of the European Vasculitis Society, and his research focus has been ANCA vasculitis, having led a sequence of international randomized controlled trials over the past 25 years. His research group conducted the first studies on disease trials of newer immu- nosuppressives and biologics in vasculitis and lupus. He has published over 400 peer-reviewed papers and has contributed to numerous guideline statements. The clinical service in Cambridge cares for over 2000 patients with complex multi- system autoimmunity and receives tertiary referrals from throughout the UK and beyond.

DRWJ reports consultancy for AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, ChemoCentryx, Chugai, CSL Behring, GlaxoSmithKline (GSK), InflaRx, Janssen, Novar- tis, Roche/Genentech, Takeda and Vifor; serving in the speaker bureau for Vifor; and grant/research support from GSK, Medical Research Council*, National Institute for Health Research*, and Roche/Genentech*.*
**Monies paid to institution.*

Vivekanand Jha, MD, DM, FRCP, FAMS, is the executive director at the George Institute for Global Health, New Delhi, India, chair of Global Kidney Health at Imperial College, London, UK, and the current presi- dent of the ISN. Dr. Jha's research is focused on finding locally appro- priate treatment and implementation strategies for patients with kidney diseases in low-resource

settings through observational, intervention, and health systems research using innovative methodologies. He also has a translational program focused on finding markers of kidney disease assessment, risk stratification, progression, and complications. He has led a number of clinical trials in membranous nephropathy, FSGS, and IgA nephropathy. He has served as a Work Group member on prior KDIGO guidelines, including the Glomerulonephritis; Care of Kid- ney Transplant Recipients; and Prevention, Diagnosis, Eval- uation, and Treatment of Hepatitis C in CKD. He has also participated in several KDIGO Controversies Conferences. Dr. Jha is an expert in the effect of tropical ecology on kidney diseases and the impact of infections on patients with kidney diseases. He has published over 300 papers and about 50 textbook chapters.

VJ reports consultancy for NephroPlus; grants/research support from Baxter Healthcare*, Biocon*, and GSK*; and speaker bureaus for AstraZeneca* and Baxter Healthcare*.*

**Monies paid to institution.*

Adrian Liew, MD, MBBS, MRCP, FAMS, FASN, FRCP, MClinEpid, is a senior consultant nephrologist and director of The Kidney & Transplant Practice at Mount Elizabeth Novena Hospital in Singapore. He received his medical degree from the Na- tional University of Singapore, Singapore. Dr. Liew is an elected member of the executive committee and council of the ISN and an elected executive and honorary secretary of the International Society for Peritoneal Dialysis (ISPD). He chairs the ISN Oceania-Southeast Asia Regional Board, the ISN End-Stage Kidney Disease Strategy Dialysis Subgroup, and the ISN Renal Disaster Preparedness Working Group. He is a member of the ISN Dialysis Working Group, the ISN Continuing Medical Education (CME) Committee, and the Asia-Pacific Society of Nephrology CME Com- mittee. He received the John Maher Award from the ISPD in 2020 for his contribution to peritoneal dialysis research. Dr. Liew is also an associate editor for the journal *Nephrology* and serves on the editorial board for *Kidney International*. His research interests include glomerular diseases, peritoneal dialysis, and diabetic kidney disease. He sits on the steering committees and is the national leader for several multicenter clinical trials. Dr. Liew chairs the Southeast Asia Glomerulonephritis Network and the Southeast Asia Peritoneal Dialysis Network. He is the co-principal investigator for the PROMiSE study, a clinical registry for peritoneal dialysis across 8 countries in Southeast Asia.

AL reports consultancy for Alnylam, AstraZeneca, DaVita, and George Clinical; and speaker bureau for AstraZeneca and Baxter Healthcare.

Zhi-Hong Liu, MD, is a professor of medicine and academician at the Chinese Academy of Engineering, Beijing, China, a director at the Na- tional Clinical Research Center of Kidney Disease, Jinling Hospital, Nanjing, China, and dean of the Zhejiang University School of Medi- cine, Hangzhou, China. Dr. Liu is the past-president of the Chinese Society of Nephrology. She was an executive committee member of the ISN and KDIGO. She is the editor-in-chief of *Kidney Diseases*, *Chinese Journal of Nephrology*, and *Dialysis & Transplantation*.

Dr. Liu has devoted herself to patient care, research, and medical education. Her primary interest is in the field of kidney disease, with a special interest in glomerulone- phritis, diabetic nephropathy, and kidney replacement therapy. She has published 650 articles, edited 5 books on kidney disease, and contributed chapters to textbooks on nephrology. She is the chief scientist of the National Basic Research Program of China (973 Program) and was hon- ored with the National Science and Technology Progress Award of China.

Z-HL declared no competing interests.

Juan Manuel Mejía-Vilet, MD, PhD, is a consultant nephrologist at Insti- tuto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, a clinical researcher for the Mexican National Research Sys- tem, Mexico City, Mexico, and a professor of medicine for the Na- tional University of Mexico, Mexico City, Mexico, Panamerican University, Mexico City, Mexico, and the Monterrey Institute of Technology and Higher Edu- cation, Monterrey, Mexico.

