Membranous nephropathy

Pierre Ronco[1,2]✉, *Laurence Beck*[3], *Hanna Debiec*[1], *Fernando C. Fervenza*[4], *Fan Fan Hou*[5], *Vivekanand Jha*[6,7,8], *Sanjeev Sethi*[9], *Allison Tong*[10,11], *Marina Vivarelli*[12] *and Jack Wetzels*[13]

Abstract | Membranous nephropathy (MN) is a glomerular disease that can occur at all ages. In adults, it is the most frequent cause of nephrotic syndrome. In ~80% of patients, there is no underlying cause of MN (primary MN) and the remaining cases are associated with medications or other diseases such as systemic lupus erythematosus, hepatitis virus infection or malignancies. MN is an autoimmune disease characterized by a thickening of the glomerular capillary walls due to immune complex deposition. Identification of the phospholipase A2 receptor (PLA2R) as the major antigen in adults in 2009 induced a paradigm shift in disease diagnosis and monitoring and several other antigens have since been characterized. Disease outcome is difficult to predict and around one-third of patients will undergo spontaneous remission. In those at high risk of progression, immunosuppressive therapy with cyclophosphamide plus corticosteroids has substantially reduced the need for kidney replacement therapy. Owing to carcinogenic risk, other treatments (calcineurin inhibitors and CD20-targeted B cell depletion therapy (rituximab)) have been developed. However, disease relapses are frequent when calcineurin inhibitors are stopped and the remission rate with rituximab is lower than with cyclophosphamide, particularly in patients with high PLA2R antibody titres. Other new drugs are already available and antigen-specific immunotherapies are being developed.

Podocytopathy
A disease of the podocyte, the main glomerular cell controlling the filtration of proteins.

Membranous nephropathy (MN) is a pathologically defined disorder of the kidney glomerulus. The specific lesion is an apparent thickening of the glomerular capillary walls, which results from immune complex formation on the outer aspect of the basement membrane[1]. The immune deposits consist of immunoglobulin G (IgG), the relevant antigens and complement components, including the membrane attack complex (MAC). The consequence of the immunological conflict is the loss of large amounts of proteins in the urine (proteinuria), which is predominantly mediated by the pathophysiological disturbance of the podocyte structure caused by immune complex deposition and MAC formation. Patients experience a decrease in serum albumin levels and generalized oedema, which define a condition called nephrotic syndrome. Most patients report fatigue as an important symptom. MN accounts for ~30% of cases of nephrotic syndrome in adults and is only surpassed in prevalence among nephrotic non-diabetic glomerular diseases by podocytopathy presenting as focal and segmental glomerulosclerosis lesions in some populations (African and Hispanic American individuals). In ~80% of patients, there is no underlying cause of MN (primary MN (pMN)) and 20% are associated with medications, such as NSAIDs, or other diseases (secondary MN (sMN)) such as lupus (also referred to as systemic lupus erythematosus (SLE)), hepatitis B or hepatitis C, and malignancies[1].

Patient outcomes are variable. For a long time, outcome was governed by the rule of thirds, with a third of the patients undergoing spontaneous remission, a third keeping variable levels of proteinuria and the remaining third progressing to advanced kidney failure. However, immunosuppressive therapy has substantially reduced the rate of kidney replacement therapy, which is ~10% with cyclophosphamide treatment but is not yet established for other newer agents such as rituximab[1].

Substantial advances in the understanding of MN pathophysiology have occurred in the past two decades, starting with the identification of neutral endopeptidase (NEP), the first discovered human podocyte antigen, which is involved in a rare subset of patients with neonatal allo-immune MN[2]. This finding paved the way for the characterization of the M-type phospholipase A2 receptor (PLA2R) as another podocyte antigen in 2009. Antibodies to PLA2R are specific for MN and found in ~70% of adult patients with the disease[3]. This discovery demonstrated that pMN is an autoimmune disease in which the podocyte is both the target of circulating auto-antibodies and probably the main source of the auto-antigen. It induced a paradigm shift in thinking about establishing diagnosis (possibly without a kidney biopsy), predicting

✉*e-mail: pierreronco@yahoo.fr*

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Author addresses

[1]Sorbonne Université, and Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche, S1155, Paris, France.
[2]Department of Nephrology, Centre Hospitalier du Mans, Le Mans, France.
[3]Section of Nephrology, Department of Medicine, Boston Medical Center and Boston University School of Medicine, Boston, MA, USA.
[4]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA.
[5]National Clinical Research Center for Kidney Disease, Nanfang Hospital, State Key Laboratory of Organ Failure Research, Southern Medical University, Guangzhou, China.
[6]George Institute for Global Health, UNSW, New Delhi, India.
[7]School of Public Health, Imperial College, London, UK.
[8]Prasanna School of Higher Education, Manipal Academy of Higher Education, Manipal, India.
[9]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA.
[10]Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia.
[11]Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, NSW, Australia.
[12]Division of Nephrology and Dialysis - Bambino Gesù Pediatric Hospital IRCCS, Rome, Italy.
[13]Department of Nephrology, Radboud University Medical Center, Nijmegen, Netherlands.

outcome and monitoring treatment in patients with pMN, including after transplantation. This discovery resulted in the rapid development of reliable assays for PLA2R antibodies and pMN can be considered as a model of organ-specific autoimmune disease and of personalized medicine. Subsequently, another podocyte antigen, thrombospondin type 1 domain-containing 7A (THSD7A) was identified[4]. THSD7A accounts for <5% of pMN[4].

Owing to the technological advances in combining laser microdissection of glomeruli and mass spectrometry of solubilized digested proteins, several further antigens have been identified such as exostosin 1 (EXT1) and EXT2, protein kinase C-binding protein NELL1 (also known as neural epidermal growth factor like 1 protein), semaphorin 3B (SEMA3B), neural cell adhesion molecule 1 (NCAM1), protocadherin 7 (PCDH7) and serine protease HTRA1 (REFS[5,6]). These antigens, like PLA2R and THSD7A, can be associated with pMN or with a specific 'cause' of sMN, such as lupus, other autoimmune disease or cancer, recognizing that the link of causality is not established in many instances. The discovery of different antigens therefore challenges the classification that opposes pMN to sMN and leads to a discussion of an antigen-based classification in which each antigen-associated MN would have its specific immunological profile (IgG subclass), pattern of associated diseases and outcome. Future studies should evaluate whether management should be driven by the antigen specificity as is the case for PLA2R-associated MN, in which positive serology now replaces kidney biopsy and quantitative assessment of PLA2R antibody levels is helpful in predicting response to therapy. Within the coming few years, similar steps forward can be expected for the other antigens (although they are rarer and large patient cohorts will not be recruited). Thus, in this Primer, we adhere to the current nomenclature of pMN and sMN, while being mindful that it will need to be adapted based on evidence from future studies.

Despite these advances, treatment of MN remains controversial. For a long time, cyclophosphamide-based regimens were the standard of care as they have been shown to prevent the occurrence of advanced kidney failure; however, they expose patients to an increased risk of malignancy[1,7]. Treatment with calcineurin inhibitors (CNIs), such as cyclosporine or tacrolimus, induces a high rate of remission but with a high rate of relapse and renal toxic effects are a concern in prolonged treatment[1,7]. Therapy protocols with CD20-targeted agents, such as rituximab, are well tolerated but only 60–70% of patients reach persistent clinical remission compared with ~80% for cyclophosphamide and their efficacy in preventing kidney disease progression has not yet been proven[1,7]. Randomized controlled trials (RCTs) published in the past few years (GEMRITUX[8], MENTOR[9], STARMEN[10] and RI-CYCLO[11]) have not clarified the dilemma between cyclophosphamide (more toxic) and CD20-targeted therapy (less efficient in the protocols used), which calls for new therapeutic approaches. The lack of RCTs with sufficient statistical power that directly compare these two treatments is a major reason for the enduring uncertainty. Furthermore, the dosage of rituximab is important to consider when effectivity is studied.

In this Primer, we summarize current knowledge of the epidemiology of MN and highlight the major advances that have led to a better understanding of MN pathophysiology, diagnosis and improved patient care. We also identify the major gaps in current knowledge and provide recommendations on how to improve long-term renal prognosis and quality of life.

Epidemiology

Incidence, prevalence and natural history

MN occurs in all regions and all ethnicities. The data on the incidence of MN and MN subtypes remain quite limited as large population-based studies that are representative across diverse international populations are not available. The annual incidence rates of MN are estimated at 10–12 per million in North America and 2–17 per million in Europe[7,12–15]. The disease affects individuals of all ages with a mean age of diagnosis at 50–60 years[16] and a 2:1 male predominance for unknown reasons[17]. Whether incidence rates of MN vary between regions or ethnicities remains unclear as most data are from North America and Europe.

pMN is the most common cause of idiopathic nephrotic syndrome in non-diabetic adults worldwide, accounting for 20–37% in most kidney biopsy series and increasing to as high as 58% in adults >65 years of age[7,18,19]. MN is uncommon in children, accounting for <7% of biopsies[13,20–24], and is often associated with other diseases such as hepatitis B[24]. The percentage of PLA2R-associated MN in adolescents is similar to that of adults.

No good data are available on the prevalence of the various aetiologies of sMN[1,25]. The main reason is that the epidemiology has varied with time, with infectious causes, such as hepatitis, strongly decreasing with vaccination, whereas others, such as lupus and drug exposure, are increasing.

In some regions, a temporal change in prevalence of MN has been reported[18,26,27]. A study in China analysed data from kidney biopsy samples of 71,151 patients in 938 hospitals in 282 cities taken over 11 years

(2004–2014) encompassing all age groups[17]. The prevalence of MN increased by 13% annually, whereas the proportions of other major glomerulopathies remained stable. Areas with higher levels of fine particulate matter with diameters ≤2.5 μm (PM2.5) air pollution had the highest rates of MN. In areas with PM2.5 levels >70 μg/m^3, each 10 μg/m^3 increase in PM2.5 concentration was associated with 14% higher odds for MN. This association was subsequently confirmed by another study in China[28]. However, whether the increase of MN is connected to a PLA2R-driven mechanism remains unclear as serum PLA2R antibody levels were not measured in most patients in these studies and whether air pollution is a causative risk of MN requires further confirmation.

The natural history of untreated MN has been reported with spontaneous complete remission rates of 20–30% and 10-year renal survival rates of 60–80% in most studies[29–31]. Despite its 'benign' presentation characteristics, MN has, for a long time, remained the second or third leading cause of kidney failure among the primary glomerulonephritis types in the USA and Europe[32]. In patients who continue to have nephrotic syndrome, kidney failure develops in 40–50% over a period of 10 years[33]. These patients are also at an increased risk of life-threatening thromboembolic and cardiovascular events[34].

Genetic factors

MN is not a typical hereditary disease in Mendelian terms but there is growing evidence to support a strong genetic component. Like most autoimmune diseases, MN has a strong association with the class II antigens of the human leukocyte antigen (HLA) system that are encoded by the relevant alleles of the HLA-D locus on chromosome 6. HLA class II molecules are involved in the regulation of immune responses: their expression is mostly limited to antigen-presenting cells, such as B cells, monocytes, macrophages, dendritic cells and Langerhans cells of the skin, and their role is to present peptide antigens to the immune system. Thus, they are associated with autoimmune diseases. It has been known since 1979 and 1989 that MN is strongly associated with HLA-DR3 and HLA-DQA1, respectively, in Caucasian populations[35,36]. An initial genome-wide association study conducted in three European cohorts including 556 patients of white ancestry found that pMN in adults was strongly correlated with risk alleles in *HLA-DQA1* (chromosome 6) and in *PLA2R1* (chromosome 2)[37]. In individuals who were homozygous for the lead risk alleles, the risk of having MN was nearly 80-fold higher than in those who had neither risk allele. Interestingly, the risk allele that is most significantly associated with pMN is localized in an intron of the gene; thus, this allele is not expected to change PLA2R antigen auto-reactivity. Further studies did not detect mutations or rare variants in the sequence and the splice sites of *PLA2R1* (REF.[38]). Thus, it is unlikely that the immune reaction is triggered by a change in antigen sequence or conformation. It is more probable that post-translational modifications or increased expression of PLA2R antigen in podocytes or other cells have an important role.

A similar strong correlation between risk alleles of *PLA2R1* and *HLA-DQA1* and the risk of developing MN was found in a large Chinese cohort that included 1,112 patients with pMN and 1,020 healthy individuals[39]. Patients with both risk alleles had an >11-fold increased risk of developing MN. The presence of risk alleles was also correlated to PLA2R antibodies.

