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Podocytopathies

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Abstract

Podocytopathies are kidney diseases in which direct or indirect podocyte injury drives proteinuria or nephrotic syndrome. In children and young adults, genetic variants in >50 podocyte-expressed genes, syndromal non-podocyte-specific genes and phenocopies with other underlying genetic abnormalities cause podocytopathies associated with steroid-resistant nephrotic syndrome or severe proteinuria. A variety of genetic variants likely contribute to disease development. Among genes with non-Mendelian inheritance, variants in *APOL1* have the largest effect size. In addition to genetic variants, environmental triggers such as immune-related, infection-related, toxic and haemodynamic factors and obesity are also important causes of podocyte injury and frequently combine to cause various degrees of proteinuria in children and adults. Typical manifestations on kidney biopsy are minimal change lesions and focal segmental glomerulosclerosis lesions. Standard treatment for primary podocytopathies manifesting with focal segmental glomerulosclerosis lesions includes glucocorticoids and other immunosuppressive drugs; individuals not responding with a resolution of proteinuria have a poor renal prognosis. Renin–angiotensin system antagonists help to control proteinuria and slow the progression of fibrosis. Symptomatic management may include the use of diuretics, statins, infection prophylaxis and anticoagulation. This Primer discusses a shift in paradigm from patient stratification based on kidney biopsy findings towards personalized management based on clinical, morphological and genetic data as well as pathophysiological understanding.

The majority of diseases underlying chronic kidney disease (CKD) present with proteinuria, that is, loss of plasma proteins into the urine. Proteinuric kidney diseases can be divided into glomerular or non-glomerular forms, depending on whether protein loss occurs across the glomerular filtration barrier or results from insufficient reabsorption of filtered protein by the proximal tubule[1]. Glomerular proteinuria is defined by a predominance of albumin whereas, in non-glomerular forms, albumin is only a minor component.

Proteinuria and proteinuria-related symptoms are the only or the main clinical presentation of diseases affecting podocytes, which are 'octopus-like' highly specialized cells in the glomerulus that act as part of the filter[2-4]. Causes of podocyte injury include all forms of immune complex glomerulonephritis that engender distinct histopathological patterns; for example, subepithelial localization of immune complexes in membranous nephropathy causes direct podocyte injury and massive proteinuria. By contrast, podocyte injuries without immune complex deposits produce different histopathological lesion patterns evident on biopsy, of which four types can be distinguished: diffuse mesangial sclerosis (DMS), which presents early in life and is characterized by mesangial matrix expansion and podocyte hypertrophy[5]; minimal changes (also referred to as minimal change disease), which are predominantly present in children and are so-called owing to a seeming paucity of histopathological abnormalities that can only be visualized by ultrastructural analysis[5,6]; focal segmental glomerulosclerosis (FSGS) lesions, which involves sclerotic lesions evident in segments of glomeruli[4]; and collapsing glomerulopathy, which presents as collapse of the glomerular capillaries and hyperplasia of parietal epithelial cells migrating to the tuft to give the appearance of 'pseudocrescents'[4,5]. The stratification of patients with these histological

lesions has been complemented by clinical criteria, particularly the response to immunosuppressive therapy[2,4,6]. For example, most patients with minimal changes who respond to steroids have a favourable prognosis[6] but, for those resistant to steroids, the information from the kidney biopsy falls short in adequately allowing a personalized prediction of prognosis and the selection of optimal treatments directed to the specific cause of proteinuria.

Increasing knowledge about monogenetic causes of proteinuria or nephrotic syndrome as a molecular diagnosis has revealed that the histomorphological lesions of DMS, minimal changes, FSGS or collapsing glomerulopathy are unspecific lesions and represent different patterns of podocyte injury rather than defining a unique disease cause or diagnosis that would imply a specific therapy. Indeed, all these pathological patterns can be associated with the same genetic disease or the same pathological pattern can be associated with many different genetic diseases or treatment responses[2-4]. Thus, it has become important to rename this family of diseases as 'podocytopathies'[3,5,7], which accomplishes several objectives. This classification localizes the injury to the podocyte and implies a cellular target for therapy. The classification also helps to overcome the outdated notion that DMS, minimal changes, FSGS or collapsing glomerulopathy are 'diseases' or define a diagnosis. Finally, this approach prompts a diagnostic workup to identify the causative trigger or triggers of podocyte injury and to define individualized prognosis and treatment.

In this Primer, we present a conceptual reappraisal of the evolving knowledge concerning the podocytopathies usually referred to as DMS, minimal changes, FSGS and collapsing glomerulopathy in kidney biopsy reports. The literature often refers to these lesions as if they were definite diagnoses, yet they are not. The combination of proteinuria and the presence of any of these lesions on kidney biopsy defines podocyte injury as a unifying underlying mechanism that can result from numerous different causes and risk factors, each of which defines a different diagnosis and, possibly, a specific treatment. As such, the conceptual attempt of this Primer is to move away from the traditional view that considered tissue lesions as diagnoses and uses the term 'podocytopathies'. This approach requires a diagnostic workup to identify the underlying disease process and/or risk factors that produce the unspecific clinical and histological constellations. Our goal is to facilitate the understanding, clinical assessment and effective management of these disorders. We do not discuss podocyte injury secondary to systemic disorders, such as diabetes, immune complex glomerulonephritis, monoclonal gammopathies, amyloidosis or metabolic storage diseases, in detail as these are defined systemic disease entities that need other disease-specific treatment approaches (BOX 1).

Epidemiology

Prevalence

Reliable epidemiological data for podocytopathies are lacking. Pathological diagnosis is based on kidney biopsy and many patients, particularly children and individuals in low-resource settings, do not undergo biopsy. This reality introduces a bias towards steroid-resistant cases and under-reports the incidence of minimal change lesions in children. International biopsy registries report FSGS or minimal change lesions; the two rarer

subtypes (DMS and collapsing glomerulopathy) are usually included among FSGS in international registries (FIG. 1). Despite this limitation, the prevalence of podocytopathies, both relative to other glomerular disease entities and in absolute terms, seems to be increasing worldwide and they are major contributors to end-stage kidney disease (ESKD)[4]. This increased prevalence is partly due to the increased diagnosis given the increased global availability of kidney biopsy and pathological examination[4] and partly due to the increased prevalence of risk factors for podocyte injury[8]. However, the available data may underestimate the prevalence of podocytopathies. Indeed, idiopathic nephrotic syndrome in children (0–18 years of age) has a prevalence of 10–50 cases per 100,000 population globally[6] and is most commonly associated with minimal changes, although, in the majority of these cases, the pathological lesion pattern is not established by kidney biopsy[6]. Idiopathic nephrotic syndrome in children has a male predominance with a ratio of 3:1, for unknown reasons, and is an interesting research question, the answer to which might lead to pathogenetic insights[6]. Globally and considering all age groups, FSGS is the most common lesion (FIG. 1), representing 10–40% of all the biopsies, except in Asia, where IgA nephropathy is prevalent[9].

Risk factors

Podocytopathies can have a single cause, as frequently in the many monogenetic forms manifesting early in life (see Supplementary Table 1) or in the forms arising from a single environmental risk factor. Alternatively, podocytopathies can have a combination of multiple genetic and/or environmental risk factors causing podocyte injury, acting in concert to reach a threshold effect for the development of proteinuria.

Susceptibility genes.—Genome-wide association studies have identified several susceptibility genes associated with podocytopathies[10-14]. These genetic variants seemingly cannot cause a podocytopathy per se but represent important risk factors in the presence of a ‘second hit’. The best-studied association is with *APOL1* (encoding apolipoprotein L1), which involves protein-changing mutations (G1 and G2 alleles) that have an unusually large effect for common genetic variants. Individuals with sub-Saharan ancestry, and particularly west African ancestry, carry a 3–5-fold higher risk for FSGS lesions and CKD than European populations[15], with this disparity being largely explained by these *APOL1* genetic variants[16,17]. The frequency of *APOL1* risk alleles (G1 and G2 variants combined) is ~35% among African Americans, 26% in central African populations and ~50% in west African populations[18]. The enhanced protective effect of these gene variants against African sleeping sickness caused by *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense* likely explains their strikingly high allele frequency in these populations[16]. In areas of Africa with a high frequency of *APOL1* risk alleles, CKD prevalence reaches 16%[19].