Dr. Mejia-Vilet received his medical degree from the University of San Luis Potosi, San Luis Potosi, Mexico. He was trained in internal medicine and nephrology at the National University of Mexico and completed an ISN Glomerular Diseases fellowship at The Ohio State University, Columbus, OH, USA. He received a Master of Medical Science and a PhD degree from the National University of Mexico for his study of lupus nephritis pathophysiology and biomarker development.

His primary research area is centered on non-invasive biomarkers and prognosis of glomerular diseases, espe- cially lupus nephritis and ANCA vasculitis. He currently follows a local lupus nephritis cohort comprising more than 700 subjects, the local glomerular diseases registry, and actively participates in clinical trials in these areas.

JMMV declared no competing interests.

Carla M. Nester, MD, MSA, FASN, is the Jean Robillard Professor of Pedi- atric Nephrology and the Division Director of Pediatric Nephrology, Dialysis and Transplantation at the Stead Family Children's Hospital, University of Iowa, Iowa City, IA, USA. She is the associate director of the Molecular Otolaryngology and Renal Research Laboratory (MORL), the largest combined clinical and research laboratory in North America with a focus on complement biology.

Dr. Nester is a National Institutes of Health–funded, tenured faculty member with a translational research pro- gram focusing on rare, complement-mediated kidney dis- eases. She is the primary clinical investigator for the C3 Glomerulopathy Natural History Study, the largest cohort of rare C3G patients in North America. As a result of the latter, she is an advisor to KidNeeds, a global C3G family commu- nity. Finally, Dr. Nester is a clinical trialist; her clinical practice has become a hub for bringing a new generation of anti-complement therapeutics to a rare disease population.

Dr. Nester's background in complement biology, com- bined with her unique training as an adult and pediatric glomerular disease clinician, facilitates her role as a highly sought-after speaker and educator in the area of complement biology and kidney disease.

CMN reports being on advisory boards for Achillion, Alexion, BioCryst, Novartis, and Pfizer; grant/research support from Achillion, Alexion, BioCryst, Novartis, and Travere (formerly Retrophin); and receiving author royalties from UpToDate.

Jai Radhakrishnan, MD, MS, MRCP, FACC, FASN, is a professor of medicine at Columbia University Medical Center, New York, NY, USA, and the clinical director of the nephrology division at New York- Presbyterian Hospital, New York, NY, USA. After completing his initial medical training in India and the , he completed his nephrology neral Hospital in Boston, MA, ia University Medical Center in New York, NY, USA. He completed his master's degree in biostatistics from the Mailman School of Public Health, Columbia University, New York, NY, USA.

His clinical and research interests are in glomerular diseases. He is an associate editor of *Kidney International* and founding editor/editor-in-chief of *Kidney International Reports*. As a clinician–educator, Dr. Radhakrishnan has served on educa- tional committees with the ASN and the ISN, and is a global education ambassador for the ISN. He has lectured extensively both nationally and internationally.

JR reports being an advisory board member for Reata; con- sultancy for Aurinia, Equillium Bio, Novartis, Reata, and Travere; and grant/research support from Travere.

Elizabeth M. Rave, MD, completed her undergraduate degree in chemi- cal engineering at the University of Toledo, Toledo, OH, USA, and worked in industry for several years before going to medical school. Dr. Rave attended medical school at the University of Toledo Medical School (formerly Medical College of Ohio, MCO) and completed both her internal medicine residency and nephrology fellowship training at The Ohio State Uni- versity, Columbus, OH, USA.

Dr. Rave has been busy as a private practice nephrologist since graduation from fellowship but also enjoys teaching students and residents who are in community-based training at several local hospitals in Columbus, Ohio. In addition to clinical responsibilities, she is heavily involved with patient care improvement through several hospital committees, including the OhioHealth Clinical Guidance Council, and serves as the Section Chair of Nephrology at Riverside Methodist Hospital. She has been a co-investigator in the Simplicity III and Reduce Hypertension trials (with OhioHealth), as well as the Reata Bardoxolone Study. She is on the Information Technology board for DaVita. She has been a board member for the Co- lumbus chapter of the NKF since 2015 and was recently honored as the NKF Medical Advisor Board member of the year for 2019. She is currently serving as the president of Ohio Kidney Consultants.

EMR reports being a board member for Davita.

Heather N. Reich, MD, CM, PhD, FRCPC, is a graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada. She completed her post-graduate clinical training and PhD at the University of Toronto, Toronto, Ontario, Canada, where she is an associate professor and holds the Gabor Zellerman Chair in Nephrology Research. She works as a nephrologist- scientist at the University Health Network (UHN) and is passionate about improving the clinical care and outcomes of patients with glomerulonephritis.

Dr. Reich directs the glomerulonephritis program at Toronto General Hospital, Toronto, Ontario, Canada. This rich program spans clinical care of patients with glomer- ulonephritis, contribution to clinical trials, and trans- lational research. Her research program objective is to identify clinical and molecular markers of progressive

glomerular diseases and to identify and evaluate novel therapeutic targets to improve outcomes of patients with glomerulonephritis. She has contributed to over 95 publi- cations, and her work has been consistently supported by peer-reviewed awards from agencies including the Kidney Foundation of Canada and the Canadian Institutes of Health Research. She enjoys training future leaders in glomerulonephritis care and research, and she was the co- director of the annual educational pre-course in glomeru- lonephritis for the ASN.