Two studies performed in Chinese cohorts revealed different HLA class II alleles associated with an increased risk of MN[40,41] and proposed that HLA associations may differ between ethnicities. This was corroborated in the largest international genetic study of MN performed to date. The study involved cohorts from East Asia (1,632 biopsy specimen-diagnosed cases and 3,209 controls) and of European ancestry (2,150 biopsy specimen-diagnosed cases and 5,829 controls) and found ethnic differences in HLA locus associations, defining *DRB1*1501* as a major risk allele in East Asian individuals, *DQA1*0501* in European individuals and *DRB1*0301* in both ethnicities[42]. The *PLA2R1* locus presented the most strongly associated non-HLA signals. In addition, two previously unreported loci, *NFKB1* and *IRF4*, which are both linked to inflammatory pathways, were identified. Genome-wide association study loci account for 32% and 25% of disease risk in East Asian and European individuals, respectively.

In addition to their likely role of presenting PLA2R antigen to the immune system, HLA-D alleles may also be modifiers of MN. Although *DRB1*1501* is a major risk allele for the disease, *DRB1*1502*, which differs from *DRB1*1501* by a single amino acid, is not. However, *DRB1*1502* has a strong predictive value when associated with *HLA* risk alleles, being associated with a lower estimated glomerular filtration rate (GFR) and a higher risk of kidney failure[43]. No data are available concerning genetic predisposition for the other antigens or sMN.

Mechanisms/pathophysiology

In the past 20 years, considerable advances have occurred in the understanding of the pathophysiology of MN with the description of the first podocyte antigens in neonatal[2] and adult[3] MN. These discoveries revealed the central role of the podocyte in MN pathogenesis. This section describes the classical antigens NEP, PLA2R and THSD7A, the newly reported potential antigens, the autoimmune reactions that lead to the development of antibodies, and the downstream events that lead to nephropathy.

Antigens

NEP. In the 1970s, studies in the Heymann nephritis rat model of MN established the basis of MN pathophysiology. The studies showed that rats express megalin both in the proximal tubular brush-border and in podocytes and that actively or passively introduced megalin antibodies induced the aggregation of immune complexes at the basal surface of podocytes. This observation has led to the concept that a podocyte antigen, megalin (now called LRP2), could serve as a target of circulating antibodies leading to the in situ formation of immune complexes[44–46]. In humans, where megalin is not or only weakly present on podocytes[36,47] and cannot therefore be the target of circulating antibodies, NEP was identified in 2002 as the responsible antigen in a subset of patients

Glomerular filtration rate
(GFR). The most reliable parameter to assess renal function and can be evaluated with formulas (eGFR) or measured (mGFR).

Heymann nephritis
A model of membranous nephropathy developed by Walter Heymann in the rat in the 1950s that is still the most reliable experimental model for human membranous nephropathy.

Allo-immunization
Immunization against a non-self human antigen (protein or sugar) as occurs after blood transfusions or in case of Rhesus incompatibility during pregnancy, resulting in the production of allo-antibodies.

with allo-immune antenatal MN[2]. In this rare condition, mothers carry a homozygous or compound heterozygous nonsense mutation in *MME* (encoding NEP), which results in the absence of the protein[48] (FIG. 1). During pregnancy, they become immunized to the paternally inherited NEP in the placenta and the resulting maternal IgG antibodies are then transferred to the fetus, which is not NEP-deficient and therefore develops active disease.

NEP is a membrane-bound zinc-dependent endopeptidase and is involved in the catabolism of regulatory peptides with vasoactive properties[49,50]. NEP is expressed in numerous tissues and its membrane form is naturally present on human podocytes at the sole of their foot processes[51]. Maternal production of complement-fixing NEP IgG1, which also inhibits NEP enzyme activity, is necessary for the disease to develop[52]. This suggests that some toxic effects of NEP antibodies may be associated with alterations of glomerular haemodynamics, endothelial permeability or tubular function. Analysis of these very rare cases strongly supports the idea that the circulating antibodies react with an intrinsic component of the podocyte membrane. Moreover, these observations suggest that similar truncating mutations of other podocyte antigens could lead to allo-immunization and renal disease in infants.

PLA2R. PLA2R is the most frequently targeted auto-antigen in MN (up to 80% of pMN cases) (TABLE 1). The antigen was initially identified by mass spectrometric analysis of an electrophoretic gel band that corresponded to a glycoprotein recognized by serum from patients with idiopathic (primary) MN but not by serum from patients with proteinuria or healthy controls[3]. PLA2R is a transmembrane glycoprotein abundantly expressed by the human podocyte[3], present at the level of the foot process as well as on the apical surface, where it can be shed into the urine in vesicular structures during disease[53]. Its specific role in the glomerulus is not known. As some small mammals lack constitutive podocyte PLA2R expression, PLA2R may not be essential to podocyte function. Initially identified as a receptor for secreted phospholipase A2 enzymes[54], PLA2R might bind and internalize these small and potentially toxic enzymes that pass through the glomerular basement membrane (GBM). The extracellular domain of PLA2R comprises 10 domains: an N-terminal cysteine-rich (CysR) domain, a fibronectin 2 domain and eight C-type lectin-like domains (CTLD) that harbour distinct humoral epitopes.

The auto-antibodies that form against PLA2R initially target the N-terminal immunodominant CysR region

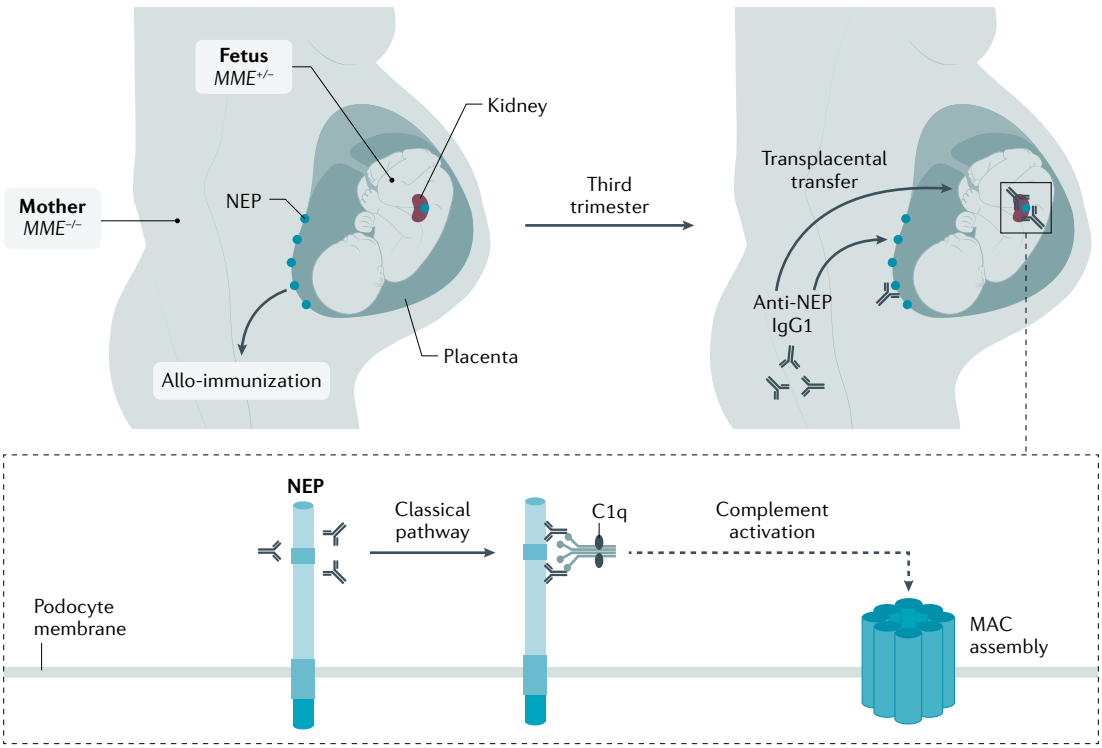

Fig. 1 | **Fetomaternal allo-immune glomerulopathy caused by maternal anti-NEP antibodies.** Antenatal membranous nephropathy is the result of a homozygous or compound heterozygous nonsense mutation in *MME* (encoding neutral endopeptidase (NEP)) in the pregnant mother, which results in the absence of NEP. The *MME*$^{-/-}$ pregnant mother develops allo-imunization against NEP that is expressed by the placenta (via paternal inheritance to the fetus) and recognized as a non-self protein by the mother's immune system. In the third trimester of pregnancy, NEP antibodies are transferred to the *MME*$^{+/-}$ fetus and bind to the NEP antigen expressed on podocytes of the fetus, who develops active disease. NEP IgG1 antibodies bind to epitopes on NEP and activate the classical complement pathway through binding of complement component C1q to the NEP IgG1 antibodies, leading to the formation of C5b–9 (membrane attack complex of complement (MAC)). MAC insertion into the podocyte membrane induces cell damage. No podocyte damage occurs in fetuses from mothers producing only IgG4, which does not bind C1q and therefore fails to activate the complement cascade.

Table 1 | **Established and new and putative antigens in membranous nephropathy**

Antigen	Size (amino acids)	Compartment	Evidence for expression by podocyte	Presence in subepithelial deposits	Circulating antibodies	Predominant subclass in deposits	Distinctive associations	Positive biopsy samples[a]
Established antigens								
PLA2R1 (REF.[3])	1,463	Transmembrane glycoprotein	Yes	Yes	Yes	IgG4	Prototype for pMN	NA
THSD7A (REFS[4,101])	1,657	Transmembrane glycoprotein	Yes	Yes	Yes	IgG4	Malignancy in some cases	~10%
New and putative antigens								
NELL1 (REFS[68,69])	810	Secreted	Weak	Yes, often segmental	Yes	IgG1	Association with malignancy (~30%), NELL1 in tumour cells	34/210 (16.1%)
SEMA3B (REF.[71])	749	Secreted	SEMA3A, strong; SEMA3B, not detected	Yes	Yes, reacting with reduced antigen	IgG1, no IgG4	Paediatric MN; early onset	5/129 (3.9%); children 6/59 (10.1%)
PCDH7 (REF.[73])	116	Transmembrane glycoprotein	Unclear	Yes	Yes	IgG1 and other subclasses	Sometimes associated with autoimmune diseases and malignancy	14/219 (6.4%)
NCAM1 (REF.[72])	858	Transmembrane glycoprotein	Weak, if any	Yes	Yes	IgG1 ± other subclasses	Lupus	14/212 (6.6%)
EXT1 and EXT2 (REFS[65–67])	746 and 718	Glycosyltransferase in Golgi and secreted	Weak (EXT2 > EXT1)	Yes	No	IgG1	Lupus (~30% of pure class V and mixed class) and other autoimmune diseases	155/460 (33.7%)
HTRA1 (REF.[74])	480	Cell membrane, possibly cytoskeleton	Yes	Yes	Yes, reduced and unreduced antigen	IgG4	None	5/118 (4.2%)

Circulating antibodies were not detected against EXT1 and EXT2 and evidence for deposition of specific antibodies in glomeruli has not yet been provided except for PCDH7. EXT1, exostosin 1; MN, membranous nephropathy; NA, not applicable; NCAM1, neural cell adhesion molecule 1; PCDH7, protocadherin 7; PLA2R, phospholipase A2 receptor; pMN, primary membranous nephropathy; SEMA3B, semaphorin 3B; THSD7A, thrombospondin type 1 domain-containing 7A. [a]Data are from the initial publications. PLA2R-negative biopsy samples were stained with the relevant antibodies. In the most recent papers, quintuple negative (PLA2R, THSD7A, NELL1, EXT1/2, SEMA3B) biopsy samples were stained; thus, the ratios of positive biopsies for the new and putative antigens are not strictly comparable. The number of biopsy samples staining positive for the antigen versus the total number of samples staining negative for PLA2R; for NCAM1 and EXT1/2, the number of biopsy samples staining positive for the antigen versus the total number of class V and mixed class (III or IV plus V) lupus nephritis cases.

and a short amino acid sequence in this domain has been shown to stimulate the production of very high-affinity antibodies[55]. In most patients, epitope spreading and the production of antibodies to distal regions of the extracellular domain occurs, including CTLD1, CTLD7 and CTLD8 (REFS[56,57]). The detection of epitope spreading in a patient seems to confer an inferior prognosis compared with individuals who have CysR antibodies only[58], although this notion has been challenged[57]. The predominant antibodies to PLA2R are of the IgG4 subclass but other subclasses, such as IgG1 and IgG3, are present in lower amounts[3,59]. Quantification of the overall titre of PLA2R antibodies has been a useful tool in monitoring the immune response to therapy in PLA2R-associated MN[13] and the decline and disappearance of PLA2R antibodies has been termed immunological remission and precedes and predicts clinical remission.

Epitope spreading
Diffusion of the immune response to additional epitopes on the same molecule or different molecules.