High-risk *APOL1* alleles in kidney transplant recipients are linked to shorter allograft survival and lower post-donation estimated glomerular filtration rate (GFR)[20]. Transgenic animal studies in mice and flies indicate that the expression of either *APOL1* risk variant is sufficient to induce FSGS, global glomerulosclerosis and CKD; in these models, disease severity increases with increased *APOL1* expression levels[21,22]. In clinical studies, kidney biopsy manifestations of *APOL1*-associated kidney disease include FSGS lesions,

collapsing glomerulopathy and non-specific focal global glomerulosclerosis (affecting the entire glomerular tuft) with arterionephrosclerosis[23], similar to that observed in ageing and so-called hypertensive nephropathy[24,25]. Indeed, *APOL1* podocytopathy is a major cause among African Americans of what was formerly called hypertensive CKD[26,27].

Obesity and diabetes.—Conditions of increased single-nephron GFR and hence increased podocyte shear stress confer an increased risk of developing a podocytopathy. The increasing global prevalence of obesity contributes to the increasing prevalence of podocytopathies as well as to serving as a factor that accelerates CKD progression[8]. Obesity is associated with a substantial increase in body mass causing single-nephron hyperfiltration, which in turn causes podocyte hypertrophy and podocyte shear stress[28]. Obesity drives foot process effacement (FPE), the earliest morphological pattern of podocyte injury, and subsequent FSGS lesions[29-32]. The regression of proteinuria after bariatric surgery suggests that the earlier stages of this process are reversible[30]. Although progression is typically slow, ESKD develops in 10–33% of those with obesity-related CKD[30,32]. Likewise, diabetes mellitus is associated with glomerular hyperfiltration[33]. The GFR increase is driven by enhanced proximal tubular glucose and sodium reabsorption, mediated by sodium/glucose cotransporters (SGLTs) that lead to a reduction in afferent arteriolar resistance and an increase in single-nephron GFR through the inhibition of tubuloglomerular feedback[34]. Increased GFR in single remnant nephrons promotes podocyte stress driving FPE and podocyte detachment, leading to macroalbuminuria that accelerates renal function decline in long-standing and poorly controlled diabetes[34]. Hence, even recent onset of diabetes can promote proteinuria and podocyte loss, whereas the ‘diabetic nephropathy’ can take several years to develop.

Low nephron mass and nephron loss.—Conditions such as congenital kidney hypoplasia, unilateral agenesis and reflux nephropathy predispose to podocytopathy with proteinuria, hypertension and secondary FSGS lesions at biopsy (so-called secondary, because the podocyte is not primarily affected but is injured by external factors). Surgical studies in rodents and humans suggest that losing >75% of renal mass (nephrons) poses the greatest risk for developing proteinuria, glomerulosclerosis and, in some cases, progressive loss of kidney function[35]. Living kidney donors or patients who lose 50% of their kidney mass are at increased risk of proteinuria and hypertension but rarely develop progressive CKD, suggesting that, for most healthy individuals, a 50% reduction in renal mass is not sufficient to trigger progressive hyperfiltration injury[36]. Similarly, low nephron endowment due to low birthweight and pre-term birth are associated with CKD and FSGS lesions at biopsy, suggesting an adaptive podocytopathy[37]. The same process operates in all forms of CKD as nephron loss increases single-nephron GFR in the remnant nephrons. As ageing is also associated with nephron loss, adaptive FSGS lesions can also occur at older age. Sickle cell disease[38], glucose-6-phosphatase deficiency, glycogen storage disease type I, von Gierke disease[39], cyanotic heart disease[40], familial dysautonomia and extreme muscular hypertrophy (most commonly associated with body building)[41] are associated with podocytopathy in conditions in which single-nephron glomerular pressure and filtration rate as well as podocyte shear stress are all increased, ultimately causing nephron loss.

Mechanisms/pathophysiology

Podocytes are terminally differentiated epithelial cells, the primary and secondary processes of which extend to wrap around the basement membrane of glomerular capillaries in the glomerulus[7,25,42] (FIG. 2). Podocytes possess primary, secondary and tertiary foot processes, all of which contain an extensive actin cytoskeleton and interdigitate with the foot processes of adjacent podocytes. The ~200 nm gap between adjacent foot processes is spanned by the tri-laminar slit diaphragm, which serves as an ~60 kDa size-selective filter. The barrier is selective for both molecular size and electric charge, the latter property being conferred by anionic charges that retard the passage of anionic proteins. Even in the healthy glomerulus, podocytes must withstand circumferential stress and shear stress (FIG. 3). Podocyte loss following injury increases mechanical stress on the remaining podocytes.

Podocyte effacement, detachment and loss

Foot process simplification and FPE are the earliest morphological patterns of podocyte injury and can be associated with massive proteinuria even without podocyte loss. Incident injuries can induce FPE, which causes the podocytes to resemble immature podocytes of the developing kidney at the ultrastructural level[42]. The reorganization of the actin cytoskeleton plays a key part in FPE[43]. A functional imbalance among key regulators of the actin cytoskeleton, such as the Rho family of small GTPases, including RhoA, CDC42 and RAC1, is usually observed and can result in FPE[44,45]. RAC1 activity promotes the formation of a branched actin network as present in the podocyte lamellipodia[43]. RhoA activity favours actin polymerization and the formation of actin bundles[43]. A finely tuned balance between active RAC1 and active RhoA seems to maintain normal foot process morphology and function[43].

Although FPE is potentially reversible, podocyte detachment or death implies irreversible podocyte loss[46,47]. Indeed, live and dead podocytes appear in the urine of patients with glomerular disorders[45], which is thought to occur through a substantial increase in the mechanical forces of fluid filtration, leading to glomerular tuft expansion or podocyte fragility. Genetic, metabolic, toxic or inflammatory factors, such as increased expression of NOTCH and WNT/β-catenin by podocytes, promotes podocyte dedifferentiation and protects cells from cell death under injury conditions; however, as cells dedifferentiate into an earlier developmental stage, the concomitant loss of markers such as nephrin and podocin occurs, leading to functional defects[48]. These defects are also thought to contribute to podocyte detachment and loss[49] (FIG. 4).

The same mechanical forces that trigger the onset of a podocytopathy also accelerate established glomerular injury[46,47]. First, the fluid drag of oncotic pressure generated by albumin in the Bowman space increases shear stress on podocytes and hyperfiltration[46,47,49] (FIG. 3). Second, nephron loss during CKD progression and normal ageing reduces the total glomerular filtration surface, which increases filtration and the vertical podocyte shear stress at the level of the single nephron[46,47]. Third, remnant nephrons undergo an increase in size (hypertrophy) to compensate the nephron loss-related decline in filtration surface, which has the potential to lead to maladaptive podocyte hypertrophy. In addition, podocyte loss reduces podocyte density in the glomerular tuft, a process that results in increased horizontal stress

forces on the remaining podocytes[46,47]. The podocyte hypertrophic capacity is limited; hypertrophic podocytes may also be unable to maintain a normal foot process structure, increasing local shear stress[50], which triggers further podocyte detachment[51].

Podocytes are postmitotic cells and, although they can replicate DNA, they cannot complete cytokinesis[25]. When podocytes are lost, a subset of parietal epithelial cells along the Bowman capsule, which are resident podocyte progenitors, can supply new podocytes[52-56]. However, regeneration is frequently inefficient or can drive focal scarring. Indeed, the proliferation, migration and differentiation of parietal epithelial cells towards the podocyte lineage are tightly temporally and spatially regulated. The chemokine CXCL12 is normally constitutively produced by healthy podocytes and serves as a podocyte-to-progenitor feedback mechanism to maintain local podocyte progenitors in a quiescent state and to suppress their intrinsic capacity to generate new podocytes[53]. After podocyte loss, the reduced expression of CXCL12 promotes NOTCH activation in parietal epithelial cells, which drives their proliferation and migration towards the glomerulus. Podocyte loss also permits the passage of circulating retinol through the damaged glomerular filtration barrier, which is transformed into the Bowman space to retinoic acid; this acts as a powerful inducer of parietal epithelial cell differentiation into podocytes[56,57]. In addition, activated parietal epithelial cells synthesize retinoic acid to self-promote their differentiation into podocytes[56,57]. Retinoic acid induces *NOTCH* gene downregulation, cell cycle arrest and the upregulation of podocyte markers in parietal epithelial cells[56,57]. However, with high-grade proteinuria, retinoic acid is sequestered by albumin in the Bowman space[58] and parietal epithelial cell differentiation into podocytes is impaired. The absence of APOL1 also promotes parietal epithelial cell quiescence; the microRNA miR-193a suppresses *APOL1* translation[59]. Under conditions of mechanical stress[60], impaired APOL1-miR-193a axis (for example, in those with the G1 or G2 genotype)[59] or persistent NOTCH expression[61], activated parietal epithelial cells cannot properly differentiate into podocytes and contribute to the formation of hyperplastic lesions and fibrous lesions, including FSGS[58,62], by synthesizing and releasing extracellular matrix[63] (FIG. 4). Interestingly, superficial and mid-cortical nephrons retain a potent capacity for podocyte regeneration, which may explain why juxtamedullary nephrons are particularly susceptible to glomerulosclerosis[53].