HNR reports consultancy for Calliditas, Omeros, Pfizer, Retrophin; and the UHN GN Fellowship is supported by the Louise Fast Foundation; conducting clinical trials for Alnylam, Calliditas, ChemoCentryx, Omeros, and Pfizer; and speaker fees from Gilead Pharmaceuticals and Omeros.

Pierre Ronco, MD, PhD, is an Emeritus Professor of Nephrology at Sorbonne Université, Paris, France. He received his PhD in immunology from University Paris 7, Paris, France, and his MD from the Medi- cal Faculty Saint-Antoine, Sorbonne Université, Paris, France. He has devoted most of his career to the care of patients with glomerular disease and identification of relevant mechanisms as head of the renal division (1995– 2018) and director of the INSERM Kidney Research Unit (1998–2018) at the Tenon Hospital in Paris, France.

Dr. Ronco's major contributions to clinical science, renal immunopathology, and rare kidney diseases resulted in over 500 research publications, including in the *New En- gland Journal of Medicine, Lancet, Science, Journal of Experimental Medicine, Journal of Cell Biology,* and other major journals of nephrology, as well as 30 textbook chapters.

He served as president of the Francophone Society of Nephrology and the 49th ERA-EDTA Congress in Paris (2012). He chaired or co-chaired the Scientific Programme Committee of 4 World Congresses of Nephrology (Madrid, Milan, Cape Town, Mexico City). He is currently serving as the editor-in-chief of *Kidney International,* a position he has held since January 1, 2018.

He has been awarded international prizes and honors, including the Jean Hamburger Award (ISN) and the prize for outstanding basic research (ERA-EDTA). He is Doctor Honoris Causa of the Louvain Catholic University and a member of the Academia Europeae, the French Academy of Medicine, the Royal Academy of Medicine (Belgium), and the Institut Universitaire de France.

PR reports consultancy for Alexion, Amicus, Idorsia, and MorphoSys; grant/research support [illegible]nd

Amgen; providing manuscript preparation for UpToDate; receiving travel expenses from the ASN, the French Society of Nephrology, and Sanofi-Genzyme.*
**Monies paid to institution.*

Jan-Stephan F. Sanders, MD, PhD, is a nephrologist and the program director of the Kidney and Pancreas Transplantation Program at the University Medical Center Gronin- gen (UMCG), Groningen, The Netherlands. Dr. Sanders received his MD degree in 2002 at the Uni- versity of Groningen. He did a research fellowship at Hammersmith Hospital, Imperial College London, UK. Thereafter, Dr. Sanders trained in internal medicine and nephrology at Medical Center Leeu- warden, Leeuwarden, The Netherlands, and at University Medical Center Groningen (UMCG). He combined this with a PhD trajectory, which he completed in 2009 with his thesis "Disease-activity in ANCA-associated Vasculitis." Since September 2010, he has been a staff member at the division of nephrology at UMCG, focusing on kidney transplantation and ANCA-vasculitis. Since October 2019, he has served as the program director of the Kidney and Pancreas Trans- plantation Program at UMCG. His primary research in- terests are ANCA vasculitis and kidney transplantation. He has received research grants from the Dutch Kidney Society and the Netherlands Organisation for Health Research and Development.

J-SFS reports grant/research support from Chiesi, Dutch Kidney Society, The Netherlands Organisation for Health Research and Development, and Novartis.

Sanjeev Sethi, MD, PhD, graduated from Assam Medical College, Dibrugarh, India. He pursued grad- uate studies thereafter at Albany Medical College, Albany, NY, USA, and received his PhD in experimental pathology in 1995. Subsequently, Dr. Sethi completed his pathology resi- dency at Yale University, New Haven, CT, USA (1995–1999) and his fellowship in renal pathology at Brigham and Women's Hospital, Harvard University, Boston, MA, USA (1999–2001). He is currently a professor at the Mayo Clinic, Rochester, MN, USA. His primary interests and research are in glomerulonephritis, with a focus on the management approach to glomerulonephritis, the role of monoclonal gammopathy in glomerulonephritis, and the role of alternative pathways of complement in glomerulonephritis, as well as the application of proteomics in renal pathology. New diseases have been identified using this novel approach. These studies have resulted in over 225 peer-reviewed publications.

SS reports consultancy for Novartis.