THSD7A. Thrombospondin type 1 domain-containing 7A (THSD7A) is a multidomain transmembrane glycoprotein expressed by the podocyte that serves as an auto-antigen in 2–3% of patients with MN[60]. Similar to PLA2R, it was identified by performing mass spectrometry on native, deglycosylated or proteolysed protein bands detectable by human auto-antibodies. Its presence in the glomerulus had not been demonstrated before its discovery as an MN target antigen, although it is now recognized as a conserved basal component of the podocyte, localizing directly between the slit diaphragm and the GBM[61]. No immunodominant epitope has been discovered and auto-antibodies seem to target multiple regions of the protein, including the N terminus[62]. Several cases of THSD7A-associated MN have been found in which a malignancy overexpresses THSD7A and may initiate the immune response that then causes MN in the kidney[63,64]. There are fewer data on using THSD7A antibodies than on PLA2R antibodies for monitoring of disease but THSD7A antibodies, similar to PLA2R antibodies, tend to decline with immunosuppressive treatment and their disappearance is associated with eventual clinical remission.

New and putative antigens. Laser microdissection of glomeruli followed by mass spectrometry has been used to identify novel antigens in MN[65]. The basic premise in the identification of an antigen is that the novel antigen

Full-house pattern
Immunofluorescence studies show staining for IgA, IgG, IgM, C1q, C3, κ and λ light chains.

Xeno-antibodies
Production of xeno-antibodies results from immunization against a non-self, non-human antigen (protein or sugar); a process termed xeno-immunization.

has accumulated in the glomeruli (immune deposits) compared with other proteins and is unique to a subset of MN. Confirmation of the novel antigen is then provided by immunohistochemistry and/or immunofluorescence studies that show granular subepithelial staining of the novel antigen along the capillary walls, followed by confocal immunofluorescence studies that show co-localization of the novel antigen with IgG along the capillary walls, ideally elution of IgG from frozen biopsy material to show that the deposited IgG is specific for the novel antigen and, finally, serum western blot analysis to show that circulating antibodies to the novel antigen are present in the serum.

Six candidate antigens have been discovered using these techniques in the past few years (TABLE 1). Putative antigens EXT1 and EXT2 were discovered in 2019, NELL1 and SEMA3B in 2020, and PCDH7, HTRA1 and NCAM1 in 2021. EXT1 and EXT2 were the first novel proteins found in a subset of patients with MN. Granular EXT1 and EXT2 deposits were detected in MN secondary to autoimmune disease, mostly lupus[65]. Patients with MN associated with EXT1 and EXT2 deposits were young, predominantly female and their kidney biopsy samples showed features of MN usually associated with an autoimmune disease such as a full-house pattern of immunoglobulin on immunofluorescence studies, tubuloreticular inclusions in the endothelial cells and mesangial deposits. However, antibodies to EXT1 and EXT2 have yet to be found and these proteins are considered putative antigens. Positive staining for EXT1 and/or EXT2 is found in 30–40% of pure lupus MN (LMN; also referred to class V lupus nephropathy) and in around the same percentage of mixed class lupus nephropathy, that is, class III or class IV associated with class V. Patients with LMN and positive staining for EXT1 or EXT2 have fewer chronicity features, including glomerulosclerosis, tubular atrophy and interstitial fibrosis, and also have a better prognosis than those who are negative for EXT1 and EXT2 (REFS[66,67]).

NELL1 seems to be the second most common antigen following PLA2R. It is present in most patients with MN and no underlying disease association (pMN) but is also present in some patients with malignancy (sMN)[68,69]. One of the unique features of kidney biopsy samples is that staining for NELL1 can be segmental in some of the glomeruli[69,70].

SEMA3B is another unique antigen in that it is primarily present in children (<2 years of age) and young adults. In children, kidney biopsy samples also show IgG staining along the tubular basement membrane. Interestingly, the tubular basement membrane deposits are negative for SEMA3B[71]. NCAM1 was identified as an antigen in both pMN and LMN[72]. Patients with NCAM1-associated LMN were younger, predominantly female and had a history of lupus, all of which are distinct features from those seen in the usual patients with MN. Similar to LMN associated with EXT1 and EXT2, NCAM1-associated LMN is not restricted to pure class V LMN but is also present in some patients with LMN who also have proliferative lupus nephritis.

PCDH7-associated MN is present in patients with a mean age of 63 years, close to that of the most common form of MN[73]. Most patients seem to not have an associated underlying disease but ~20% of patients with PCDH7-associated MN have a history of malignancy. Kidney biopsy samples lack complement deposits on immunofluorescence study. In addition, non-nephrotic-range proteinuria (proteinuria <3 g/day) is observed and remission follows conservative management in some patients with PCDH7-associated MN.

HTRA1-associated MN is present in patients with a mean age of 67 years and characterized by an IgG4-dominant subclass in the immune deposits without association to another disease except for anti-neutrophil cytoplasmic antibody-associated vasculitis in 1 of 14 patients[74]. Sera from two patients reacted by immunoblotting with glomerular extracts and with recombinant human HTRA1 under reducing and non-reducing conditions. Longitudinal sampling in these two patients suggests that HTRA1 antibody levels are correlated with clinical activity.

Whether these new antigens are true antigens or biomarkers is controversial as they have only been characterized in the past few years. As described, each antigen-associated MN has its own specific features, including demographic characteristics, immunopathological and sometimes morphological features, and associated diseases. The minimal definition of an antigen is the presence of the relevant antibodies in the blood and, ideally, in biopsy samples. Although co-localization of antigen and antibody by confocal microscopy is suggestive, definitive evidence of the reactivity of the deposited antibody against the potential antigen requires elution experiments that are hampered by the small size of the tissue specimen. Among the new potential antigens, such demonstration has only been achieved for PCDH7 (REF.[73]). Further evidence of the pathogenic effect of the antibodies can be provided by correlation of antibody levels with clinical course, early recurrence in the transplanted kidney and development of experimental models. A few cases showing the parallel outcomes of immunological and clinical activity have been reported[69,71,73,74]. No observation of early recurrence after transplantation has been reported and animal models are not yet available.

Of note, more than a decade after the discovery of PLA2R, the only experimental model of PLA2R-associated MN is with the mouse antigen[75] and evidence of pathogenicity in humans mostly relies on early recurrence after transplantation[76,77] and time-course measurement of PLA2R antibody levels that precedes proteinuria[78,79]. Yet, the discovery of the role of the PLA2R antibody in MN has induced a paradigm shift in patient care, showing the way for future well-conducted clinical studies that aim to define the diagnostic and predictive values of potential antigens involved in MN. The pathophysiology of these new antigens is essentially unknown and will require further studies.

Exogenous antigens. Exogenous proteins, whether they are present or not in humans, can induce the production of allo-antibodies or xeno-antibodies, respectively. Important features of these proteins are their specific physicochemical properties that may lead to their

trapping in the GBM. The first observation implicating a food antigen was reported in children with cationic bovine serum albumin (BSA)-related MN[80]. This observation was also inspired by an experimental model[81,82]. Some patients, mostly infants, with MN had high serum titres of anti-BSA antibodies reacting with one peptide region of BSA but not with human serum albumin. Only infants had circulating cationic BSA, which could interact with the negatively charged glomerular capillary wall. Why cationic BSA was formed is not known but differences in food processing or in the intestinal microbiota might be responsible for BSA modifications.

Other food antigens or non-dietary antigens from the environment might also be involved in MN. Extremely rare forms of allo-immune MN have been described in children affected with rare lysosomal storage diseases (mucopolysaccharidosis type VI and Pompe disease) receiving enzyme replacement therapy[83,84]. Because of the absence of enzymes, therapeutic proteins are potential allo-antigens that trigger immunization.

Autoimmune reactions

Regardless of the target antigen, the common denominator in MN is the accumulation of discrete deposits containing immunoglobulin and antigen that form and expand beneath the basal surface of the podocyte (FIG. 2). The mechanisms underlying the loss of tolerance to these self-antigens are not well understood but likely involve genetic factors, heightened expression of target antigens owing to polymorphisms in regulatory elements, upregulation by environmental factors, or even pathologic and dysregulated production of the antigen as might occur in malignancy. It is also not known why some patients have circulating antibodies well before the onset of nephrotic syndrome and even proteinuria[85].

Several studies suggest an overall dysregulated immune phenotype in MN[86,87] characterized by a decreased proportion of regulatory T cells among all lymphocyte subpopulations in untreated patients with MN[88]. Numbers of plasma cells and regulatory B cells were statistically higher in patients with MN compared with healthy individuals or individuals with non-immune kidney disease and the amount of in vitro-expanded PLA2R-specific memory B cells could be correlated with circulating PLA2R antibody titres[89]. The specific site at which the immune response to PLA2R is initiated remains speculative[90] but intrarenal B cells in tertiary lymphoid follicles have been noted[91,92]. These tertiary follicles could represent the propagation of the immune response triggered by PLA2R shed from podocytes as exosomes into the tubular lumen[93] and later captured by intrarenal dendritic cells. The observation that the risk of recurrence after kidney transplantation is dependent on the donor's gene variants of HLA-D and PLA2R1 can be seen as further evidence of a kidney-based source of antigen exposure[90].

The paradigm of podocyte injury induced by the subepithelial immune deposits was elucidated in the experimental rat model of Heymann nephritis[94]. In this model, activation of the complement system and assembly of the terminal complement components C5b–9 were both necessary to induce podocyte injury and proteinuria. In the absence of complement-activating IgG or factors such as complement component C6, subepithelial deposits would form but no further injury would occur. Evidence for complement activation in human MN has been circumstantial and based on the consistent presence of specific complement factors within the subepithelial deposits. In routine immunofluorescence staining, IgG and C3 are present but C1q is usually weak or absent, suggesting that the classical complement pathway activation has a minor role in established disease. However, the fact that early deposits contain more IgG1 and IgG3 whereas later-stage deposits are enriched in IgG4 suggests that the classical complement pathway might initiate disease, which is then propagated by the alternative pathway or the lectin pathway[95]. The consistent presence of C4 (REF.[96]) and of mannan-binding lectin (MBL) in many[97] but not all[98] patients with MN implicates the lectin pathway, but many components of the alternative pathway are also detected when assayed by mass spectrometric techniques[99]. The common final pathway is thought to involve the insertion of C5b–9 (also known as the MAC) channels into the podocyte membrane. This breach of cell integrity causes sublethal cell injury and the activation of maladaptive pathways causing cytoskeletal disassembly, loss of slit diaphragms and, over time, the production of normal and ectopic basement membrane elements[100].

Mouse models using passive transfer of human or rabbit antibodies to PLA2R[75] or THSD7A[101,102] have been developed but they have not yet convincingly established a definite role for complement. Sophisticated co-culture models, such as the glomerulus-on-a-chip, hold promise for investigating the harmful effects of human anti-podocyte antibodies[103]. In a culture model of PLA2R-expressing podocytes, PLA2R IgG4 antibodies, especially those bearing glycan chains that lack terminal galactose residues, stimulated the lectin pathway through MBL and MBL-associated serine proteases to cause podocyte injury[104]. A novel finding from this work is the upregulation of receptors for C3a and C5a on the podocyte, also observed in human MN biopsy specimens, that may augment the cytotoxicity instigated by C5b–9 through cytoskeletal degradation in response to the anaphylatoxins generated by subepithelial activation of complement.

Research continues into non-complement-dependent mechanisms, for example, direct interference in normal pathways by the auto-antibodies. THSD7A antibodies seem likely to have direct effects on the slit diaphragm structure and function[102,103] given the close association of THSD7A with this structure. Intermolecular epitope spreading to intracellular antigens[105] or complement regulatory factors[106] may also augment the injury process.

Nephropathy

The downstream effects of injury caused by the subepithelial deposits are enormous, starting with the failure of the glomerular filtration barrier owing to the complement-mediated podocyte injury and the spilling of massive amounts of protein into more distal nephron segments. One consequence of delivery

Anaphylatoxins
One of several proteolytic fragments generated by complement activation that promote acute inflammation and mediation of the immune response.