Podocyte injury

In addition to associations with low nephron number and increased body mass, podocyte injury can result from genetic, immunological, infectious (for example, hepatitis C virus (HCV) infection) and toxic (for example, from various drugs and metals) causes. The prevalence of these syndromes differs across the lifespan and different contributing factors (and with different relative contributions) can occur in combination to reach a threshold of podocyte injury and loss.

Genetic causes.—Next-generation sequencing techniques have greatly facilitated the identification of ≥50 causal genes in hereditary podocytopathies (Supplementary Table 1). Moreover, DNA sequencing has revealed mutations in unexpected genes[64,65] and has widened the extrarenal phenotypes associated with podocyte gene mutations. For example, these approaches have identified that genes expressed in podocytes as well as genes

expressed in other tissues in the context of syndromic disorders are affected. Additionally, many small effect variants, mostly non-coding, conferring susceptibility for podocytopathies have been described in adults.

More than 50 genes mutated in hereditary podocytopathies have been identified to date, encompassing genes expressed in podocytes (FIG. 5). The discovery of these genes as monogenetic causes of steroid-resistant nephrotic syndrome (SRNS) has shown that particular proteins are critical for glomerular function. For example, the identification of mutations in *NPHS1* (encoding nephrin) and *NPHS2* (encoding podocin) demonstrated the central role of the slit diaphragm in glomerular function. Identification of *ACTN4* (encoding α-actin 4) and *ANLN* (encoding anillin) mutations emphasized the importance of the podocyte actin cytoskeleton in kidney physiology and pathophysiology[64,66-69]. A rare subset of patients carrying mutations in genes encoding Rho-like small GTPases are, at least partially, sensitive to immunosuppression, suggesting that glucocorticoids may also directly affect podocyte function[70]. Rare cases of steroid-sensitive nephrotic syndrome (SSNS) with apparent Mendelian transmission also exist but the gene or genes involved are unknown[71]. The discovery of recessive mutations in genes that participate in coenzyme Q_{10} biosynthesis (namely *COQ2*, *COQ6* and *ADCK4*) illustrates the opportunity for a 'personalized medicine approach' to specific podocytopathies as these patients may respond to oral coenzyme Q_{10} supplementation[72,73]. Thus, the availability of effective therapies for several genetic podocyte diseases supports the notion that genetic discovery can enable personalized medicine.

In the context of a syndromic disorder involving multiple organs, pathogenetic variants in genes expressed in other tissues can also cause podocytopathies[74] (Supplementary Table 1). For example, Alport syndrome, Dent disease and Fabry disease can all present as a podocytopathies, sometimes with minimal or absent extrarenal manifestations, and may manifest isolated FSGS lesions as a pattern of injury[64]. Often, there is an extra-renal phenotype in an organ that expresses the affected gene, for instance, sensorineural deafness in Alport syndrome, due to mutations in genes encoding collagen[75]. However, SRNS or isolated proteinuria, even in the nephrotic range, can sometimes be the only evident clinical sign of these disorders, at least at the time of presentation[65].

Immunological and soluble factors.—The effectiveness of glucocorticoids and other immunosuppressive drugs in many podocytopathies for which a genetic cause can not be determined suggests a central role of the immune system in the pathogenesis of these disorders; the direct effects of these agents on cultured podocytes have also been demonstrated[76] and, therefore, a local, non-immune effect is also possible. Several genome-wide association studies have revealed that HLA-DR and HLA-DQ are the strongest susceptibility loci for childhood SSNS in various populations[11-14]. These features, along with the absence of immune complex deposition and the spontaneous remission of proteinuria after measles infection, originally led to the consideration of these forms as T cell-mediated diseases[77]. Early studies proposed a 60–160 kDa glomerular permeability factor released from T cells isolated from a patient with nephrotic syndrome and minimal change lesions[6]. In a rat model, this factor induced proteinuria and tertiary FPE of podocytes but the causative protein has not been conclusively identified[6].

Subsequently, alterations in circulating T cell subsets and in cytokine profiles have been described in patients with podocytopathies, suggesting a shift towards a T helper 2 cytokine profile with a possible role for IL-4 or IL-13 as the circulating permeability factors[78-80]. Indeed, peripheral $CD4^+$ and $CD8^+$ T cells in children with SSNS express IL-13, a cytokine that can, upon experimental overexpression, induce a podocytopathy in rats[81]. The number of regulatory T cells (those that suppress immune responses) is also reduced in patients with podocytopathies compared with healthy controls and tends to normalize when remission of proteinuria is achieved[79,82,83]. Consistently, renal disorders including podocytopathy with a minimal changes lesion pattern and SSNS are reported in 20% of individuals with immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, a rare congenital immunodeficiency with severe regulatory T cell defects[84].

Evidence of persistent remission of proteinuria after treatment with rituximab or ofatumumab[85,86], both of which deplete B cells, sparked renewed interest in the role of B cells in these disorders, However, these agents may have effects independent of their effects on B cells. Rituximab has been reported to stabilize the podocyte actin cytoskeleton through its binding to a cross-reactive epitope of sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b)[87]. Ofatumumab was also effective in rituximab-resistant nephrotic syndrome[88]; whether it also binds to SMPDL3b remains unknown[88]. B cell-derived IL-4 promotes proteinuria in mice[89]; however, human studies have not been reported and so its relevance to proteinuria in humans remains to be established. Selective extracorporeal immunoadsorption induces the remission of nephrotic syndrome relapses, suggesting that the factor responsible for proteinuria could be an immunoglobulin or could bind to immunoglobulins[90]. B cells can also act as antigen-presenting cells and their depletion may also modify T cell function in patients with steroid-dependent nephrotic syndrome (SDNS)[91]. In a subset of patients, hyposialylated IgM on the surface of T cells predisposes patients to steroid dependence[92]; rituximab can reverse this phenomenon and improve outcomes. Furthermore, B cells may contribute to podocyte injury by other mechanisms; activated antigen-specific B cells can induce FPE and proteinuria through local release of IL-4 in vivo[89].

Other observations suggest a role for circulating permeability factors in patients with primary podocytopathies. First, some patients experience a relapse of nephrotic syndrome immediately after kidney transplantation but enter remission following plasma exchange[93]. Second, kidneys with minimal changes from deceased donors can undergo remission of proteinuria after transplantation into a non-proteinuric recipient[94]. At least three candidates for circulating permeability factors have been put forwards: cardiotrophin-like cytokine 1, soluble urokinase plasminogen activator receptor (suPAR) and anti-CD40 IgG[95]. Serum suPAR levels are reportedly higher in patients with FSGS than in those with other forms of proteinuric kidney disease such as membranous nephropathy[96,97], although numerous subsequent studies have attributed this finding to differences in GFR[98]. One study reported angiopoietin-related protein 4 (ANGPTL4), a glucocorticoid-sensitive secreted glycoprotein, as a circulating permeability factor in minimal change lesions[99] but this was not confirmed by other studies[100]. Overall, none of the proposed permeability factors elicits consistent proteinuric effects in vitro or in vivo and further testing of these interesting hypotheses is needed, including in large cohorts that encompass patients with FSGS and glomerular and non-glomerular disease controls[98].