Yusuke Suzuki, MD, PhD, is currently a professor of nephrology at the Juntendo University Faculty of Medicine and Graduate School of Juntendo University, Tokyo, Japan. His academic positions include director of Japanese Society of Nephrology (JSN), councilor of the Japanese Society of Internal Medicine, Japanese Society of Dialysis Therapy, Japanese Society of Hypertension, and the ISN council, deputy chair of the ISN North and East Asia Regional Board, sub-chief (2011–2016) and chief (2017–present) researcher of the Special Research Group of IgA Nephropathy in Progressive Renal Diseases Research from the Ministry of Health, Labor and Welfare of Japan. Dr. Suzuki is also the chief researcher of a biomarker project on IgA nephropathy from Research on Intractable Disease from the Japan Agency for Medical Research and Development. His research mainly focused on the pathogenesis of IgA nephropathy. He has more than 160 English publications in peer-reviewed journals, including *Kidney International, Journal of the American Society of Nephrology, Journal of Clinical Investigation, JAMA Internal Medicine, JAMA Network,* and *Natural Medicine Journal.* He is now an editorial board member for *Kidney International, Nephrology,* and the *American Journal of Kidney Diseases.*

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Sydney C.W. Tang, MD, PhD, FRCP, FACP, FHKCP, FHKAM, is Chair of Renal Medicine and Yu Professor in Nephrology at the University of Hong Kong, Hong Kong, China and an honorary consultant physician at Queen Mary Hospital, Hong Kong. He trained in internal medicine and nephrology and has been a research fellow at King's College London, London, UK, and the University of Washington, Seattle, WA, USA. As a clinician–scientist, his research interests are in the pathogenesis of diabetic and chronic kidney disease and the treatment of IgA nephropathy. He has published over 270 scientific papers and contributed over 30 book chapters, including one on diabetic kidney disease (DKD) in *Comprehensive Clinical Nephrology*. He is currently editor-in-chief of *Nephrology (Carlton)*, theme editor (DKD) of *Nephrology Dialysis Transplantation*, associate editor of *Glomerular Diseases*, and on the editorial boards of *Kidney International*, *Clinical Journal of the American Society of Nephrology*, *Seminars in Nephrology*, *American Journal of Nephrology*, and *Kidney Diseases*. He is president- elect (2019–2022) of the Asian Pacific Society of Nephrology, a member of the KDIGO Executive Com- mittee (from 2020), deputy chair (from 2018) of the CME Advisory Committee of the ISN, an International Honorary Member of the Japanese Society of Nephrology, and past- chairman (2016–2018) of the Hong Kong Society of Nephrology.

SCWT reports consultancy for Novartis and Travere (formerly Retrophin); grants/research support from Sanofi; and speaker bureau for AstraZeneca.

Vladimír Tesar, MD, PhD, FERA, FASN, is head of the Department of Nephrology, 1st Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic. He is a member of the Executive Committee of the ISN, former chair of the Immunoneph- rology Working Group of ERA-EDTA, and the former member of the council of ERA- EDTA. He is a member of the editorial board of the *Clinical Journal of the American Society of Nephrology*; *Nephrology Dialysis Transplantation*; and *Journal of Nephrology*, and former editor-in-chief of *Kidney and Blood Pressure Research*. His main interests are glomerular disease, inherited diseases of the kidney, and cardiovascular complications of chronic kidney disease. He participated in many genetic and biomarker studies in glomerular diseases and on the steering committees of many randomized, controlled (including investigator-initiated) clinical trials. He has co-authored more

than 400 papers in international journals, mostly dedicated to glomerular disease.

VT reports consultancy for Abbvie, Amgen, Baxter, Bayer, Boehringer Ingelheim, Calliditas, ChemoCentryx, and Fre- senius Medical Care, Omeros, and Travere; speaker bureaus for Bayer and Boehringer Ingelheim; and receiving travel expenses for AbbVie.

Marina Vivarelli, MD, trained in pediatrics at the University of Pavia, Pavia, Italy, is working in pediatric rheumatology in Dr. Fabrizio De Benedetti's lab, on the pathogenesis of juvenile idiopathic arthritis. She completed a 2-year research fellow- ship at Children's Hospital, Boston, MA, USA with Professor Raif Geha, studying a mouse deficient in RIP, a protein that is pivotal in B cell response to toll-like receptor 4.

Since 2006, in the Division of Nephrology of the Bambino Gesù Pediatric Hospital in Rome, Italy, she has worked to establish a new front of translational research in pediatric immune-mediated kidney diseases. Her focus has been on nephrotic syndrome, and her expertise in B cell biology has led her to address the question of why B cell–depleting therapy is effective in some forms of this disease.

She has designed and conducted a phase 1 trial on the use of mesenchymal stem cells in difficult forms of nephrotic syndrome and has also contributed to the design and conduct of trials evaluating the use of belimumab and comparing rituximab and mycophenolate mofetil in pediatric nephrotic syndrome.

She treated the first patient with dense deposit disease (DDD) with eculizumab and has participated in trials eval- uating complement inhibitors for children with aHUS and C3 glomerulopathy.

MV reports consultancy for Apellis, Novartis, Roche, and Travere (formerly Retrophin).

Jack F.M. Wetzels, MD, PhD, is a professor of nephrology at Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands. He studied medicine at the University of Nijmegen and received his MD in 1980. He undertook his training in internal medicine and nephrology at the Radboud University Nijmegen Medical Center. He received his PhD in 1989. From 1990 to 1992, he studied ischemic kidney tubular injury as a post- doctoral fellow under the supervision of Robert W. Schrier at the University of Colorado Health Sciences Center, CO, USA. He has been a nephrologist since 1992. In 2002, he was

appointed professor of nephrology in the Department of Nephrology at Radboud University Nijmegen. His chair is committed to teaching and research with an emphasis on the diagnosis and treatment of patients with glomerular diseases. Dr. Wetzels is a member of the steering committee of the European Reference Network for Rare Kidney Diseases (ERKnet) and co-chair of the Immune-glomerulopathies Working Group within ERKnet.