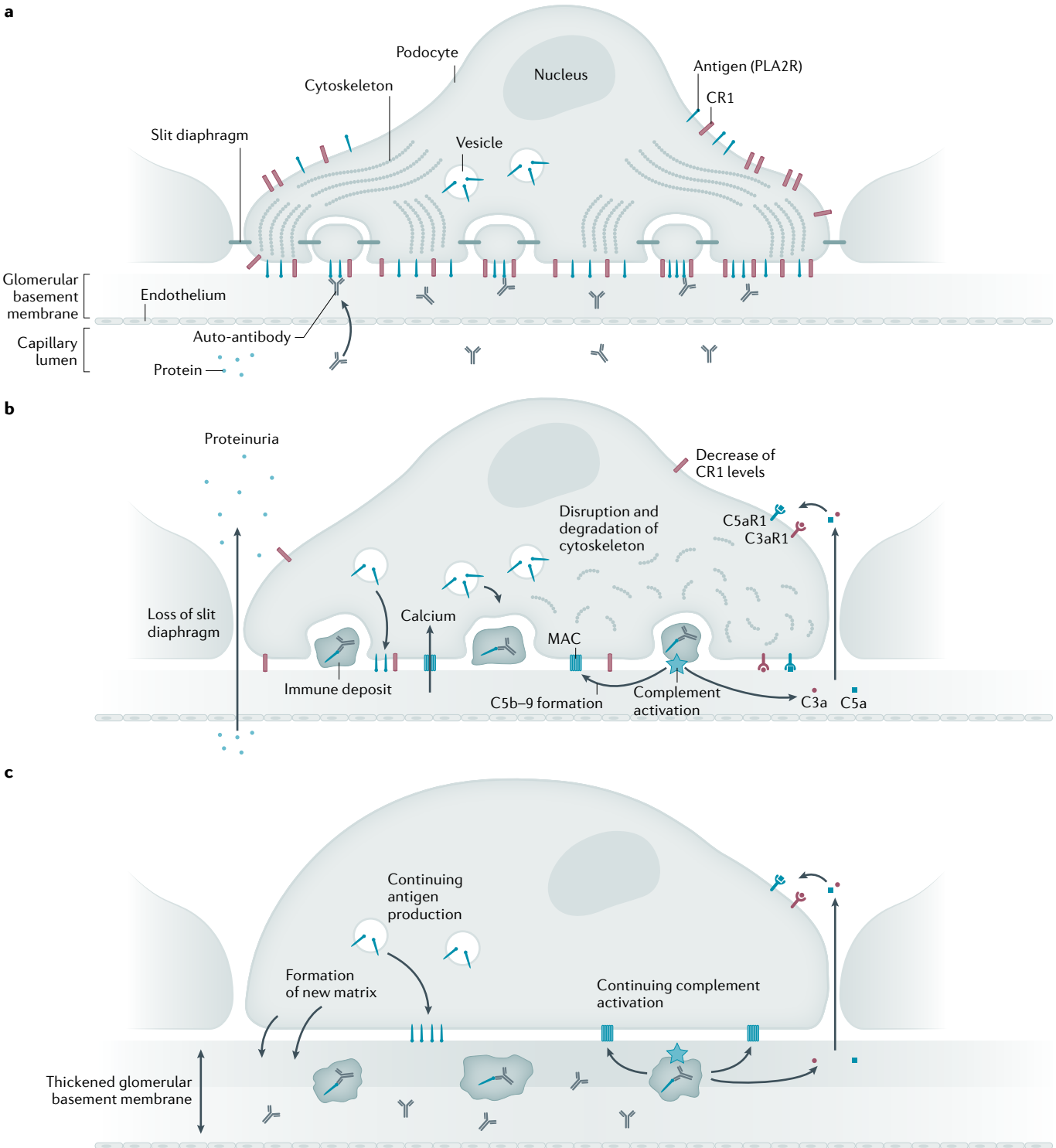

Fig. 2 | **Pathomechanisms of injury in PLA2R-associated membranous nephropathy. a** | At the initiation of the humoral autoimmune response, the podocyte expresses phospholipase A2 receptor (PLA2R) and complement inhibitors such as complement receptor 1 (CR1) at the cell surface and has a cytoskeleton reflective of the differentiated podocyte state, with interdigitating foot processes bridged by slit diaphragms. Circulating auto-antibodies begin to target PLA2R on the basal aspect of the podocyte. Ongoing synthesis and delivery of PLA2R to the cell surface enables continued deposit formation and growth in the presence of circulating auto-antibodies. **b** | Immune deposits (stage 1) containing antigen and immunoglobulin form beneath the podocyte, where they begin to activate complement. The terminal complement components C5b–9 (membrane attack complex (MAC)) insert into the podocyte membrane and enable calcium influx, which initiates several maladaptive pathways. C3a and C5a generated by the complement cascade bind to and activate their cognate receptors C3aR1 and C5aR1, stimulating pathways that lead to the degradation of cytoskeletal elements. CR1 is downregulated, which enables complement-mediated cytotoxicity. The result is the simplification of the podocyte cyto-architecture, loss of slit diaphragms and increased flux of protein into the urinary space. PLA2R continues to be produced by the podocyte, leading to an increased mass of the immune deposits and ongoing complement activation. **c** | With ongoing injury, the podocyte secretes additional extracellular matrix components between (stage 2) and around (stage 3) the immune deposits, leading to the increased overall thickness of the glomerular basement membrane.

Anasarca
Severe and generalized form of oedema, with subcutaneous tissue swelling, that usually involves the cavities of the body.

Thrombophilic state
A pathological condition that predisposes to thrombosis.

of these large amounts of protein, including specific proteases, to the distal nephron is the activation of the epithelial sodium channel ENaC, which is responsible for sodium reabsorption in the collecting duct, causing volume overload, weight gain, and localized oedema or generalized anasarca. The imbalance of promoters and inhibitors of the coagulation system in the setting of increased urinary losses and hepatic synthesis favours the thrombophilic state, which is more pronounced in MN than in other nephrotic disorders for as yet unknown reasons[107,108]. Deep vein thromboses, renal vein thrombosis and pulmonary embolism are all potential consequences of the nephrotic state in MN and are associated with the severity of hypoalbuminaemia[108,109]. Other consequences of the nephrotic state include mixed hyperlipidaemia, vitamin D deficiency and a general state of immunosuppression due to urinary loss of innate and humoral immune effectors such as complement factors and immunoglobulins. Similar to other glomerular diseases with sustained proteinuria over months to years, renal function can decline with progressive tubular atrophy and interstitial fibrosis[33]. Patients who develop end-stage MN and receive a kidney transplant are at risk of recurrence of the disease in the allograft if the circulating antibodies are still present or recur after transplantation.

Diagnosis, screening and prevention

Adults

Clinical presentation. Nephrotic syndrome, defined as proteinuria >3.5 g per day and serum albumin <3.5 g/dl (when measured by bromocresol green) or <3.0 g/dl (when measured by bromocresol purple or immunonephelometric methods), respectively, is present in around two-thirds of patients with MN at presentation and can be severe[1,110]. The other third of patients present with asymptomatic proteinuria, usually ≤3.5 g per day. In most patients, GFR is normal and urinary sediment is unremarkable, although microscopic haematuria may be present in <25% of patients. Hypertension at presentation is uncommon (<20% of patients), which explains why most patients do not tolerate high-dose angiotensin II blockade. Thromboembolic events are reported in up to 8% of patients, with renal vein thrombosis accounting for 30% (BOX 1). Hyperlipidaemia is common and characterized by an increase in total and LDL cholesterol and a decrease in HDLs, which is associated with a markedly increased risk of both myocardial infarction and coronary death compared with that of healthy individuals as well as with an increased risk for thromboembolism[111]. Rare cases of crescentic MN, usually presenting with proteinuria >3.5 g per day, haematuria and reduced GFR, in the absence of anti-neutrophil cytoplasmic antibodies or GBM antibodies, have been reported[112].

Histopathology. Kidney biopsy is the standard diagnostic approach for MN. On light microscopy, early stages of MN may show normal-appearing GBMs[113]. At later stages, basement membrane spikes and pinholes can be seen on silver methenamine and periodic acid-Schiff stains (FIG. 3).

Proliferative features, such as mesangial and endocapillary proliferation, are typically absent[113]. In very rare cases, a concurrent crescentic pattern of injury is observed. In immunofluorescence microscopy, diffuse and granular staining for IgG, C3, and κ and λ light chains is seen along the capillary walls in pMN. In electron microscopy, numerous electron-dense deposits are seen in the basement membrane beneath the podocytes that show extensive foot process effacement even at the early stages. These subepithelial deposits are separated by expansions of basement membrane material or covered with extracellular matrix at later stages[114].

Four stages are defined according to the location of the subepithelial deposits and matrix accumulation: stage 1, sparse small deposits without thickening of the GBM; stage 2, more extensive subepithelial deposits with the formation of basement membrane spikes between the deposits and thickening of the GBM; stage 3, a combination of stage 2 with deposits completely surrounded by basement membrane (intramembranous deposits); and stage 4, incorporation of deposits in the GBM, which are irregularly thickened (burned-out disease). In stage 4, the deposits are often fading, becoming less electron dense.

Features suggestive of sMN include mesangial or endocapillary proliferation; a full-house pattern of immunoglobulin staining, including staining for IgA and C1q on immunofluorescence microscopy; mesangial and/or subendothelial electron-dense deposits or deposits along the tubular basement membrane and vessel walls; substructures in the deposits; and endothelial tubuloreticular inclusions on electron microscopy[115]. The presence of scant superficially scattered subepithelial deposits on electron microscopy suggests drug-associated or malignancy-associated sMN. Staining for IgG subclasses may help in differentiating pMN from sMN. IgG1, IgG2 and IgG3 predominate in class V lupus nephritis, whereas IgG4 is the prevailing subclass associated with variable amounts of IgG1 in

Box 1 | **Complications of membranous nephropathy and its treatments**

Nephrotic syndrome
Tiredness, oedema, dyspnoea, nausea, anorexia, ascites, venous thrombosis, arterial thrombosis, infections, kidney failure.

Diuretics
Hypokalaemia, hyponatraemia, hypomagnesaemia, alkalosis, gout, ototoxicity (with high-dose furosemide), muscle aches.

Prednisolone
Cushing face, obesity, skin bruising and striae, diabetes, osteoporosis, cataracts, infections, wound healing.

Cyclophosphamide
Anaemia, leukocytopenia, thrombocytopenia, infections, nausea, anorexia, bladder mucosal irritation with haematuria, liver function abnormalities, hair loss, infertility, malignancy, myelodysplasia.

Calcineurin inhibitor
Nephrotoxicity, diabetes, hair growth, gingiva hyperplasia, hypertension, liver dysfunction, neurotoxicity.

Rituximab
Infusion reaction, infections, hypogammaglobulinaemia, antibody formation.

See also Supplementary Table 1.

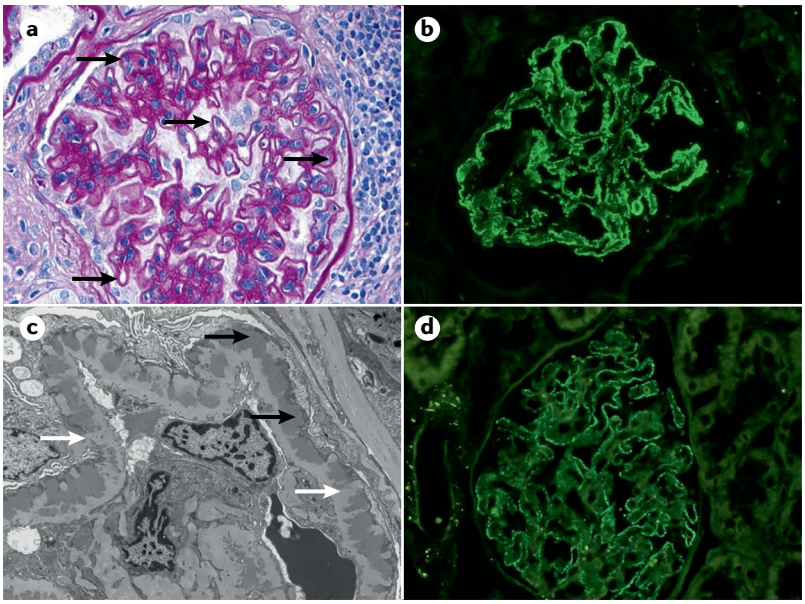

Fig. 3 | **Kidney biopsy findings of membranous nephropathy properties of the glomerulus in membranous nephropathy. a** | Light microscopy image showing thickened glomerular basement membranes (arrows; periodic acid-Schiff stain, 40×). **b** | Immunofluorescence microscopy image showing granular staining for IgG along the capillary walls (40×). **c** | Electron microscopy image showing subepithelial electron-dense deposits (black arrows) and basement membrane material between the electron-dense deposits (white arrows; 4,800×). **d** | Immunofluorescence microscopy image showing staining for phospholipase A2 receptor (PLA2R) along the capillary walls (40×).

PLA2R-associated and THSD7A-associated pMN[69,71,116]. The prevailing subclass in MN associated with newly characterized antigens is IgG1 (REF.[117]). In early reports in malignancy-associated sMN, IgG4 staining was usually absent[118]. However, one study found no differences in the IgG subclass distribution between patients with pMN and those with malignancy-associated sMN[119]. Furthermore, levels of antigen-specific IgG4 antibodies were not different between primary and malignancy-associated sMN and levels of all IgG subclasses did not differ between these groups.