Infectious agents.—Viral infections are common causes of podocytopathies, especially with a lesion pattern of collapsing glomerulopathy[101]. HIV infection can cause a characteristic podocytopathy with nephrotic syndrome and rapid disease progression. Histologically, HIV-associated nephropathy presents as the combination of collapsing glomerulopathy and marked tubular-interstitial disease, including microcystic tubular dilatation[102]. Other patients who are HIV-positive develop FSGS lesions without collapsing features[102]. Both forms of glomerular disease are associated with *APOL1* high-risk status, with 72% of African Americans with these disorders carrying two *APOL1* risk alleles[102]. Additionally, HIV infects podocytes in vivo and elicits cytotoxicity[102]. The associated type 1 interferon-mediated antiviral immune response promotes *APOL1* gene transcription, inducing inflammatory cell death pathways[21]; in addition, it further promotes podocyte death by mitotic catastrophe[103]. The estimated global prevalence of HIV-related CKD is of 6–12% of people who are HIV-positive[104]. HIV-related CKD is particularly prevalent in sub-Saharan Africa, where the high prevalence of both uncontrolled HIV1 infection and *APOL1* risk alleles predispose to CKD and to rapid progression to ESKD[105].

Chronic HCV infection also causes several immune-mediated glomerular disorders, including podocytopathy with FSGS lesions[106,107]. Although the pathogenic mechanisms are unclear, it is hypothesized that, similar to HIV, HCV directly injures podocytes, leading to glomerulosclerosis[107]. Eliminating HCV using antiviral medications can clear the virus from >95% of individuals with chronic HCV infection and improve the outcome by reducing proteinuria and preventing or delaying CKD[106].

Podocytopathy with FSGS and collapsing glomerulopathy may also occur as a consequence of the common childhood infection with parvovirus B19 (REFS[108,109]), with DNA evidence of parvovirus B19 in kidney tissue[109]. However, only a few individuals who are infected develop FSGS lesions and the predisposing factors to glomerular injury are unknown. Clearance of the virus can be associated with an improvement of proteinuria[108]. Epstein-Barr virus, cytomegalovirus infection and SARS-CoV-2 (the virus that causes COVID-19)[110] also cause podocytopathy[101]. SARS-CoV-2 can directly infect podocytes or indirectly harm them by promoting cytokine secretion, causing proteinuria with the pathological feature of a collapsing glomerulopathy[110]. Other pathogens that can trigger podocytopathies include *Borrelia* spp.[111], the plasmodium *Schistosoma mansoni* and filarial nematodes[4].

Pregnancy-related VEGF inhibition.—Renal physiological changes characteristic of pregnancy include increased renal blood flow and increased glomerular filtration. Factors that oppose the actions of podocyte trophic factors may cause podocyte injury and detachment. For example, podocyte-expressed vascular endothelial growth factor (VEGF)[112] acts in paracrine and autocrine ways to protect podocytes[113]. Pre-eclampsia is a disorder of pregnancy characterized by the onset of hypertension and often manifests with high proteinuria. Increased plasma levels of soluble FMS-like tyrosine kinase 1 (sFLT1), produced by the hypoxic placenta, antagonize VEGF action and cause podocyte loss and proteinuria[113]. In these patients, a podocytopathy can result from the combination of VEGF antagonism and pregnancy-related glomerular hyperfiltration, particularly when associated with excessive weight gain, diabetes or a multiple pregnancy, all of which increase

glomerular hyperfiltration[113]. In other contexts, treatment with anti-VEGF or anti-VEGF receptor agents, which are commonly used to prevent vascular proliferation in tumours and retinal diseases, can cause proteinuria and hypertension[114] and are associated with renal thrombotic microangiopathy and with podocytopathies, chiefly minimal change lesions and collapsing glomerulopathy[115].

Drugs.—Certain drugs can cause podocytopathies via direct toxic effects[4]. Interferon therapy can be associated with the development of collapsing glomerulopathy; indeed, IFNβ promotes podocyte death and IFNα inhibits the migration of podocyte progenitors. In addition, interferon inhibits the differentiation of podocyte progenitors into podocytes[6,116]. Finally, interferon is a potent stimulus to *APOL1* gene expression, driving podocyte damage in individuals with two *APOL1* risk alleles[117].

Bisphosphonate therapy, which is used to treat the loss of bone density, is rarely associated with a toxic podocytopathy and presents histologically as minimal change lesions with FPE, FSGS lesions or collapsing glomerulopathy[116]; the molecular mechanisms remain obscure. Lithium therapy to treat conditions such as bipolar disorders rarely causes proteinuria and minimal changes or FSGS lesions, which can resolve within weeks after stopping the drug[118]; however, the mechanism is controversial[119,120]. Sirolimus, doxorubicin and daunomycin can each cause a podocytopathy with FSGS lesions by directly inducing podocyte death[121-123]. Doxorubicin, used as a cancer chemotherapy in humans, is a podocyte toxin that is widely used to induce podocyte injury lesions in mice; it promotes mitotic catastrophe in podocytes, with consequent detachment, followed by FSGS lesions[124]. As already mentioned, VEGF antagonists cause a usually transient podocytopathy[114].

Clinical manifestations

Substantial proteinuria, with at least 50% of the protein being albumin, is the defining feature of the podocytopathies. The magnitude of urinary protein excretion defines a spectrum of conditions with increasing degrees of severity: sub-nephrotic proteinuria, nephrotic-range proteinuria and nephrotic syndrome (TABLE 1). In addition, podocyte injury and loss can contribute to a range of other clinical manifestations, including oedema and hyperlipidaemia, and increase the risk of infection.

Hypoalbuminaemia.—When the amount of albumin lost in the urine exceeds the capacity of the liver to replace the losses, the level of plasma albumin declines. The prevalence of hypoalbuminaemia varies even among patients with the same genetic disorder[65] for reasons that are unknown. One factor may be a variability in the capacity of the proximal tubule to catabolize albumin, returning amino acids to the circulation[125]. Why the liver, which normally produces ~15 g per day of protein in an adult, is unable to compensate for protein loss of 4–6 g per day in some patients but not in others is also unclear. One hypothesis is that TNF and IL-1 expression may suppress hepatic albumin synthesis and contribute to hypoalbuminaemia, at least in podocytopathies associated with inflammatory conditions[126].

Oedema.—Two main factors contribute to oedema development. First, sodium reabsorption in the renal tubules is influenced by proteinuria and proteasuria (overfill scenario)[127,128]; these patients are more likely to show arterial hypertension as a sign of hypervolaemia[128]. In adults, the onset of proteinuria is typically gradual and causes a parallel drop of oncotic pressure in plasma and in the renal interstitium, such that substantial extra-cellular volume shifts and acute kidney injury (AKI) do not typically occur. In adults, oedema develops from a positive sodium balance via increased sodium retention in the kidney. In children, acute onset of massive proteinuria typically develops together with severe hypoalbuminaemia (often <1 g/dl) without an equivalent drop of albumin in interstitial tissues throughout the body; this leads to a fluid shift from plasma to the relatively hyperoncotic interstitium[129].

An extracellular volume shift is the second factor contributing to oedema and is associated with a hypovolaemic state (underfill scenario). In some cases, hypovolaemia may present as shock, with hypotension, tachycardia, peripheral vasoconstriction, oliguria (including AKI), and compensatory elevations of plasma renin and aldosterone[130]. Intravascular hypovolaemia, despite total body sodium excess, may be sustained by diuretic therapy, sepsis or diarrhoea[131]. Interstitial oedema, ischaemic tubular injury, and the use of NSAIDs, diuretics and a renin–angiotensin system inhibitor (RASi) may contribute to AKI in such patients[127].

Thromboembolism.—Patients with nephrotic syndrome, even if asymptomatic, have a hypercoagulable state[132] related to a multitude of factors. These factors include urinary losses of endogenous anticoagulants, such as antithrombin III, plasminogen, protein C and protein S, as well as increased platelet activation, hyperfibrin-ogenaemia, inhibition of plasminogen activation by type 1 plasminogen activator inhibitor (PAI1) and the presence of high-molecular-weight fibrinogen moieties in the circulation[133]. The exit of saline from the glomerular capillaries into the urinary space, due to reduced plasma oncotic pressure, promotes haemoconcentration in the post-glomerular circulation, which is worsened by diuretic therapy. All of these factors likely contribute to the tendency to form thrombi, particularly in the renal vein[134].