JFMW reports serving as an international scientific advisory board member for Alexion; consultancy for MorphoSys, Novartis, and Travere (formerly Retrophin); grant/research support from Alexion, MorphoSys*, and Novartis; and speaker bureau for Novartis.*
Monies paid to institution.

KDIGO Chairs

Michel Jadoul, MD, received his medical degree in 1983 at the Université Catholique de Louvain (UCLouvain) in Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He has served as chair at the Department of Nephrology of the Cliniques Universitaires Saint-Luc, Brussels, Belgium since 2003 and is currently a full clinical professor at UCLouvain. Dr. Jadoul's clinical activities focus on the follow-up of hemodialysis and CKD patients, and his main research interests include b2-microglobulin amyloidosis, hepatitis C, and other complications (e.g., falls, bone fractures, sudden death) in hemodialysis pa- tients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (e.g., drug-induced).

Dr. Jadoul has co-authored over 260 scientific papers, most of them published in major nephrology journals. He is currently serving as a theme editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS; 2001–present). In 2008, he received the international distin- guished medal from the US NKF. He was previously a member of the KDIGO Executive Committee (2010–2015) and the ERA-EDTA Council (2013–2016). Presently, Dr. Jadoul is a KDIGO Co-Chair.

MJ reports consultancy for Astellas, AstraZeneca*, Merck Sharp & Dohme*, Mundipharma*, and Vifor Fresenius Medical Care Renal Pharma*; providing expert testimony for Vifor Fresenius Medical Care Renal Pharma*; grants/research support from Amgen*, Janssen-Cilag*, Otsuka*, and Roche*; speaker bureau for Amgen*, Menarini*, Merck Sharp & Dohme*, Mundipharma, and Vifor Fresenius Medical Care Renal Pharma*; and travel fees paid by Amgen* and Sanofi*
Monies paid to institution.

Wolfgang C. Winkelmayer, MD, MPH, ScD, is the Gordon A. Cain Chair of Nephrology and professor of medicine at Baylor College of Medi- cine in Houston, TX, USA. Dr. Winkelmayer received his medical degree (1990) from the University of Vienna, Vienna, Austria, and later earned a Master of Public Health in healthcare management (1999) and a Doctor of Science in health policy (2001) from Harvard University, Cambridge, MA, USA. He then spent 8 years on the faculty of Brigham and Women's Hospital and Harvard Medical School, Boston, MA, where he established himself as a prolific investigator and leader in the discipline of comparative-effectiveness research as it pertains to patients with kidney disease. From 2009 to 2014, he was the director of clinical research in the Division of Nephrology at Stanford University School of Medicine, Palo Alto, CA, USA. He assumed his current position as chief of nephrology at Baylor College of Medicine in September 2014. His main areas of research interest include comparative effectiveness and safety research of treatment strategies for anemia, as well as of various interventions for cardiovascular disease in patients with kidney disease. Dr. Winkelmayer is a member of the American Society of Clinical Investigation. His clinical passion lies in providing quality kidney care to the predominantly disadvantaged and un(der)insured population in the public safety net health system of Harris County, Texas. Dr. Winkelmayer has authored over 300 peer-reviewed pub- lications, and he has a particular interest in medical pub- lishing. He currently serves as an associate editor for the *Journal of the American Medical Association*, was a co-editor of the *American Journal of Kidney Disease* from 2007 to 2016, and has been appointed to several other editorial boards of leading nephrology and epidemiology journals. He also vol- unteers his time toward important initiatives of the ASN (e.g., Public Policy Board). He joined the KDIGO Executive Committee in 2015 and has served as KDIGO Co-Chair since

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METHODS Chair

Marcello A. Tonelli, MD, SM, MSc, FRCPC, is senior associate dean (clinical research) at the Cumming School of Medicine in Calgary, Alberta, Canada. He is associate vice president (health research) at the University of Calgary, Calgary, Alberta, Canada. He received a medical degree from the University of Western Ontario, Ontario, Canada, a Master of Science in

epidemiology from Harvard University, Cambridge, MA, USA, and a Master of Science in health policy from Imperial College London, UK. He is a nephrologist and professor at the University of Calgary.

Dr. Tonelli has served in the past as president of the Ca- nadian Society of Nephrology, councilor of the ISN, and a member of the KDIGO Executive Committee. Dr. Tonelli is chair emeritus of the Canadian Task Force for Preventive Health Care, a national panel of experts that makes recom- mendations about preventive health services to Canada's 36,000 family physicians.

A unique aspect of Dr. Tonelli's research program includes partnering with regional, provincial, and national decision makers to ensure that the findings will be used to produce rational health policy.

*MT has received honoraria from AstraZeneca and Travere (formerly Retrophin).**
**Monies donated to charity*

Evidence Review Team

Jonathan C. Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD, Evidence Review Team Di- rector, is an internationally recog- nized clinician and scientist and holds the position of vice president and executive dean of the College of Medicine & Public Health at Flinders University, Adelaide, South Australia, Australia. Professor Craig has made a significant contribution to the clinical research landscape in the prevention, identifi- cation, management, and treatment of CKD, particularly in relation to children and in indigenous communities.