Staining of kidney biopsy samples for PLA2R can also diagnose PLA2R-associated MN in patients who have negative PLA2R antibody serology[80]. This might occur if serum samples are collected when the patient is in immunological remission either spontaneously or following immunosuppressive therapy or PLA2R antibody serology may be falsely negative early in the disease course owing to the phenomenon of the kidney behaving like a 'sink'[120]. In this scenario, circulating PLA2R antibodies bind to the target antigens on the podocyte and are rapidly cleared from the blood. Only when the antibody production rate exceeds the buffering capacity of the kidney will seropositivity become apparent. Hence, serial assessment of PLA2R antibody levels should be performed in patients with positive glomerular PLA2R staining who are initially seronegative but have persistent proteinuria[12]. By contrast, positive PLA2R antibody serology and negative glomerular PLA2R staining are uncommon[121,122] and very likely reflect differences in staining techniques[123].

Indications for kidney biopsy. Kidney biopsy is costly and can result in major complications[123–127]. Given the high specificity of PLA2R antibodies in patients with MN and the fact that PLA2R antibodies have not been detected in other glomerular diseases or healthy individuals, deferral of a kidney biopsy has been suggested in patients who have nephrotic syndrome and PLA2R antibodies[12,19]. This proposal has been supported by a study that showed that, in patients with preserved kidney function (eGFR >60 ml/min/1.73 m^2), no evidence of secondary cause (BOX 2) and no diabetes mellitus, a positive serum PLA2R antibody titre equals a 100% probability of diagnosing MN and is therefore a reliable non-invasive method for the diagnosis of pMN[128]. In these patients, kidney biopsy did not provide any valuable information that altered treatment. This non-invasive diagnostic approach might be especially important for those at high risk of complications or in whom a kidney biopsy is contraindicated[129]. However, if kidney function is impaired or the patient has evidence of a potential secondary cause for MN, including diabetes mellitus, a kidney biopsy is needed to exclude concomitant kidney disease (for example, underlying diabetic nephropathy, acute interstitial nephritis or crescentic glomerulonephritis) and to estimate the extent of interstitial fibrosis and tubular atrophy, which may add useful information to guide management. BOX 2 provides guidelines for the evaluation of associated conditions in patients with MN regardless of serology. The non-invasive diagnostic approach is supported by the new Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on the management of glomerular disease[130]. In patients with a PLA2R$^-$ biopsy sample, staining for THSD7A, EXT1, EXT2, NELL1, NCAM1, SEMA3B, PCDH7 and HTRA1 antibodies should be performed depending on age, immunofluorescence pattern (segmental) and associated condition (autoimmunity).

pMN, sMN and a new antigen-based classification. In ~80% of patients, MN appears without an underlying cause and presents as a kidney-specific autoimmune disease. The target antigen in ~70% of patients is PLA2R, followed, in decreasing percentages, by NELL1, PCDH7, THSD7A, HTRA1 and SEMA3B (mainly in children and young adults), NCAM1, and unknown in the remaining 10–15% of patients with pMN. In ~20% of patients, MN occurs in association with other clinical conditions and is categorized as sMN[5]. Patients with pMN and those with sMN have similar clinical renal presentations.

However, this dichotomization of MN into primary and secondary has been challenged[5,131]. The complexity arises from the fact that clinical findings of the presence of antibodies do not accurately align with the definitions of pMN and sMN. Some patients with apparently sMN are also positive for PLA2R antibodies, most commonly those with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or sarcoidosis[132–135]. Whether these patients have true sMN or coincidental PLA2R-associated MN with a secondary disease is unclear. The facts that patients may enter spontaneous remission without treatment of the secondary cause or that treatment of the secondary cause does not result in remission of MN support the

view that these antibodies occur coincidentally[136]. The same is true for patients with THSD7A-associated MN, for which an association with malignancy exists[64,137]. In these patients, remission has been observed with treatment of the malignancy alone[63,64,137,138], but most patients with THSD7A-associated MN, with or without concomitant malignancy, respond to immunosuppression therapy[139,140]. In addition, most patients with NELL1-associated MN present without evidence of concomitant disease, but a concomitant malignancy is present in some of these patients[68,69,137]. Thus, a new molecular classification for MN based on target antigen has been proposed[5,131]. Future studies should enable the proposition of a better disease classification based on the presence of antibodies and the antigen specificity as well as the proven association (or not) with an underlying cause.

PLA2R antibody assays and identification of other target antigens. Various assays are available to detect PLA2R antibodies. The most commonly used assay is the ELISA commercialized by Euroimmun, which is 99.6% specific and enables the quantification of PLA2R antibody levels. The indirect immunofluorescence assay (IFA) from the same provider is a bit more sensitive than the ELISA and is 100% specific but does not enable quantitative assessment[141]. The currently recommended reference ranges for the ELISA assay are <14 relative units (RU)/ml (negative), 14–20 RU/ml (borderline) and >20 RU/ml (positive). Improved sensitivity without affecting specificity has been suggested by reducing the cut-off from 20 RU/ml to 2 RU/ml (REFS[142,143]) or by using a combination of IFA and ELISA[128]. In this study, all patients with ELISA values >2 RU/ml and <20 RU/ml and a positive IFA had MN confirmed on biopsy. An addressable laser bead immunoassay, showing similar performance to the IFA assay, has been developed but is not clinically available[144]. ELISA and IFA remain less sensitive than western blot analysis (not used in clinical practice) and antigen staining of the kidney biopsy sample[121,145]. Thus, these techniques may fail to detect PLA2R antibodies in patients with proven PLA2R-associated MN.

An indirect immunofluorescence assay for THSD7A antibodies is commercially available (Euroimmun) but tests for NELL1, NCAM1, SEMA3B, PCDH7 and HTRA1 antibodies have not yet been developed. However, antibodies specific for the antigens are commercially available and can be used for the detection of antigen after retrieval in paraffin-embedded kidney biopsy samples[117].

MN and malignancies. The prevalence of malignancy in patients with MN is estimated at 6–22%, most commonly occurring in patients >60 years of age with most cancers discovered before or at the time of the diagnosis of MN[146]; whether these are coincidental events or represent an aetiological association is unclear. Three criteria to ascertain an aetiological association have been proposed: remission occurs after complete removal of the tumour, renal relapse accompanies recurrence of the neoplasia, and the detection of tumour antigens and antitumor antibodies within subepithelial immune deposits[147]. However, clinical application of this paradigm can be difficult, in part because culprit antigens are generally unknown. Although fulfilment of these criteria provides strong support for an aetiological link, especially in patients with THSD7A-associated MN, their absence does not refute it.

The role of malignancy in patients with MN who are PLA2R antibody positive is debatable[148]. PLA2R antibody positivity has been reported in a minority of patients with MN associated with solid tumours but, in one study, no patient with PLA2R-associated MN went into remission with malignancy treatment alone, suggesting a coincidental process rather than a causal relation[131]. However, 10% of the patients tested negative for all seven known antigens associated with MN and 25% of these had a malignancy[131]. In a large series of 91 patients with NELL1-associated MN, 33% had an associated malignancy[68]. Patients with NELL1-associated MN were older than patients with PLA2R-associated MN (mean age 66.8 ± 10.8 years versus 56.4 ± 13.9 years, respectively) and patients with NELL1-associated MN with malignancy were significantly older than patients with NELL1-associated MN without malignancy (71.0 ± 8.6 years versus 65.0 ± 10.5 years; $P = 0.01$). By contrast, in a study from China that included 15 patients with NELL1-associated MN (median age 49 years, range 44–50 years), no association with malignancy was found[149].

In practice, we recommend that patients who present with MN should undergo a thorough evaluation for

Box 2 | **Evaluation for associated conditions (regardless of serology)**

Laboratory

- Phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A) antibody testing
- Complete blood count
- Extensive laboratory analysis with serum albumin
- Urinalysis
- 24-hour urine collection for protein quantification[a] and creatinine clearance
- Antinuclear antibodies and anti-double-stranded DNA antibodies
- Hepatitis B and C virus serology
- Serum C3 and C4 complement levels
- Monoclonal protein studies, including serum-free light chains and serum protein immunofixation

Age-appropriate cancer screening

Sarcoidosis

Autoimmune thyroiditis

Drug exposure

- NSAIDs, penicillamine, elemental mercury, antitumour necrosis factor agents

Bone marrow transplant and graft-versus-host disease

IgG4-related disease

- In patients with pancreatitis, tubulointerstitial nephritis or sialadenitis

Rare infectious causes

- Schistosomiasis, malaria (specifically quartan fever), and congenital and secondary syphilis

The initial work-up for associated conditions may vary depending on local clinical practice.
[a]A reasonable compromise is to collect an 'intended' 24-hour urine sample and measure a urinary protein to creatinine ratio in an aliquot of the collection.

possible occult malignancy, especially if they are negative for PLA2R antibodies or positive for THSD7A or NELL1 antibodies. The evaluation should consist of most age-appropriate screening tests, including colon cancer screening, mammography, kidney ultrasonography, a prostate-specific antigen assay in men and a chest radiograph (or a chest CT in patients at high risk) (BOX 2; Supplementary Box 1)[134]. Ongoing vigilance is necessary because the diagnosis of cancer may not be immediately obvious.

Children

MN rarely affects children (0.1 cases per 100,000 per year)[150]. However, its frequency may be underestimated in this age group as children <10–12 years of age with nephrotic-range proteinuria are usually treated empirically with oral glucocorticoids without performing a renal biopsy. As childhood progresses, MN as a cause of nephrotic syndrome becomes more frequent, increasing from 1–2% at ages 1–5 years to 18–22% at ages 18–20 years. A rare form of congenital MN that is limited to only a few families worldwide is caused by a maternal homozygous mutation in *MME*, which encodes NEP[52,151]. The SEM3B-associated form of pMN typically occurs in children (even <2 years of age) and in young adults[70]. BSA-related MN should also be considered in children <5 years of age[80].

Similar to adults, particularly in regions with endemic HBV infection, young children presented with HBV-associated MN that is responsive to antiviral treatment[152]. This form of MN has decreased steeply with widespread vaccination against HBV[152]. In adolescents, MN can occur in patients, typically female, with renal involvement secondary to SLE (class V lupus nephritis). At this age, pMN also occurs, especially but not exclusively associated with PLA2R[153].

When MN is diagnosed in a child, the most likely causes must be identified, taking into account the child's age[153]. Briefly, the congenital NEP form of MN must be suspected in neonates; the BSA-related form in infants; the SEMA3B form in children aged 1–3 years; the enzyme replacement therapy form in children with a metabolic disease receiving recombinant human arylsulfatase B or α-glucosidase;[154] the HBV-associated form in children living in areas with endemic HBV infection, particularly in those aged 5–7 years; and either SLE or primary forms of MN driven by one of the known antigens, particularly PLA2R, in children aged >10–12 years. In addition to SEMA3B-associated MN, the actual incidence of MN involving other known antigens in children still needs to be investigated; forms of MN associated with THSD7A have been described as well as a single patient each with NCAM1-associated and with EXT1 and EXT2-associated forms of MN.

The outcome of pMN in children is unpredictable and spontaneous remission occurs in ~30% of patients. Overall, prognosis in paediatric forms of MN seems better than in adults[153]. In a retrospective study of 217 children with pMN, after a median follow-up of 45 (23.5–74.0) months, the cumulative kidney survival rates at 5 years and 10 years after renal biopsy were 95.3% and 67.8%, respectively[155].

Low-income regions

In low-income settings, patients with nephrotic syndrome due to MN often present with late-stage disease, sometimes with complications[156]. The presence of vascular thrombosis might prevent a kidney biopsy as patients need immediate therapeutic anticoagulation. Lack of specialist facilities limits the ability to fully evaluate these patients, including investigations to rule out secondary causes of MN, serological testing and kidney biopsy. Special attention needs to be given to rule out locally prevalent infections such as HBV or HCV. According to the Global Kidney Health Atlas, laboratory facilities for assessment of urinary protein levels or albumin creatinine ratios were available in <5% and <55% and renal pathology services were available in only 12% and 46% of low-income and lower-middle-income regions, respectively[157]. Even where pathology is available, immunofluorescence microscopy, PLA2R staining or electron microscopy are not routinely performed in many centres.

Prevention

Infections with HBV, HCV or HIV are important preventable causes of MN. Of these, HBV infection can be prevented with a vaccine. According to the WHO, the prevalence of HBV infection is above the global median of 3.5% in sub-Saharan Africa, Southeast Asia, and Central Asia and exceeds 10% in several African regions. Universal HBV vaccination has effectively eliminated HBV-associated MN in high-income regions[25]. However, vaccination coverage remains dismal in low-income regions, with only 6% coverage in the WHO African region[158].

Ingestion of heavy metals is associated with the development of MN. Heavy metals are often identified as contaminants in indigenous medications in India and China[159]. Better regulation of their use can help prevent MN. A study from China[18] identified a strong association between air pollution and the increasing prevalence of MN. These data identify important gaps in our knowledge of the broader environmental determinants of this condition. The findings highlight the need to develop sustainable approaches to address the preventable causes of MN through actions that regulate the use of indigenous medicines and address emerging environmental challenges[160].