Hyperlipidaemia.—Marked elevations in the plasma levels of cholesterol, LDL, triglycerides and lipoprotein A often occur in nephrotic syndrome[135]. Decreased plasma oncotic pressure probably stimulates hepatic lipoprotein synthesis, resulting in hypercholesterolaemia[135]. HDL cholesterol levels are usually normal or reduced in nephrotic syndrome and there is often a pronounced decline in the cardioprotective HDL2 fraction[135]. Nephrotic syndrome may manifest elevated levels of apolipoproteins B, C-II and E, which are associated with VLDL and LDL particles; on the other hand, the levels of the major apolipoproteins associated with HDL (apolipoproteins A-I and A-II) are usually normal[136]. ANGPTL4 contributes to a feedback loop driven by hypoalbuminaemia and free fatty acid concentrations that promotes hypertriglyceridaemia[137]. Altogether, these changes in lipid and lipoprotein profiles increase the risk of thromboembolism, premature atherosclerosis and progressive kidney disease[135].

Anaemia.—Patients with persistent nephrotic syndrome may develop anaemia due to urinary losses of iron, transferrin, erythropoietin, transcobalamin and other metals such as copper[138].

Endocrine disturbances.—Due to thyroglobulin loss in the urine, thyroid hormone (total T4 and T3) levels may be low, with normal serum free T4 and T3 and thyrotropin (thyroid-stimulating hormone) concentrations, and, as a result, patients are usually clinically euthyroid. Serum 25-hydroxyvitamin D and total calcitriol concentrations may also be reduced, but the functionally relevant free calcitriol concentrations are typically normal[139]. Hypocalcaemia is common owing to hypoalbuminaemia; this does not affect the physiologically important ionized calcium concentration. For these reasons, vitamin D replacement therapy is not routinely recommended to these patients.

Infections.—Patients with nephrotic syndrome, particularly children, are at increased risk of developing serious bacterial infections, including pneumonia, empyema and peritonitis[140]. Sepsis, meningitis and cellulitis are other serious infections that can occur in children with nephrotic syndrome[141]. Bacteriuria is common[140,141]. The increased risk for infection is related to renal losses of IgG leading to hypogammaglobulinaemia, reduced levels of the alternative complement factors B and D lost in urine, and the use of immunosuppressive therapy, all of which promote a state of acquired immunodeficiency. Loss of opsonizing factors may specifically increase the susceptibility to encapsulated bacterial infection, in particular to pneumococcal infections that are potentially lethal[142,143].

Diagnosis screening and prevention

The approach to patients with substantial proteinuria or nephrotic syndrome can be different depending on the resources available, which may limit the ability to make a tissue diagnosis as well as management (BOX 2). Importantly, different risk factors and/or causes of podocytopathies can present at certain phases of life or be preferentially associated with a certain sex or ethnicity. Risk factors frequently combine in the same patient and the individual constellation determines the onset of proteinuria and its severity (FIG. 6). Recognizing the likelihood of these causes or risk factors throughout the lifespan can help to improve diagnostic accuracy.

Clinical features and initial assessment

In children, podocytopathies frequently present with periorbital and/or peripheral oedema because of hypoalbuminaemia and saline excess. Less commonly, proteinuria is discovered on a routine urinalysis. It must be considered that a positive dipstick for protein on a random urinalysis (defined as ≥1 on dipstick testing) will be positive in 5–10% of normal school-age children and adolescents. However, only 0.1% of such children will have persistent proteinuria[144], defined as repeated detection in at least two exams over a period of >3 months, and only these children should be considered as possibly having a podocytopathy. Patients with deafness or with syndromic features should undergo phenotyping for other manifestations of a specific syndrome and, when proteinuria is noted, should be referred to a paediatric nephrologist. A careful patient and family history for kidney diseases or

extrarenal manifestations, particularly visual or hearing problems, is important and should prompt evaluation for a syndromic podocytopathy[64,65,67,145].

By contrast, in adults, both sub-nephrotic and nephrotic-range proteinuria (TABLE 1) may be incidental findings on a routine urinalysis as adults develop overt nephrotic syndrome less frequently. In these patients, it is important for the initial clinical assessment to investigate possible causes of podocytopathies such as exposure to drugs and toxins, syndromic features, elevated body mass index, signs and symptoms of viral and bacterial infections, autoimmune disorders, and malignancy. Kidney ultrasonography may identify a reduced renal size, renal masses or malformations, or cystic disease, which more typically present with non-nephrotic proteinuria[29,50] and are more prevalent in adults than in children. On the other hand, the onset of nephrotic syndrome with marked oedema, and sometimes anasarca, venous thrombosis or infections, should prompt investigation for a podocytopathy of immunological or genetic origin[146,147]. A positive sodium balance and hypertension are usually present in patients with podocytopathies[146].

Kidney biopsy.—In children with persistent non-nephrotic proteinuria, the decision about whether and when to proceed to kidney biopsy is controversial[148]. Many experts recommend close monitoring of blood pressure, protein excretion and GFR in children with a urinary protein excretion of <500 mg/m^2 per day; if any of these parameters shows evidence of progressive disease, a kidney biopsy may be warranted[149]. Retrospective analyses suggest that children with sub-nephrotic proteinuria and a urinary protein to creatinine ratio of ≥0.5 g/g can have a podocytopathy, typically expressed as FSGS lesions[150] (FIG. 7). By contrast, in patients with a urinary protein to creatinine ratio of <0.5 g/g, the risk of FSGS lesions at biopsy is low[150,151]. DMS shows a histological pattern of small, sclerosed glomeruli that have a reduced number of capillary loops with often prominent podocytes lining the tuft (FIG. 7) and is sometimes diagnosed in small children with genetic podocytopathies[5]. Biopsy is initially not performed in children with isolated nephrotic syndrome lacking other features because 75–80% of podocytopathies with minimal changes respond to standard steroid therapy with complete remission[6,152]. In addition, the response to initial steroid therapy is a better predictor of long-term prognosis than the results of kidney renal biopsy[6,152]. In those 10–20% of children with idiopathic nephrotic syndrome who do not respond to steroids, a kidney biopsy shows minimal change lesions (FIG. 7) in 25% and FSGS lesions in most others[6,152].

As the differential diagnosis of proteinuric nephropathies in adults is broad, kidney biopsy is generally performed in all adults presenting with nephrotic-range proteinuria to guide management and provide a prognosis. Common biopsy findings suggesting a podocytopathy include minimal change lesions, FSGS lesions and collapsing glomerulopathy (FIG. 7). Podocytopathies can be distinguished from other glomerular diseases based on the light microscopy appearance and immunoglobulin staining; electron microscopy provides additional information about the extent of FPE and abnormalities of the glomerular basement membrane. A detailed differential diagnosis of the type of podocytopathy may require a family history, serological testing and imaging exams as well as, in some cases, genetic analyses.

Genetic testing.—Genetic testing is highly advised in all children or young adults (<30 years of age) who do not respond to a course of glucocorticoids (FIG. 8) because, in these individuals, the possibility of making a molecular diagnosis of a genetic disorder can reach 30–60%[65,67,68]. The proportion of patients newly diagnosed with genetic podocytopathies declines with age at onset. Nevertheless, pathogenetic mutations occur in 14–21% of adults with steroid-resistant glomerular disorders and, therefore, genetic testing is warranted in adults with treatment-resistant proteinuria[68,153,154] (FIG. 9). A family history of kidney disease and syndromic features should also trigger genetic testing[155]. Next-generation sequencing with computational filtering for a panel of all known genes causing podocytopathies plus collagen genes has a diagnostic rate of ~30%[64,65,67,68,145].

Genetic variants in >50 nuclear and mitochondrial genes have been associated with FSGS and most cases are resistant to steroid therapy[65,67,156]. Inheritance patterns include autosomal recessive, autosomal dominant and sex-linked. Genetic causes of FSGS can be identified using gene panel testing, which involves resequencing a limited set of genes in which mutations are known to cause a podocytopathy. The gene panels may differ by age of podocytopathy onset. This approach has the advantages of being relatively fast, requiring a fairly simple consent form and having results that can often be conveyed by a nephrologist. Alternatively, whole-exome sequencing yields copious amounts of data, including on novel variants in genes associated in podocytopathies and novel variants in genes not previously associated with podocytopathies. Expanding the analysis for other genetic syndromes reported to occasionally present with isolated SRNS (that is, as phenocopies of podocytopathies) can double the diagnostic rate to 60%[65]. In these patients, re-evaluation of the patient and their family upon indication of genetic testing is mandatory to establish the correct diagnosis[65]. Thus, whole-exome sequencing is now the first choice in every centre where this analysis is possible for an isolated case or the first case in a family. However, the correct interpretation of variants of unknown clinical significance or in unexpected genes remains challenging and patients need to be counselled about the possibility of genetic diagnoses unrelated to kidney disease.