He has led the formation of state, national, and interna- tional networks to conduct high- quality, relevant trials in children. He has been instrumental in the development and implementation of best-practice methods and guidelines relating to CKD in Australia and globally. Professor Craig's many current advisory roles include member of the National Health and Medical Research Council's (NHMRC) Health Translation Advisory Committee, the Pharmaceutical Benefits Advisory Committee, Medical Services Advisory Committee, and Commonwealth Department of Health Life Savings Drug Program.

He is a past member of the World Health Organization expert review panel for global strategy and plan of action on public health, innovation and intellectual property, a past chairman of the Steering Group of the Cochrane Collabora- tion, and a past member of the Expert Advisory Group for the Structural Review of NHMRC's Grant Program.

JCC declared no competing interests.

Suetonia C. Palmer, MBChB, FRACP, PhD, Evidence Re- view Team Co-Director, is an academic nephrologist at the

University of Otago at Christchurch in New Zealand. She studied medicine at the University of Otago, graduating in 1995. She became a fellow of the Royal Australasian College of Physicians in Nephrology in 2005. She later completed a PhD in 2010 on the link between kidney function and heart health, and a 2-year postdoctoral fellowship in Boston, MA, USA, at the Brigham and Women's Hospital.

Dr. Palmer began as an author with the Cochrane Kidney and Transplant Group in 2004 during her training to become a nephrologist. Through systematic reviews, she discovered a passion for understanding more about the amount and quality of evidence that are required to make good clinical decisions in nephrology. She is actively engaged in the conduct of systematic reviews of interventions (the treatments we use), prognosis (whether risk factors for disease link to important outcomes), and trial quality (how good is the ev- idence on which to base our decisions).

Dr. Palmer enjoys training others in systematic review and meta-analysis using an evidence-based approach to research. She has strong collaborative links with researchers in Italy, Australia, Europe, and North America with an increasing research output, including recent publications in key internal medicine and nephrology journals.

SCP declared no competing interests.

Giovanni F.M. Strippoli, MD, MPH, M Med (Clin Epi), PhD, Evidence Review Team Co-Director, has made sig- nificant contributions to clinical research in CKD, with particular focus on prevention of kidney disease and man- agement of kidney failure, including hemodialysis, peritoneal dialysis, and kidney transplantation. He has contributed strongly to the development of policy in the area of kidney disease management through an international network designing and conducting epidemiologic studies in the field, including systematic reviews, randomized trials, and cohort studies, among others. Professor Strippoli has been an active contributor in his positions as chairman, deputy chairman, and council in nephrology societies, including the ISN and the Italian Society of Nephrology, as well as editorial positions in nephrology and general medicine scientific journals.

GFMS declared no competing interests.

Martin Howell, PhD, Assistant Project Director, is a senior research fellow in health economics in the Sydney School of Public Health (University of Sydney), Sydney, New South Wales, Australia. Since 2009, Martin has been responsible for evi- dence review and synthesis and the development of over 20 clinical practice guidelines for the Kidney Health Australia—Caring for Australasians with Renal Impairment (KHA-CARI) guidelines group. His research focuses on applied health economics, predominantly in the areas of assessment of

preferences using discrete choice methods and economic evaluations. His PhD project involved the application of a type of choice experiment known as a Best Worst Scaling survey to elicit preferences of recipients of kidney transplants for outcomes after transplantation. This methodology has since been applied to address a diverse range of health-related issues. He is currently leading the economic evaluations of 9 active clinical trials. He is an author of 57 publications (first author on 10). These publications show the broad application of his research from clinical trials to translation of clinical evidence to clinical practice guidelines and patient-centered care.

MH declared no competing interests.

David J. Tunnicliffe, PhD, Evidence Review Project Team Leader and Project Manager, is a research fellow at the University of Sydney, School of Public Health, Sydney, and the Centre for Kidney Research at the Children's Hospital at Westmead, New South Wales, Australia. He was awarded his PhD in 2018 at the University of Sydney and was awarded a National Health and Medical Research Council (NHMRC) Emerging Leadership 1 Investigator Grant (APP1197337) to examine the implementation and evaluation of living evidence in kidney disease. David has a research interest in meta-research of CKD and teaching epidemiology, which he performs through the Masters (Medicine) Clinical Epidemiology program, as a unit coordinator of introductions to systematic reviews.

As part of Cochrane Kidney and Transplant, David has served as the evidence review project team leader and project manager for the 2020 KDIGO update of the KDIGO Clinical Practice Guideline on the Management of Blood Pressure in CKD, providing methodological expertise on evidence synthesis and guideline development. His role was key in coordinating the formation of key clinical questions to guide literature searching and leading data extraction, critical appraisal, meta-analysis, and evidence grading.

DJT declared no competing interests.