Management

The initial non-immunosuppressive treatment of patients with pMN is guided by the complaints and (expected) complications at presentation and depends on the severity of proteinuria. Intensive monitoring enables the estimation of whether the patient is at risk of progressive kidney function deterioration. Immunosuppressive therapy, targeting the abnormal autoimmune response, should be considered in patients at risk. The introduction of a quantitative ELISA assay to measure antibody levels (only available for PLA2R antibodies) has enabled improved risk prediction and treatment guidance. For the time being, treatment approaches overall do not differ for the pMN forms associated with different antigens but most data are available

for PLA2R-associated MN, which can facilitate more tailored management in patients with this form of MN. In patients with sMN, treatment of the underlying cause is warranted; however, patients with sMN who do not respond should receive therapy as proposed for pMN.

Supportive treatment of nephrotic syndrome

In nephrotic syndrome, oedema formation is dependent on water and sodium retention. Oedema contributes to immobility, fatigue, discomfort, skin blistering, infections and anxiety. Treatment is empirical and not evidence based[161]. Initial treatment includes a sodium-restricted diet and loop diuretics (furosemide or bumetanide). In patients with insufficient response, a second diuretic is added (thiazide, acetazolamide or a potassium-sparing diuretic). Theoretically, amiloride should be most advantageous in view of the evidence of increased activation of collecting duct ENaC[162]. In clinical practice, combinations of diuretics are often effective and the choice is guided by serum electrolyte levels and adverse effects of medications (BOX 1). Patients with severe oedema often require hospital admission for treatment with intravenous diuretics, sometimes supplemented with albumin infusions[161]. In patients with hyponatraemia, water restriction is advised. After attaining sodium balance, blood pressure treatment should continue, targeting a blood pressure of 125–130/75–80 mmHg (REFS[130,163]). Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers are preferred as they have antiproteinuric effects and evidence suggests that their use may increase spontaneous remission rates in patients with pMN[164].

Patients with nephrotic syndrome often develop hypercholesterolaemia. Guidelines advise the use of statin therapy in patients with persistent proteinuria and hypercholesterolaemia, especially in patients >50 years of age, to provide cardiovascular protection[130]. The use of statins in MN is further supported by their suggested role in the prevention of venous thromboembolic events[165].

Indeed, patients with MN are at high risk of venous and arterial thrombotic events and the incidence is highest within 6–12 months after disease onset[165]. Thus, already at the time of presentation and diagnosis, prophylactic anticoagulation must be considered, taking into account individual patient characteristics, disease severity, and patient and family history (Supplementary Box 2). Most guidelines suggest the use of early, prophylactic anticoagulation according to algorithms that consider all parameters that affect the risk of thrombotic events and bleeding[130]. Treatment with warfarin is often used as standard therapy; however, there are good arguments to start treatment with low-molecular-weight heparin (at low to moderate dose intensity) at the time of diagnosis and switch to warfarin after 3 months if nephrotic syndrome persists[166]. In patients who are not candidates for warfarin or are treated with low-intensity low-molecular-weight heparin and have other risk factors for atherosclerotic vascular events, the use of aspirin must be considered[167]. The use of the new class of direct-acting oral anticoagulant drugs for thrombosis prophylaxis in nephrotic syndrome cannot be recommended[168]. Direct-acting oral anticoagulant drugs have not been studied in nephrotic syndrome and some patients with nephrotic syndrome developed thrombosis while using them[169]. High protein binding, the contribution of renal clearance to drug elimination, and the role of CYP3A4 and p-glycoprotein in drug metabolism (interfering with the kinetics of CNIs) could all affect their use in nephrotic syndrome[168].

Immunosuppressive therapy

Cyclophosphamide and corticosteroids. Long before the identification of pathogenic antigens and specific auto-antibodies, pMN was recognized as an immune-mediated kidney disease, which fostered the use of prednisolone and other immunosuppressive drugs. RCTs showed that a combination of an alkylating agent (preferably cyclophosphamide) and prednisolone attenuated the progression to kidney failure in patients with MN[170]. However, the 2012 KDIGO guidelines did not recommend the unrestricted use of this therapy in patients with MN[163]. First, ~40% of untreated patients do not progress to kidney failure and many develop spontaneous proteinuria remission. Second, treatment with cyclophosphamide and corticosteroids is associated with considerable adverse effects (BOX 1). Thus, it was advocated to restrict cyclophosphamide-based therapy to patients with MN and a high risk of kidney failure[171]. The guideline used persistent proteinuria of >4 g per day after 6 months of non-immunosuppressive therapy as the criterion of high risk. This criterion is not very accurate as the rate of spontaneous remission in these patients can be 45%[8]. The optimization of therapy (in terms of risk–efficacy balance) in patients with MN requires the early and accurate identification of patients who will progress to kidney failure (or will develop severe complications of nephrotic syndrome) and the introduction of effective, less toxic and alternative immunosuppressive therapies.

Risk prediction. Serum creatinine levels and proteinuria are the oldest biomarkers to estimate the risk of progressive disease associated with increased cardiovascular morbidity and mortality, and ultimately leading to kidney failure. Many other reported biomarkers lack sensitivity and/or specificity and have not been validated[172] (TABLE 2). Baseline serum creatinine levels (cut-off value 1.5 mg/dl) identify patients at high risk relatively late at a time when kidney function is already compromised. While patients with persistent non-nephrotic proteinuria do not develop renal insufficiency[173,174], nephrotic syndrome by itself is not an accurate prognostic biomarker as 40–45% of patients with nephrotic syndrome do not progress. One study showed that no less than 22% of patients with baseline proteinuria >12 g/day develop spontaneous remission[164]. Monitoring the course of kidney function and proteinuria during follow-up improves risk prediction[164,175,176]. The Toronto risk score combines kidney function and proteinuria parameters. This score has been validated and showed good performance[177] but it can only be calculated after 12–24 months of follow-up. Measurement of low-molecular-weight proteins in urine at baseline provided similar accuracy as the Toronto risk score[178]. PLA2R antibody levels had no added value in

Table 2 | **Clinical criteria for assessing the risk of progressive loss of kidney function**

Criterion	Cut-off	Remarks
Validated and clinically relevant		
Serum creatinine	1.5 mg/dl	Toronto risk score combines these three parameters; risk score denotes chance (%) of progression; requires follow-up of 12–24 months
Change in eGFR	>20% decrease in <24 months	
Proteinuria	>8 g/day for >6 months	
Change in proteinuria	>50% decrease in 12 months	Unlikely to progress; high likelihood of remission
Urinary α_1M excretion	50 µg/min	Urinary β_2M cannot be measured if urine pH <6; α_1M easier to use in clinical practice; can be used at baseline, accuracy is equal to Toronto risk score; accuracy increases with repeated measurement after 6–12 months
Urinary β_2M excretion	1 µg/min	
Urinary IgG	250 mg/day	Less accurate than urinary low-molecular-weight proteins
Not validated, clinically useful		
Serum albumin	Not precisely defined; <20 g/l by bromocresol purple or immunometric assay	Large bias between different albumin assays; cut-off values not validated
Serum PLA2R antibody levels	Not precisely defined; >150 RU/ml	In univariate analysis prognostic predictor; levels >150 RU/ml can be considered high
Not validated, limited added value		
Age	NA	Increased age is risk factor, mainly explained by reduced eGFR at baseline
Gender	NA	Increased risk in men, explained largely by worse baseline characteristics
Urinary complement C3 and C5b–9	NA	Not validated
Blood pressure	NA	Not validated in the current era of strict blood pressure control and use of ACE and/or ARB
Kidney biopsy markers (FSGS, IFTA)	NA	No independent predictive value
Kidney injury markers (KIM1, NGAL, βNAG, L-FABP, H-FABP)	NA	Less accurate than α_1M or β_2M
Urine protein selectivity index	0.20	Less accurate than total urinary IgG excretion

α_1M, α_1-microglobulin; β_2M, β_2-microglobulin; βNAG, *N*-acetyl-β-glucosaminidase; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; H-FABP, heart-type fatty acid-binding protein; IFTA, interstitial fibrosis tubular atrophy; KIM1, kidney injury molecule 1; L-FABP, L-type fatty acid-binding protein; NA, not available; NGAL, neutrophil gelatinase-associated lipocalin; PLA2R, phospholipase A2 receptor. Data from REFS[164,172,175–179,186,233,234].

a prognostic model that included proteinuria and serum creatinine levels but, in univariate analysis, high PLA2R antibody levels were specific (>80%) for predicting progression, with positive predictive values of 77% for 150–300 RU/ml and 87% for >300 RU/ml (REF.[179]).

On the basis of biomarker assessment, the KDIGO 2021 guideline defines four risk categories: low, moderate, high and very high risk[130] (TABLE 3). Although the disease characteristics of most patients may not perfectly fit one category and risk classification is not very accurate and partly based on low-quality data, the classification provides guidance in patient management. Because patients are seen at various phases of the disease, some entering immunological remission while others having increasing immunological activity, one cannot rely on a snapshot measurement of PLA2R antibody levels and proteinuria to predict the risk of progression but rather on the trajectory of these variables[180]. Thus, risk evaluation is a dynamic process and it is important to re-evaluate risk prediction at 3 months and 6 months after diagnosis as the changes in PLA2R antibody levels and clinical parameters may affect treatment indications. For example, a severe nephrotic syndrome with persistently high PLA2R antibody levels at 3 months will prompt starting immunosuppressive treatment. Further studies are needed to define more specific biomarkers that would predict progression at baseline ideally from the urine via exosomes, although the varying time points of sampling in the natural history of the disease will probably make interpretation difficult.

CNIs and CD20-targeted therapy. The introduction of novel immunosuppressive agents offered hope for effective, less toxic therapy in patients with pMN. CNIs, such as cyclosporine and tacrolimus, indirectly affect B cell function and were proven effective in preventing immunological rejection after kidney transplantation. In addition, experimental studies suggested that CNIs directly target the podocyte, thereby reducing proteinuria[181]. The development of CD20 antibody treatments, such as rituximab, enabled effective depletion of B cells and thus the selective targeting of antibody production.

Both CNIs and rituximab, alone or in combination, are considered less toxic than cyclophosphamide and

prednisolone. A review of clinical trials concluded that CNIs increased the likelihood of partial and complete proteinuria remission compared with no treatment (72–75% versus 22%)[170]. Additionally, remission rates at 12-month follow-up were comparable and numerically higher than those of cyclophosphamide treatment (CNIs 71–89%; cyclophosphamide 65–77%); however, the disease relapses after withdrawal of CNIs in most patients. In one RCT, relapses within 12 months after remission occurred in 40% of patients treated with tacrolimus and in 7% of patients treated with cyclophosphamide[182]. The efficacy of rituximab was also studied in RCTs. In the GEMRITUX trial, after 23 months of follow-up, the remission rate was 66% in patients treated with rituximab (total dose 750 mg/m^2) and 45% in those who received conservative treatment[8]. In the MENTOR trial, although rituximab (total dose 4 g) was non-inferior to cyclosporine in inducing remission at 12 months after treatment start, more patients who received rituximab maintained remission at 12 months after withdrawal of therapy (60% versus 20%)[9]. In the STARMEN trial, although sequential therapy with tacrolimus (for 6 months) and rituximab (single dose 375 mg/m^2) was inferior in inducing remission than the combination of cyclophosphamide and prednisolone (84% versus 58% at 24 months), the single dose of rituximab prevented relapse after withdrawal of tacrolimus[10]. The most recent RI-CYCLO trial compared rituximab (total dose 2 g) with cyclical cyclophosphamide and corticosteroids[11]. This study was underpowered and included mostly patients at moderate risk with low anti-PLA2R antibody levels. Although the authors concluded that the study provided "no signal of more benefit or less harm associated with rituximab", the per-protocol analysis showed a significantly lower complete remission rate at 12 months in patients treated with rituximab than patients treated with cyclophosphamide and corticosteroids (13% versus 34%; OR 0.28, 95% CI 0.08–0.95). Subgroup analysis suggested superiority of cyclophosphamide treatment in men and in patients with increased proteinuria and decreased serum albumin levels.

Thus, there is evidence that CNIs and rituximab (alone or in combination) induce remission of proteinuria, which should translate into improved renal outcomes, although this has not yet been proven. However, overall failure rates with these agents are 30–35%, raising controversies on the ideal dosage and best protocol. Some data suggest that cyclophosphamide is more effective in patients at high risk[183]. The guidelines argue against the use of CNIs or rituximab in patients with deteriorating or decreased GFR; however, other data with rituximab are encouraging[184].