A different approach to African Americans with FSGS on kidney biopsy is warranted, as 72% of these individuals have two copies of *APOL1* renal risk alleles. For these individuals, it makes sense to proceed directly to *APOL1* testing for the G1 and G2 variant alleles.

Management

Progressive CKD is infrequent in children or adults with minimal change lesions[6,152] but it is common among those with a podocytopathy, persistent proteinuria and FSGS lesions[157]. Response to glucocorticoids is critical in defining patient subsets[158] and prognosis[156], as those who achieve remission (75–92% with minimal change lesions[146,159] and 47–66% in those with FSGS lesions[160]) do not usually develop ESKD[161]. Conversely, resistance to steroids is the strongest independent predictor of kidney function decline, with a kidney survival of 30% at 10 years from diagnosis. Massive proteinuria, impaired kidney function and interstitial fibrosis with tubular atrophy on kidney biopsy are also associated with progression to ESKD[162,163]. The prognosis of patients with a genetic podocytopathy is generally poor, with >50% of patients developing ESKD within 5 years of the diagnosis;

patients who lack a genetic cause of the disease have a better prognosis, particularly when they are responsive to immunosuppressive treatment[65,164]. In syndromic podocytopathies, the overall prognosis is also affected by extrarenal manifestations; the prognosis reflects that of the underlying disorder[65]. Recently, a novel subset of patients has challenged the concept that podocytopathies with a defined genetic cause have a poor prognosis. For example, C-terminal *CUBN* pathogenetic variants, although associated with FSGS at biopsy, are characterized with albuminuria and normal GFR in large population-based cohorts, even in the absence of response to immunosuppressive treatments and to angiotensin-converting enzyme inhibitors[165].

Current guidelines rely on clinical trial evidence and adhere to a 'one-fits-all' concept. However, it is becoming evident that, beyond the initial treatment with steroids, a substantial proportion of patients with podocytopathies needs a personalized approach to avoid drug toxicity from unnecessary medications and to apply specific treatments[64,65,72,73,164,166]. As personalized medicine for podocytopathies has only recently been in development, we will first describe the traditional approach.

Non-nephrotic proteinuria

Children and adults with persistent, non-nephrotic proteinuria are treated with a RASi and salt restriction[157], which are frequently effective even in patients with maladaptive podocytopathies with FSGS lesions[167]. A low-dose thiazide diuretic (such as hydrochlorothiazide) will potentiate the anti-proteinuric effect of these therapies and may be tolerated even in normotensive patients. Such secondary podocytopathies require treatment of the underlying disorder whenever available (FIGS 8,9)

New-onset nephrotic syndrome—Oral steroid therapy for at least 2–3 months is typically initiated with new-onset nephrotic syndrome without histological confirmation by kidney biopsy in children and adolescents, in patients without hypertension, gross haematuria or marked elevation in serum creatinine, in patients with normal complement levels, and in patients with no extrarenal symptoms[168]. Approximately 80–90% of patients will experience complete remission within the 4 weeks of initiating therapy[169] but some centres also administer three intravenous pulses of methylprednisolone every other day at this point[169]. Patients who do not undergo complete remission (and perhaps those with only a modest partial remission) are categorized as having SRNS and require prompt kidney biopsy and genetic testing[170,171]. Only 30% of children with SSNS maintain remission, 10–20% will have fewer than four relapses and the remaining will have frequent relapses (frequently relapsing nephrotic syndrome, FRNS) or will relapse while on a steroid taper (SDNS). The doses and length of treatment are personalized for each child as the clinical behaviour and response to steroids are heterogeneous (FIG. 8)

In adults, kidney biopsy at the time of presentation and identification of the underlying cause of the podocytopathy are essential to guide treatment (FIG. 9). In cases in which a specific cause cannot be identified, glucocorticoids represent the first-choice treatment[157]. Recommended regimens[158] derive from paediatric trials as only few adequately powered studies in adults are available[172-174]. Response to therapy is typically slower in adults than

in children, justifying prolonged steroid courses before defining treatment failure. Mycophenolate mofetil (an immunosuppressant) combined with low-dose steroids may induce disease remission in adult podocytopathies at rates comparable with standard therapy[175,176], possibly alleviating the risk of steroid-related adverse effects such as diabetes and hypertension in high-risk patients. Slow tapering of immunosuppressive drugs over 6 months is a widely accepted measure to reduce the risk of relapse[177].

SDNS and FRNS

Approximately 80% of steroid-responsive children and 70% of adult patients[178,179] undergo one or more relapses, which typically remain sensitive to steroids[180,181]. However, many patients become steroid dependent[146] or experience frequent relapses[182] (TABLE 1) after treatment discontinuation. The risk of relapse is greatest in children aged <5 years at onset, for reasons unknown. Almost all children with FRNS experience a progressive decrease in the number of relapses over time and many ultimately go into sustained or even permanent remission[160,183]. Limited long-term outcome data in adults suggests that patients who have frequent relapses or SDNS during childhood are at risk of experiencing relapses during adulthood and adverse drug effects[183-185] (TABLE 2). Kidney function remains normal in adulthood as long as patients remain responsive to treatment and long-term sequelae are generally related to medication adverse effects[184,185].

Various glucocorticoid regimens have been used to treat FRNS and SDNS[186,187]. Frequent relapses usually require steroid dose adjustment above the individual threshold. Alternate-day steroid dosing (in children) and steroid-sparing agents are commonly used to avoid long-term steroid toxicity. These agents include immunosuppressive drugs such as calcineurin inhibitors (ciclosporin or tacrolimus), rituximab, levamisole and cyclophosphamide. Calcineurin inhibitors are frequently chosen as steroid-sparing agents based on evidence from small trials[188] despite relapse rates as high as 75% upon discontinuation. These events often lead to prolonged treatment courses, which pose a considerable risk of calcineurin inhibitor-induced nephrotoxicity (TABLE 2). An increasing number of studies strongly suggests that rituximab can effectively reduce the number of relapses in SDNS and FRNS[85,86], minimizing the steroid dose, but relapses can occur after stopping rituximab.

Low-quality evidence supports the use of alkylating agents such as cyclophosphamide in SDNS and FRNS podocytopathies to reduce the cumulative dose of steroids[146] but these regimens have been progressively abandoned in developed countries owing to their unfavourable safety profile (TABLE 2). In paediatric patients, mycophenolate mofetil seems equally as effective as levamisole[189] but not as effective as ciclosporin in achieving remission[190-192], although the evidence is still limited[157]. In addition, higher doses of mycophenolate mofetil than those used in kidney-transplanted recipients seem to be necessary in children with nephrotic syndrome to achieve remission[192]. Adrenocorticotropic hormone has been used but its efficacy is controversial because studies yielded conflicting results[193,194]. Finally, in a very small number of cases, patients who were initially steroid sensitive become steroid resistant but can be usually successfully treated with alternative immunosuppressive therapies[195]. However, these patients are at increased risk for ESKD[195].

SRNS

Steroid resistance is defined as the lack of complete remission despite full-dose steroids for an adequate period of time (FIGS 8, 9). Screening for genetic mutations should be performed in all children as well as in adults with SRNS before considering additional immunosuppressive therapies as these are rarely effective in podocytopathies with a genetic cause. However, as genetic testing results take at least 4–6 weeks to become available, it may be appropriate to start a second-line therapy in selected patients in the interim. In patients in whom a genetic mutation is identified, immunosuppressive treatments can usually be discontinued and anti-proteinuric regimens with a RASi become the mainstay of therapy to attenuate CKD progression.