Fiona Russell, PhD, *Cochrane Kidney and Transplant*, Managing Editor, has more than 20 years' experience at media organizations such as News Corp and Fairfax Media, Sydney, Australia in a variety of editorial positions, including reporter, sub-editor, deputy editor, and production editor. Two years as an information technology supervisor led to an ongoing technological change management role at both

companies, developing new system procedures and work- flows, and providing training solutions for new and existing staff.

During her editorial career, Dr. Russell also gained a bachelor's degree in journalism, international relations, and literary studies, a graduate degree in cognitive science, and a PhD in comparative cognition research. She has been the managing editor of *Cochrane Kidney and Transplant* since October 2015.

FR has grants/grants pending from the National Health and Medical Research Council of Australia.

Gail Y. Higgins, BA, Grad Ed, Grad Dip LibSc, Information Specialist, completed a bachelor's degree in arts, a graduate diploma in education from the University of Sydney, Sydney, New South Wales, Australia, and a graduate diploma in Li- brary Science from Kuring-gai College of Advanced Educa- tion, Sydney, New South Wales, Australia. Following a number of years as a teacher–librarian, she changed tack and spent 3 years with the New South Wales Technical and Further Education (NSW TAFE) Information Systems Divi- sion. After that, she joined the University of Sydney Library and worked as a pharmacy librarian and then as an internet training librarian. She has worked as an information specialist for the Cochrane Haematological Malignancies Group in Cologne, Germany, and the Cochrane Cancer Network in Oxford, UK. In 2007 and 2008, she completed a secondment with the World Health Organization in Geneva, Switzerland, on the International Clinical Trials Registry Platform (ICTRP) project.

GYH declared no competing interests.

Brydee Cashmore, MPH, Research Associate, has a Master of Public Health from the University of Sydney, Sydney, New South Wales, Australia, as well as a bachelor's degree in sci- ence, a double major in physiology and human nutrition, a graduate diploma in science in psychology, and a post- graduate diploma in science in human nutrition from Mas- sey University, Palmerston North, New Zealand. She is a researcher at the Centre for Kidney Research at the University of Sydney, where she undertakes evidence review and syn- thesis for *Cochrane Kidney and Transplant* and the KHA-CARI Guideline group. She was involved across all of the KDIGO Clinical Practice Guideline for the Management of Glomer- ular Diseases subtopics and undertook key aspects of the evidence review, including data extraction, evidence synthesis, and the writing and preparation of evidence summaries in MAGICapp.

BC declared no competing interests.

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Anthony Cabrera, Ingoberg Rojas Calderón, Monica Calvo, Emigdio Mendez Camacho, Perez Canga, Fernando Cardenas, Antonio Carlos Cardoso, Marcia A. Carvalho, Dawn J. Caster, Giovani Cersosimo, Michael Chang, Payupol Chansomboon, Stephen Chew, Ho Jun Chin, Kiran Chintam, Hov Chom- roeun, Hoon Loi Chong, Gabriel Choukroun, Hugo Cil- ocioni, Melissa Cintra, Rolando Claure-Del Granado, Luis Ernesto Gomez Contreras, Rosanna Coppo, Frank B. Corta- zar, Matija Crnogorac, Xiaoyun Cui, Richard D'Souza, Iara da Silva, Kader Daghastanli, Ian H. de Boer, Kirsten de Groot, Meltem Sezis¸ Demirci, Inge Derad, Pedro Augusto Macedo de Souza, Ajaya Kumar Dhakal, Manuel Fidalgo Diaz, Biagio Raffaele Di Iorio, Cristiane Dias, Jonathan Dick, Ameth Dieng, Nida Dinçel, Prodip Doley, Mary Anne Dooley, Linda Egan, Rihab Elidrisi, Emma Elphick, Basim Elsawi, Magdy El- Sharkawy, Montserrat Mercedes Díaz Encarnación, Lavinia Ene, Mar Espino-Hernandez, Gerard Espinosa, Pasquale Esposito, Pei Chun Fan, Rawan Farghal, Rehab Fatani, Val- kercyo Feitosa, Sandro Feriozzi, Loreto Fernandez, Jose Enrique Fernandez, Isis Figueiredo, Jeanette Finderup, Juan Carlos Flores, Alessia Fornoni, Kevin J. Fowler, Barry I. Freedman, Emma Frew, David J. Friedman, Tibor Fülöp, Daniel P. Gale, Maurizio Gallieni, Joana Gameiro, Venkat Gangaram, Alvaro Garcia, Ilse Garcia, Martha Nelida Lahoz Garcia, Philippe Gauthier, Mohammed Abdel Gawad, Tamara Gcar cia, Susie Gear, Duvuru Geetha, Jutta Gellermann, Bil- jana Gerasimovska, Osama Gheith, Farhad Gholami, Glom- Con Latinoamerica, Abdellatif Goda, Natashia Gongora, Marsha Gooden, Sreedas Gopalkrishnan, Cécile Gosset, Xhensila Grabocka, Noble Gracious, Jon Waarst Gregersen, Ryszard Grenda, Megan Griffith, Adriana Guardado, Felipe Guedes, Patsy Gundim, Nimish Gupta, Jean Carlo Tibes Hachmann, Fathin Hadi, Dieter Haffner, Rasha Hagag, Isa- belle Haggiag, William E. Haley, Nabila Hamdan, Seung Hyeok Han, Seungyeup Han, Jamey Hardesty, Elizabeth Harrison, Alejandro Hernandez, Elizabeth Herrera, Ngô Hoàng, Elisabeth M. Hodson, Yu Ah Hong, Lai Seong Hooi, Alvaro Hostia, Peter F. Hoyer, Zbigniew Hruby, Christine Hsu, Chiu-Ching Huang, Azm ul Hussain, Nahla Hussein, Holly Hutton, Francesco Iannuzzella, Shivananda Illalu, Kunitoshi Iseki, Renee Jack, Anjana Jagalur, Awatiff Jalaludin, Aamir Jamal, Maneesha Jayasiri, Chandra Mauli Jha, Prem Mohan Jha, Shan Jian, Lilian Johnstone, Roshin Joseph, Mikhail Kagan, Antroula Pastelli Kakouri, Mahmoud Kallash, Manivarma Kamalanathan, Elaine Kamil, Nada Kanaan, Ammar Kanbar, Shuzo Kaneko, Hee Gyung Kang, Karthik Kannegolla, Sergei Karpov, Hassani Kawtar, Rümeyza Kazancio glu, Junaid Khan, Basem Youssef Khedr, Masoud Khosravi, Arif Khwaja, Dana Kidder, Chang Seong Kim, SungGyun Kim, Aaron Kirkemo, Gianna Mastroianni