Individualized treatment. Risk biomarkers, clinical characteristics, adverse effects, and patient and physician preferences can all be used to individualize therapy in patients with MN (FIG. 4). Patients at low risk do not need immunosuppressive therapy[130]. Patients at moderate risk can receive rituximab or a CNI — the controversial use of CNI in this indication is to decrease the duration of proteinuria in those with a high potential of spontaneous remission. In patients at high risk, single-agent rituximab treatment is now established in addition to combinations of cyclophosphamide and prednisolone. However, the

Table 3 | **Risk classification of patients with membranous nephropathy**

Risk category	Definition	Remarks
Low risk	Normal eGFR, proteinuria <3.5 g/day and serum albumin >30 g/l	Non-nephrotic, progression preceded by the development of overt nephrotic syndrome; serum albumin measured by BCP or immunoassay
	Normal eGFR and proteinuria decrease >50% in 6–12 months	Unlikely to progress; high likelihood of remission
Moderate risk	Normal eGFR; proteinuria >4 g/day for >6 months; proteinuria decrease <50% in 6 months; not fulfilling high-risk criteria	Likelihood of spontaneous remission ~40%
High risk	Serum creatinine <1.5 mg/dl, proteinuria >4 g/day for >6 months; proteinuria decrease <50% in 6 months AND at least one of the following: Toronto risk score >80%; proteinuria >8 g/day for >6 months; eGFR <fifth percentile (age adjusted); PLA2R antibody levels >50 RU/ml; urinary α_1M >40 µg/min; urinary β_2M >1 µg/min; urinary IgG >250 mg/day	Prefer using serum creatinine criteria over eGFR; when using eGFR consider the age-dependent decrease of eGFR; Toronto risk score combines proteinuria, eGFR and eGFR change; risk score denotes chance (%) of progression; PLA2R antibody levels need validation
Very high risk	Serum creatinine >1.5 mg/dl; eGFR decrease >20% attributed to membranous nephropathy; severe nephrotic syndrome; high risk AND PLA2R antibody >150 RU/ml	Severe nephrotic syndrome: untreatable oedema, dyspnoea due to pleura effusion; serum albumin <15 g/l; PLA2R antibody >150 RU/ml: low rate of response using standard-dose rituximab

There are no hard cut-offs between risk categories. The classification should be used as a guide and, in the individual patient, all available clinical and laboratory characteristics should be used to narrow the risk profile. Age, sex, blood pressure, kidney biopsy (focal segmental glomerulosclerosis, interstitial fibrosis tubular atrophy), other kidney injury markers (kidney injury molecule 1, neutrophil gelatinase-associated lipocalin, *N*-acetyl-β-glucosaminidase, L-type fatty acid-binding protein, heart-type fatty acid-binding protein, protein selectivity index) are suggested risk biomarkers and, although inferior to the validated risk biomarkers, they can add to individual risk assessment, if available. α_1M, α_1-microglobulin; β_2M, β_2-microglobulin; BCP, brome cresol purple; eGFR, estimated glomerular filtration rate; PLA2R, phospholipase A2 receptor. Adapted from REF.[130], KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.

long-term benefit on kidney function of CD20 antibody therapy remains unclear and its efficacy to induce immunological remission seems to be reduced in patients with very high antibody titres[183], although this view has been challenged[185]. Patients at very high risk should receive a combination of cyclophosphamide and prednisolone.

In the individual patient, the ultimate choice of treatment requires a discussion of benefits and risks considering the expected burden of adverse effects (Supplementary Box 3; Supplementary Tables). Future studies should define the best dosage and protocols adapted to the patient and integrate the new advances in the field of immunotherapy, including new CD20 antibodies, belimumab (a monoclonal antibody that inhibits the B cell-activating factor (BAFF)), anti-plasma cell therapy and anti-complement therapy. These new agents should be discussed in patients with refractory disease in expert centres.

Monitoring immunosuppressive therapy. Immunosuppressive therapy is usually given according to standard treatment protocols of therapy dosing and duration[130]. Patients should be monitored for adverse effects (BOX 1) and therapy efficacy is ascertained by improvements in proteinuria, serum albumin levels and (if applicable) serum creatinine levels. Clinical response to cyclophosphamide or rituximab is notably slow and partial remission of proteinuria only develops after 6–18 months, often after withdrawal of therapy[10,78]. Thus, in patients with persistent nephrotic syndrome but stable eGFR after 6 months, no change in treatment is required.

In PLA2R-associated MN, measurement of PLA2R antibody levels aids treatment decisions (FIG. 5). Cyclophosphamide was more effective than rituximab in inducing immunological remission in patients with high PLA2R antibody levels[186], which explains the low (30%) remission rate after one dose of rituximab in patients with high antibody levels[79]. Treatment should induce immunological remission. The disappearance of PLA2R antibodies (using the IFA; when using ELISA, the titre should fall below 2 RU/ml) predicted remission of proteinuria, whereas persistence of PLA2R antibodies after therapy was associated with progressive disease[78,187].

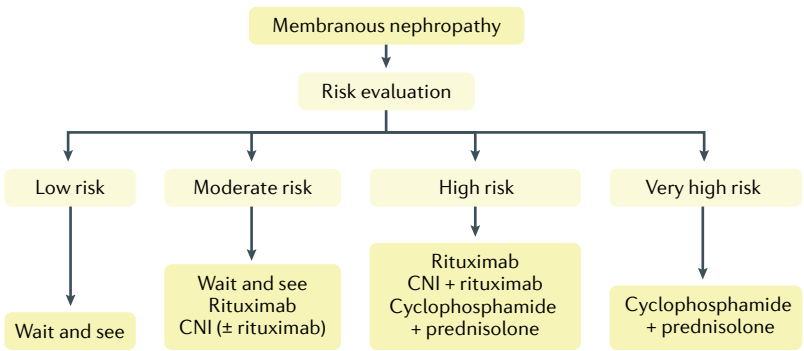

Fig. 4 | **Risk-based therapy in membranouse nephropathy.** In patients with primary membranous nephropathy (MN), efforts must be made to estimate the risk of kidney function deterioration using clinical criteria (TABLE 2) and risk classification (TABLE 3). As the risk profile will change during the follow-up period, risk should be evaluated regularly. Immunosuppressive therapy should not be used in patients at low risk. By contrast, patients at very high risk should receive the most effective but also most toxic therapy with cyclophosphamide and prednisolone. Different treatment options can be considered in patients at moderate and high risk, guided by patient and physician preference, expected adverse effects, therapy reimbursement, and other factors. Although calcineurin inhibitor (CNI) monotherapy is probably less effective, it is an option in patients at moderate risk of progression. CNIs shorten the period of proteinuria and can be used in a regimen combined with rituximab. Adapted from REF.[130], KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.

Children

Given the rarity of paediatric MN, children with MN should be managed in expert centres and treatment should be targeted. Secondary forms of MN require management of the underlying condition (for example, HBV infection or SLE)[188]. Primary forms of MN, especially in adolescents, can be treated similarly to adults. Supportive therapy with inhibitors of the renin–angiotensin system and low-salt diet is essential. A key difference to the situation in adults is that many children, especially if <10–12 years old, are diagnosed with MN after already having received oral prednisolone for 4–8 weeks. Treatment with CNIs or rituximab follows the same dosing regimen employed for adults. When these therapies are available, cyclophosphamide is rarely used[189].

Low-income regions

In resource-poor settings, patients often do not present until the disease has progressed to a severe nephrotic state and/or a complication has occurred, for example, vascular thrombosis or infection such as pneumonia. This prevents the timely initiation of non-immunosuppressive antiproteinuric therapies with drugs that block the renin–angiotensin system. The lack of specialist nephrologists limits the application of personalized medicine principles such as individualizing evidence-based therapies according to the patient's risk status[190]. Finally, the full range of treatments may not be available because a drug (for example, rituximab) is not marketed in the country or is too expensive. New treatments that are currently under investigation and monitoring approaches, such as PLA2R antibody assays, are likely to further increase treatment costs and therapeutic inequity. Treatment compliance can be a problem and contribute to suboptimal responses.

Potential solutions include a resource-sensitive adaptation of clinical practice guidelines by global organizations such as KDIGO and ISN[191], using information technology tools to support the implementation of standard treatment pathways through the available workforce via linking with expert centres by international cooperations (for example, through ISN Sister Centers programmes or Project ECHO), greater use of generic compounds and clinical trials of therapies to optimize the risk–benefit balance (for example, eliminating methylprednisolone pulses in the Ponticelli regimen). Advocacy is needed for greater involvement of low-resource regions in clinical trials of novel therapies with the commitment to make these treatments available as has been done for HIV therapeutics and SARS-CoV-2 vaccination.

Patients with a kidney allograft

Patients with pMN who do not tolerate or do not respond to immunosuppressive therapy will develop kidney failure and need kidney replacement therapy.

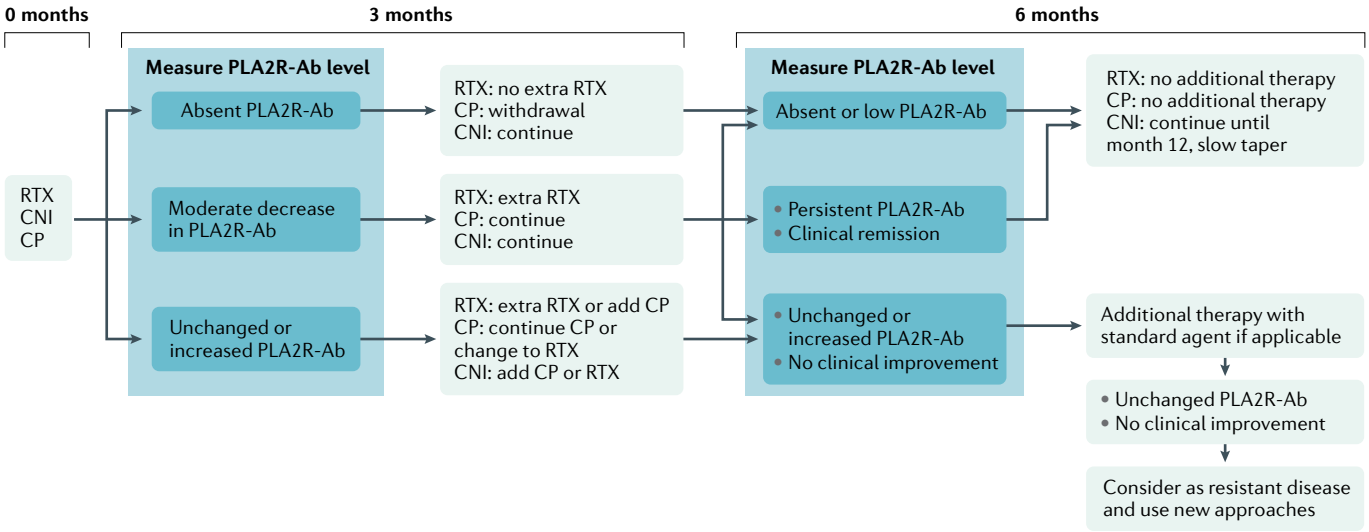

Fig. 5 | **Adjustment of therapy using PLA2R antibody monitoring.** In patients with phospholipase A2 receptor (PLA2R)-associated primary membranous nephropathy, regular evaluation of the course of PLA2R antibody (PLA2R-Ab) levels after the start of immunosuppressive therapy enables the optimization of immunosuppressive therapy in the individual patient. Immunological remission is the goal of therapy. The disappearance of antibodies can be used to taper or withdraw therapy, whereas persistence or increasing antibody levels should lead to continuation of therapy or to switching to an alternative drug regimen. No validated cut-off values exist. A negative immunofluorescence assay result or PLA2R ELISA titre <2 RU/ml defines the absence of PLA2R-Ab. When measuring PLA2R-Ab at regular intervals (every 2–3 months), a large decrease of antibody levels (>50%) to values <50 RU/ml may be sufficient as an initial response criterion. CNI, calcineurin inhibitor; CP, cyclophosphamide; RTX, rituximab. Adapted from REF.[130], KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.

Kidney transplantation is considered the best treatment option provided there are no contraindications for this surgical procedure. Apart from the routine pretransplant evaluation, in patients with pMN, the risk for recurrent disease after kidney transplantation should be assessed and discussed. In these patients, the histological recurrence rate is 50–60% and the clinical recurrence rate is 30–40%[192–197]. Increased age, short waiting time to receiving the transplant, heavy proteinuria at pretransplant evaluation, and corticosteroid-free maintenance immunosuppression after transplantation are associated with an increased risk of recurrence[192,193,197,198]. Recurrence rates are approximately threefold higher after transplantation of an organ from a living related donor[195,196], compatible with the observation that the risk of recurrence is dependent on donor HLA-D and PLA2R1 variants[90].

Pretransplant and post-transplant measurement of PLA2R antibody levels aids patient management (Supplementary Box 4). The most critical step is to unequivocally establish that MN is associated with PLA2R. In PLA2R-associated MN, the pretransplantation presence of PLA2R antibodies, especially at high titres, is associated with a high risk of recurrence, whereas undetectable PLA2R antibody levels predict a low risk[195,197,199]. A gradual decrease and disappearance of PLA2R antibodies after transplantation are associated with a reduced risk of recurrence (25% versus 71%)[195]. Although PLA2R antibody level measurement is therefore helpful, there are pitfalls and exceptions to the rule (Supplementary Box 4).