Approximately 60% of steroid-resistant patients may respond to ciclosporin or tacrolimus at moderate doses with reduced proteinuria and slower or halted CKD progression[196]. A genetic cause is usually not found in these patients[65,67,156]. As relapse is frequent after the withdrawal of these drugs[196], prolonging treatment for 1–3 years after remission is achieved is advisable[157]. Mycophenolate mofetil alone achieves remission in fewer than half of patients[197,198] but its use as maintenance treatment might reduce the calcineurin inhibitor dose and limit nephrotoxicity[199]. Thus, mycophenolate mofetil in combination with calcineurin inhibitors may be a rescue approach. The initial report of abatacept efficacy in treating SRNS[182] was challenged by subsequent studies[200,201] and the effect of other therapies such as rituximab[202] and adalimumab (targeting TNF)[203] seems to be limited, especially in adult patients. Instead of immunosuppression, SRNS requires rigorous control of glomerular hyperfiltration with a RASi and by reducing dietary salt. Recently, sparsentan, a dual endothelin type A (ET_A) and angiotensin I type 1 receptor antagonist showed a robust anti-proteinuric effect in a phase II clinical trial compared with monotherapy with the angiotensin receptor blocker irbesartan[204]. In secondary podocytopathies, management is focused on treating the underlying disorder.

Personalized treatment

Genetic testing identifies the diagnosis underlying SRNS in up to 30–60% of children and young adults, and some of these patients may benefit from avoiding unnecessary immunosuppressant therapies and from receiving specific treatments[65]. For example, patients with pathogenetic mutations in coenzyme Q_{10} biosynthesis (*COQ2, COQ6* and *ADCK4*) may respond to oral coenzyme Q_{10} supplementation[72,73,166]. Patients with pathogenetic mutations in collagen genes benefit from early diagnosis and administration of a RASi, while avoiding calcineurin inhibitors to prevent CKD progression[154,205]. Patients with Dent disease should be treated to avoid failure to thrive and kidney stones[64,65,206]. Similarly, patients with Fabry disease or cystinosis will likely benefit from early treatment, with enzyme replacement therapy or cysteamine depleting therapy, respectively[65,207]. Patients with pathogenetic mutations in exon 8 or 9 of *WT1* will benefit from regular screening for Wilms tumour and some may undergo prophylactic nephrectomy[208]. In addition, some patients with moderate proteinuria may benefit from genetic testing. For example, early recognition of patients with C-terminal *CUBN* pathogenetic variants is paramount as they tend to have a good prognosis without any treatment[165]. This underscores

the need to personalize the diagnosis of distinct types of podocytopathies owing to the important implications for prognosis and treatment.

Complications

Nephrotic syndrome requires additional treatment for symptoms and to prevent complications.

Oedema.—Patients are initially treated with loop diuretics and dietary sodium restriction to ~2 g per day and are monitored closely for clinical signs of hypovolaemia[209]. Most patients require high doses of diuretics owing to hypoalbuminaemia, expanded extracellular volume (larger volume of drug distribution) and a slower rate of delivery to the target cells within the kidney[210]. Thiazide diuretics or, alternatively, triamterene [211] or acetazolamide[212] can be combined with loop diuretics in patients with refractory oedema. As proteasuria activates the amiloride-sensitive epithelial sodium channel, amiloride can also be useful[213,214].

Dyslipidaemia.—Hyperlipidaemia is problematic in patients with nephrotic proteinuria as it increases the risk for progressive loss of renal function and cardiovascular disease[135]. Statins are the treatment of choice if hyperlipidaemia persists after treatment of the underlying kidney disorder with immunosuppressive therapy and/or a RASi[135,215]. Drug interactions, for example, with cytochrome P3A4 inhibitors such as cyclosporin, increase plasma levels of statins and require dose adaptations of the statins. Pro-protein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors may have a role when statins are insufficient or are not tolerated but these agents are currently very expensive[135].

Thromboembolism.—Adults with nephrotic syndrome have a high incidence (10–40%) of arterial and venous thrombosis, particularly deep vein and renal vein thrombosis, in some cases leading to pulmonary embolism[216]. By contrast, venous and arterial thromboses are reported in only 2–3% of children with nephrotic syndrome, although this may be an underestimate because many episodes are asymptomatic[217]. Venous thrombosis, particularly of the renal vein, deep leg veins, inferior vena cava and cerebral vein, account for most cases[217]. Thromboses of the pulmonary, femoral, iliac, cerebral and meningeal arteries are less common[218]. Adults and infants with congenital nephrotic syndrome are at increased risk for renal vein thrombosis but this complication is rare in children[218]. Pulmonary embolism should be suspected in patients with pulmonary or cardiovascular symptoms and can be confirmed by radioisotope scanning[219]. Prophylactic anticoagulation with oral anticoagulants is recommended only after the first thromboembolic episode or when albumin concentration is <2 g/dl, fibrinogen is >6 g/l or antithrombin III is <70% of normal, and is continued for as long as these alterations persist[220].

Infections.—To prevent pneumococcal infections, children with nephrotic syndrome should receive 1–2 doses of conjugate 13-valent pneumococcal vaccine (PCV13) preceding the 23-valent polysaccharide (PPSV23) pneumococcal vaccine, if not previously immunized. Varicella can also cause major morbidity and mortality in these patients[221]. Adults with nephrotic proteinuria who have not been previously immunized should receive both pneumococcal vaccines, with PCV13 followed 8 weeks later by PPSV23.

Although the use of live attenuated viral vaccines has been discouraged in the past for children receiving immunosuppressive therapy, a recent prospective study suggested that two doses of varicella vaccine can be safely administered to children with a $CD4^+$ T cell count of >500/mm^3, a normal lymphocyte blast transformation in response phytohemagglutinin (to assess cell-mediated immune responses), and serum IgG levels of >300 mg/dl (REF.[222]).

Centre-specific guidelines on influenza vaccination should be followed. In general, vaccinations pose a minimal risk for relapse of nephrotic syndrome; further, the protection gained greatly outweighs this risk[222].

Relapse after transplantation—Up to one-third of patients with FSGS lesions at biopsy who undergo kidney transplantation show recurrent nephrotic syndrome in the allograft[223]. The strongest predictive clinical feature of relapse for patients who undergo kidney transplantation is a previous response to steroids or immunosuppressive drugs for the nephrotic syndrome that caused ESKD[223]. This finding suggests that the podocytopathy is related to one or several immunological or circulating factors. A younger age at diagnosis, severe hypoalbuminaemia and rapid progression to ESKD (for example, within 3 years of diagnosis) are also more common in patients who experience recurrence after transplantation. Apolipoprotein A-Ib, a high-molecular-weight form of apolipoprotein A-I, was recently proposed as a possible biomarker for recurrent forms of podocytopathies after kidney transplantation[224]. Typically, relapses occur in the first 2 weeks after kidney transplantation and often respond to combined treatment with plasma exchange, rituximab and intensified immunosuppression, although the response may be transient[225,226]. Post-transplantation relapses are exceptional in those with a definite genetic diagnosis or with forms of podocytopathies related to increased single-nephron GFR or a low nephron mass[226,227].

Quality of life

The symptoms of nephrotic syndrome and the relapsing nature of most podocytopathies greatly compromise the quality of life of patients and their families. In general, patient-reported questionnaires identify oedema as the symptom that most negatively affects the quality of life[228]. Certain patients are at higher risk of developing drug-related adverse events linked to dose and length of exposure[229,230]. In steroid-dependent patients, the adverse effects of steroids frequently occur with long-term exposure (that is, prednisone doses of >5 mg per day for ≥3 months)[231]. These adverse events include cataracts, delayed growth in children, obesity, Cushingoid features, osteoporosis and psychological disturbances[232,233]. In adolescents, steroid-induced striae rubrae (stretch marks) and ciclosporin-related hypertrichosis (hair growth) can greatly affect self-confidence and mood[234]. Aesthetic medicine interventions and psychological support can improve these psychosocial impacts. In multidrug-resistant patients, nephrotoxicity from the prolonged use of calcineurin inhibitors may contribute to CKD progression and ESKD[229].

For patients with ESKD, dialysis (peritoneal dialysis, centre haemodialysis or home-haemodialysis) negatively affects the quality of life[235]. However, when patients reach ESKD, oedema and other symptoms of nephrotic syndrome typically improve because

urinary protein losses decline and finally cease with progressive oligo-anuria. Kidney transplantation can improve the quality of life and longevity in these patients[164,236]. However, the recurrence of nephrotic syndrome after transplantation is an important risk factor for allograft loss and the need to return to dialysis[223], with a major negative effect on quality of life and increasing the need for psychological support.