Kirsztajn, A. Richard Kitching, Wonngarm Kittana- mongkolchai, Radko Komers, Kirill Komissarov, Boonhuei Kong, Jonathan Kooiman, Jeffrey B. Kopp, Ghaly Kotb, Magdalena Krajewska, Jens Kristensen, Vikram Sakaleshpur Kumar, Dirk Kuypers, Gaetano La Manna, Pedro Jesus Lab- rador, Richard A. Lafayette, Jorge Laguna, Caroline Lamarche, Stewart Lambie, Ivo Laranjinha, Nicholas Larkins, Hajeong Lee, Lauren Lee, Alice Leite, Claudia F. Leiva, Kevin V. Lemley, Adama Lengani, Rachel Lennon, Wenxue Liang, Miguel Liern, Liz Lightstone, San Lin, Mark A. Little, Mieczysław Litwin, Wenbin Liu, José António Lopes, William Lopez, Khaled Lotfy, Kuo-Cheng Lu, Eduardo Luciano, Leonella Luzardo, Fabiani Palagi Machado, Valentina Madjova, John K. Mae- saka, Manish Mahajan, Nicolas Maillard, Indradip Maity, Aruni Malaweera, Rakesh Malhotra, Samir Mallat, Anthony Rivera Mallqui, Partha Pratim Mandal, Sreedhar Mandayam, Lucila Maria, Joana Moita Marques, Silvia Marsili, Irene Martin-Capon, Guillermo Martin-Reyes, Gilberto Martinez, Diana Masso, Naveen Kumar Mattewada, Drew Maxted, Yulia Mazur, Sandro Mazzaferro, Florencio McCarthy, P. McKillen, Mohamed Megahed, Francisco Calderon Mendieta, Nathalie Menendez, Carlos Mercado, Asad Merchant, Guido Merlotti, Mohamed Mesmeh, Ingrid Viviana Raoch Michaels, Sharon Millhouse, Nyi Minhan, Dana C. Miskulin, Gerardo Mogni, Abd El-Rahman Hassan Mohyeldein, Mahmoud Montasser, Vincent Mooren, Thyago P. Moraes, Eugen Mota, Bruno Moulin, Marwa Mounir, Shanza Mujeeb, Giovanna Arteaga Muller, Mariana Murea, Ghassan Mustafa, Nandhakumar Nagarajan, Oana Naidin, Dharmesh Nama, Sharat Kumar Naorem, Shoba Narayan, Anghelo Narváez, Alice Naseri, Shobhana Natarajan, Bharat Nathoo, Aaron Ng, John Ngigi, Anh Nguyen, Kathleen Nicholls, Mustafayeva Nilufar, Oscar Noboa, Maurizio Nordio, Achim Obergfell, Eshetu Obole, Budimir Obradovic, SE Won Oh, Andrzej Oko, Nestor Oliva- Damaso, Stephen Olson, Alvaro Orjuela, Leixuri Ortega, Alberto Ortiz, Marlies Ostermann, Maria Ottati, Leszek Pa˛czek, Aparna Padiyar, Sasanka Pakalapati, Lars Pape, Norman Valdivia Paredes, Sun-Hee Park, Rocio Meleiro Pascual, Malagouda Patil, Bandana Paudyal-Nepal, Shko- divskyi Pavlo, Saime Paydas, Marcos Paz, Michail Pazarlogou, Adalberto Peña, Ana Cecilia Acosta Pena, Adriana Penalba, Gerson Marques Pereira Junior, Perla Perez, Ivan Perez, Hai An Ha Phan, Marie Philipneri, Phuoc Phung, Dilukshi Pila- pitiya, Evangéline Pillebout, Carlos Eduardo Poli-de-Figueir- edo, Martin R. Pollak, Wanjak Pongsittisak, Daman Poudel,

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