Rituximab treatment is effective in patients with recurrent MN following kidney transplantation[193,197]. Most patients (>80%) respond with complete or partial remission of proteinuria, which is preceded by the disappearance of the antibodies in patients who are PLA2R antibody positive. In 20–30% of patients, recurrent disease is non-progressive[193]. Thus, rituximab should be withheld in patients with persistent proteinuria at <1 g/day. There is no evidence-based benefit on the post-transplant outcome of treatment with rituximab before transplantation.

Quality of life

According to the WHO, health-related quality of life (HRQOL) is defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[200]. This broad concept encompasses multiple dimensions, including a person's physical health, psychological status, level of independence, social relationships and personal beliefs[200]. Systematic reviews have shown that various measures for quality of life (for example, Short Form Health Survey (SF-36); EuroQoL 5 dimensions (EQ-5D); Kidney Disease Quality of Life Instrument (KDQOL)) have been used in patients with chronic kidney disease[201,202]. However, data on the quality of life in patients with MN are limited[203].

Patients with MN have impaired quality of life and functioning compared with age-matched and gender-matched individuals in the general population[204,205], which may be further exacerbated by symptoms, for example, fatigue and oedema, and treatment burden[206]. Some unique features of MN can also affect quality of life such as the increased risk of thrombotic events.

A study by the Cure Glomerulonephropathy Network (CureGN) involving 478 children and 1,115 adults with glomerular diseases, including MN, found that oedema, female sex, weight (obesity) and estimated GFR correlated with decrements in HRQOL domains[203]. The findings also indicated that HRQOL was similar across different types of primary glomerular disease[203]. Another study conducted in patients with primary glomerular disease found that HRQOL was lower compared with healthy controls and was associated with proteinuria[205].

The need to include patient goals and preferences in the shared decision-making and assessment of interventions and care is increasingly recognized[207]. This is particularly relevant in MN because of the lack of well-defined tools for risk stratification to help with treatment decisions. Patient-reported outcomes, which reflect how patients feel and function, are assessed and reported directly by patients to provide a quantitative assessment of the effects of disease and treatment from the patient perspective[208,209]. However, patient-reported outcomes are infrequently reported in trials in patients with MN. HRQOL is an example of a patient-reported outcome; however, other outcomes are also important to patients, which may be implemented in research, practice and policy.

As part of the Standardized Outcomes in Nephrology – Glomerular Disease (SONG-GD) initiative, 134 patients with glomerular disease from Australia, the USA, the UK and Hong Kong identified and prioritized outcomes of importance and discussed the reasons for their choices. The highest-ranked patient-reported outcomes were life participation (defined as the ability to do meaningful activities), fatigue, anxiety, family impact and the ability to work[210]. The prioritization was driven by constraints on patients' day-to-day existence, impaired agency and control over health, and threats to future health and their family[210].

Further data on quality of life in patients with MN are needed, which may be gathered through routine measurement and reporting of HRQOL in research and clinical practice. Additionally, more evidence on interventions to improve quality of life and other patient-important outcomes, including life participation, fatigue, depression and anxiety, and the ability to work, is required. Ultimately, this may help to improve the care and outcomes of patients living with MN.

Box 3 | **Overcoming the gaps in membranous nephropathy knowledge**

Despite substantial progress, major gaps remain in our understanding of human membranous nephropathy (MN). The following points should be addressed as the field moves forwards.

1. Understand clinical variability and unpredictable disease outcomes with the goal of improving prognosis.
2. Assemble large databases of genetic, epigenetic and phenotypic information to fully define genetic control of disease susceptibility and expression.
3. Identify triggering factors for disease, such as air pollution, infection, tumour antigens and the target organ in which initial immunization occurs; explain why MN subtypes present at different patient ages.
4. Characterize the B cell and T cell populations involved at onset, remission, and relapse of disease and understand how they interact to modulate disease.
5. Identify precise B cell and T cell epitopes of phospholipase A2 receptor (PLA2R; and other antigens) at the molecular level, which is a prerequisite for targeted immunotherapy.
6. Establish the physiological roles of PLA2R, thrombospondin type 1 domain-containing 7A (THSD7A) and new antigens within the podocyte, glomerulus and/or extra-renal tissues.
7. Identify the as yet unknown antigens in uncharacterized forms of adult and paediatric MN as well as the composition of immune deposits in secondary MN.
8. Further analyse the role of complement, including the contribution of antibodies against complement regulatory proteins and functional polymorphisms in complement and complement regulatory proteins.
9. Fully establish the pathogenic mechanisms of antibodies, pathways of podocyte injury and glomerular basement membrane disorganization as well as repair mechanisms.
10. Use the emerging information to design new therapies such as anti-complement, anti-B cell-activating factor (BAFF) and targeted (epitope-specific) therapies.

Outlook

Despite the tremendous progress made over the past two decades, considerable gaps in our understanding of MN remain (BOX 3). The application of new technologies and opportunities to adopt investigative strategies from other disciplines will enable a continued exponential growth in our understanding of MN. The use of mass spectrometric techniques, initially used to subtype the deposits of renal amyloidosis, has led to an unprecedented discovery of new antigens in MN and this progress should continue with the identification of additional target antigens in paediatric, adult idiopathic and secondary forms of MN in addition to a better understanding of the similarities and differences in complement and matrix proteins involved in the disease subtypes. Mass spectrometric imaging can surpass the resolution of more conventional glomerular laser capture approaches by limiting analysis to even more defined regions of the cell or GBM[211,212].

Our ability to interrogate human and experimental biospecimens has become much more sophisticated. Advances in microscopy and cell labelling now include multiplexed immunofluorescence imaging technology for analysis of a large number of antigens or biomarkers (including complement components) and super-resolution imaging of the altered filtration barrier and molecules comprising the subepithelial deposits[213]. Single-cell RNA sequencing of human biopsy samples or experimental tissues can offer in-depth analysis of injury and repair pathways of all glomerular cell types as well as of downstream tubular and renal parenchymal and immune cells[214]. Similarly, single-cell RNA sequencing of circulating lymphocyte populations can characterize blood signatures of active disease, remission and progression, which could be used for patient monitoring and to define the antigen-specific B cell and T cell repertoire and their associated B cell and T cell receptors. These molecular data and computational analyses will further the efforts to develop novel antigen-specific or epitope-specific therapies, such as chimeric autoantibody receptor T cells that could target autoantibody-producing B cells[215], or to develop the use of antigen-derived peptides coupled to MHC class II to study or target T cells[216]. Targeted multi-omics of the urine[217] should continue to be developed, with special emphasis on shed complement and matrix components to characterize signatures of active disease, remission and

progression that enable better correlation of this 'liquid biopsy' with defined molecular features of kidney tissue.

High-resolution genetic data assembled from global registries of MN and control populations should be examined in the context of atlases of tissue-specific epigenetic regulatory elements and should be matched using machine learning approaches with records of phenotypic variation using information stored in electronic health records[218]. If this is possible at a large enough scale, previously unrecognized associations, susceptibilities and disease pathways in MN may come to light.

These knowledge gaps and new technologies should be prioritized in the next 5–10 years to focus on three major areas. First, understanding how genetic makeup, immune phenotype and exposures coalesce to cause disease initiation should be an overarching research goal, which in turn may lead to better prognostication, precision-guided therapeutics and monitoring, and avoidance of conditions that lead to relapse. Second, research should continue into the specific molecular mechanisms and pathways that cause glomerular injury and, in some individuals, rapid progression of parenchymal damage with ongoing proteinuria. Third, the field needs to move from broad immunosuppression of disease activity, which brings with it risks of infection and other substantial adverse effects, to more personalized and targeted therapeutics. Inhibition of the complement system seems to be the next therapeutic frontier in MN but further molecular understanding of the underlying pathological mechanisms could lead to even more novel ways to limit injury or stimulate reparative pathways. Our understanding of and ability to manipulate the immune system in MN is in its infancy but advances in immunology, oncology and infectious diseases (especially with the global emphasis on understanding the response to SARS-CoV-2) will drive our ability to rapidly interrogate the immune system in MN.

It is likely that substantial progress will be made in the therapeutic armamentarium in the near future, including new regimens to decrease the toxic effects of cyclophosphamide and corticosteroids, improving the use of CD20 antibodies with humanized, more potent molecules, such as obinutuzumab[219], and new therapeutic approaches (anti-BAFF, anti-plasma cell and anti-complement therapy), which should be discussed in patients with resistant disease.

At present, the therapeutic armamentarium has already been enriched with new drugs. CD20-targeted humanized antibodies (ofatumumab, obinutuzumab and ocrelizumab) are now available. They induce prolonged B cell depletion with a very low risk of immunization[219]. These are currently mostly indicated in patients who have developed serum sickness with rituximab and in those with refractory or multi-relapsing MN[220–222]. One can predict a growing role for these more potent biotherapies as ~30% of patients treated with rituximab will not undergo clinical remission and relapses are frequent.

Belimumab is a human IgG1λ monoclonal antibody that inhibits BAFF, thereby affecting B cell proliferation and survival[223]. Because rituximab increases the circulating levels of BAFF, combination therapy with belimumab could be considered[224]. Belimumab was used successfully in patients with lupus. At the end of a 2-year RCT, the renal response was better in patients who received belimumab plus standard therapy than in those who received standard therapy alone[225]. Belimumab was used with some efficacy in patients with MN in a small open-label, prospective, single-arm study[226] but further studies are needed.

Biotherapies targeting plasma cells must be seriously considered. Indeed, the relatively low rate of sustained complete remission in patients treated with rituximab is usually attributed to the involvement of $CD19^{-}CD20^{-}CD38^{+}CD138^{+}$ long-lived memory plasma cells that are niched naturally in the bone marrow and ectopically in the native and inflamed kidney. These non-proliferating plasma cells lacking CD19 and CD20 markers provide the basis for humoral memory and refractory autoimmune diseases[227]. These cells are targeted by anti-CD38 antibodies, which are used in ongoing trials (NCT04145440)[228]. Immunoadsorption and plasmapheresis have been used by several groups to enhance the depletion of circulating THSD7A antibodies and PLA2R antibodies in patients with severe MN[229,230]. Refractory disease is a current indication.

There is a strong interest in anti-complement therapies in glomerular diseases. MN seems to be among the most suitable for these treatments as complement is considered the main mediator of proteinuria, at least in experimental models. There are two windows of opportunity for anti-complement therapy: early before immunosuppressive drugs reach full efficacy and later in patients with partial or no remission. Several compounds targeting the lectin pathway and the alternative pathway are in early-phase trials[231].

New drugs are urgently needed but preclinical models of the disease remain limited in their ability to assess the efficacy of novel therapeutics. The development of MN models using rodents with humanized components of the immune system may enable a more effective translation and relevance to human disease. The field has come to understand how human IgG4 PLA2R antibodies can activate the lectin pathway of complement activation using human podocytes grown in standard culture models[104] but such single-cell-type in vitro systems ignore the complex interplay of closely apposed cell types within the glomerulus. New model systems, such as the glomerulus-on-a-chip that combines podocytes with endothelium in a microfluidic flow chamber[103] or induced pluripotent stem cells (from healthy individuals or patients) in vascularized organoid cultures[232], have the potential to enable a better understanding of the cell–cell interactions that drive disease and are amenable to high-throughput screening of compound libraries for drug discovery.

The future is bright for research into the pathogenesis and treatment of MN in all its forms and we encourage clinicians, scientists, patients, industry and regulatory agencies to come together with innovative and forward-reaching approaches. The involvement of patients both in defining the gaps and contributing to registries, biorepositories and research themes will be key to our common success.

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Author contributions

Introduction (P.R.); Epidemiology (P.R. and F.F.H.); Mechanisms/pathophysiology (L.B., H.D. and S.S.); Diagnosis/screening/prevention (F.C.F., V.J. and M.V.); Management (V.J., M.V. and J.W.); Quality of life (V.J. and A.T.); Outlooks (P.R. and L.B.); Overview of the Primer (P.R.).

Competing interests

L.B. is co-inventor on the patent "Diagnostics for Membranous Nephropathy" and has received consultancy fees from Alexion, Ionis, Genentech and Visterra for topics related to membranous nephropathy as well as research support from Sanofi Genzyme and Pfizer. P.R. has received consultancy fees from Alexion and MorphoSys for topics related to membranous nephropathy. F.C.F. has received consultancy fees from Alexion and MorphoSys for topics related to membranous nephropathy. F.F.H. has received consultancy fees from AbbVie and AstraZeneca. J.W. has received consultancy fees from Novartis and MorphoSys for topics related to membranous nephropathy. The other authors declare no competing interests.

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