Outlook

The concept of ‘podocytopathies’ replacing DMS, FSGS, minimal changes and collapsing glomerulopathy as clinical entities is based on research and will continue to evolve. Indeed, with recent advances in our understanding of molecular and cellular mechanisms, the time is now to move from histologically defined entities of proteinuria to identifying and treating each patient’s podocytopathy. Each podocytopathy arises from some combination of genetic, epigenetic, transcriptional, proteomic, physiological, metabolic, immunological, viral and, possibly, psychological factors — and perhaps other factors that we do not yet appreciate.

Mechanisms

Knowledge about the genetic basis of glomerular disease is rapidly evolving and has generated new opportunities as well as new challenges for clinicians and patients. Close contact between clinicians and geneticists are neither available everywhere nor are genetic evaluations always affordable. These limitations imply that patients with SRNS are not being treated optimally in every region and may have to travel longer distances to reach a specialized centre. Access to geneticists is important, for example, when trying to interpret the clinical relevance of genetic test results, including the many ‘variants of unknown significance’. The rapidly increasing knowledge of human genetics has clearly given rise to the need for genetically oriented nephrologists or nephrogeneticists, similar to nephropathologists, to follow the latest advances in data and interpretation in a highly dynamic field. Initiatives like ClinGen and ClinVar, US NIH-funded initiatives dedicated to building a central resource, can define the clinical relevance of genes and variants for use in precision medicine and research and will make access to genetic information more readily and widely available.

Diagnosis

The promise of personalized diagnosis and management puts into question several aspects of the traditional morphology-based disease classifications and guideline-based patient management. Genetic testing may provide a precise molecular diagnosis and protect the patient from unnecessary immunosuppressive treatments. However, a genetic diagnosis may generate new questions for families, including whether to test other family members. Benefits of genetic testing include the opportunity for early diagnosis through screening and for selecting the optimal therapy. Risks include anxiety about test results, access to health insurance in some countries and the possibility of unexpected information about biological relationships among family members. The universal right to not know, especially for clinically unaffected family members, should be respected.

Big data

We need to better understand the primary nephrotic diseases at the molecular, cellular and clinical levels, addressing the symptoms, signs and effects on physical function and psychosocial well-being in a holistic approach. In the past decade, extensive resources have been brought to bear on these issues, including investigator and patient efforts, to answer questions not yet satisfactorily addressed by single-centre studies. The Nephrotic Syndrome Study Network (NEPTUNE) brings together investigators from throughout North America to enrol children and adults with nephrotic syndrome, currently numbering >500 patients, in a long-term natural history study that encompasses clinical, genetic, transcriptional, proteomic and metabolomic approaches to understand the pathogenesis, to enable testing of novel therapies and to determine the optimal treatment strategies[237]. The Cure Glomerulopathy (CureGN) consortium brings together investigators from 70 sites, predominantly in the United States as well as in Canada and Europe, with a mandate to enrol 2,400 children and adults with prevalent glomerular diseases, including minimal changes, FSGS, membranous nephropathy and IgA nephropathy, for prospective natural history studies[238]. Both studies will serve as valuable platforms to develop new knowledge, to bring new investigators into the nephrotic syndrome field and to provide training to the next generation of researchers.

In Europe, the European Rare Kidney Disease Reference Network (ERKNet), a virtual network involving health-care providers across Europe co-funded by the European Commission, was founded with the aim to facilitate discussion on complex or rare renal diseases and conditions that require highly specialized treatment, concentrated knowledge and resources. The ERKnet has facilitated the exchange of information between nephrologists in Europe and permits the review of patients' diagnoses and treatments by virtual advisory panels of medical specialists across different disciplines, using a dedicated platform and telemedicine tools.

Pharmaceutical and biotechnology companies have shown increasing interest in developing novel therapies for podocyte disorders and will be the major source of the development of innovative therapies. Governmental funding agencies are essential partners. Patient organizations have an important role as they are highly motivated by the unmet medical needs and are strong advocates for the relevance of patient-oriented outcomes; they play essential and formal parts in the NEPTUNE and CureGN studies mentioned above. In nephrology, patient groups, including NephCure, the American Kidney Fund, the National Organization for Rare Disorders, the National Kidney Foundation, the Dutch Kidney Foundation, the Federation for Each Renal Genetic Disease, the Nephrotic Syndrome Association Italy, and La Nuova Speranza non-profit foundation, have served as powerful and compelling ambassadors, sources of research funding, and supporters of scientific meetings that stimulate international exchange and collaborations.

Management

Given the value of rituximab as a treatment in SSNS and immune-mediated podocytopathies, other CD20-targeting or B cell-targeting drugs are being considered. Ofatumumab is a more potent $CD20^+$ B cell depleter and may replace rituximab in patients

with drug hypersensitivity[88,239]. Another agent, belimumab (which targets B cell-activating factor), is an established maintenance therapy in systemic lupus erythematosus and reduces proteinuria in lupus nephritis[240] and might control B cell activity also in other forms of nephrotic syndrome.

Many attempts to find new treatments for podocytopathies beyond the traditional immunosuppressive drugs have been unsuccessful. One likely contributing factor is the fact that patients in clinical trials were stratified based on unspecific pathological patterns; in reality, these individuals likely had diverse disorders and potentially required specific therapeutic approaches. Successful trials will possibly require the selection of agents that target specific molecular pathways shown to be altered in the underlying podocytopathy, with enrolment of only those patients who manifest alterations in these pathways. We do not yet have all the tools needed to make such selections but some approaches for selection include genetic studies, kidney transcription profiling and urinary single-cell transcriptional profiling. Encouragingly, several clinical trials for podocytopathies are ongoing (TABLE 3).

Another high priority is to develop specific podocyte-directed therapies to protect podocytes from injury, detachment and loss. These strategies include stem cell therapy for genetic disorders, the use of genetically modified cells, induced pluripotent stem cells, small interfering RNA therapeutics and other approaches, although none has reached the domain of clinical podocytopathies. Intriguingly, a recent study reported that lowering *APOL1* expression using antisense oligonucleotides significantly ameliorated kidney disease in a transgenic animal model of *APOL1* podocytopathy[117].

Another promising area is the promotion of cell regeneration. The discovery that lost podocytes are potentially replaceable from a pool of local progenitor cells within the parietal epithelial cells is raising new hope to stimulate that system therapeutically, especially in non-genetic podocytopathies[53,62]. To avoid unwanted effects in other progenitor cell niches, such an appropriate drug target should be specific for podocyte progenitors. Whether such treatments would increase the risk of kidney cancer is currently unknown and will be an important consideration.

In conclusion, this is an exciting era for podocytopathy research and clinical care. New therapies to slow and possibly halt the progression of podocyte injury are in clinical trials and, in the future, therapies to stimulate podocyte regeneration may become available. Renewed energy from patients and patient organizations, academic researchers, pharmaceutical and biotechnology companies, and government agencies is spurring collaboration to develop novel, safe and effective therapies for patients with podocytopathies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1 |

Systemic diseases with podocyte injury

Diabetic nephropathy

Long-standing, poorly controlled diabetes mellitus can cause diabetic nephropathy with macroproteinuria as a manifestation of podocyte injury. Although hyperglycaemia, impaired insulin receptor signalling, advanced glycation end-product toxicity and glomerular inflammation can directly affect podocyte function, clinical trials have demonstrated that haemodynamic factors promoting single-nephron glomerular hyperfiltration represent the central pathogenetic mechanism of diabetic nephropathy. Dual blockade of the sodium/glucose cotransporter 2 and the renin-angiotensin system and glucose control can control such hyperfiltration.

Immune complex glomerulonephritis

Glomerular immune complex deposits result from adaptive immune responses directed against infectious organisms, circulating autoantigens or autoantigens within the glomerulus. Immune complexes that activate the complement system cause glomerular injury. When immune complexes directed at podocyte antigens (for example, in membranous glomerulonephritis) cause podocyte injury, particularly severe proteinuria, treatment aims to control aberrant adaptive immunity with immunosuppression.

Fibrillary glomerulonephritis

Fibrillary glomerulonephritis involves glomerular deposits of immunoglobulins and fibrils of DNAJB9, a protein of the unfolded protein response pathway. Such deposits cause indirect podocyte injury.

Monoclonal gammopathies and amyloid light-chain amyloidosis

Plasma cell clones producing aberrant immunoglobulins or light chains can affect the kidneys in many different ways. Some of these proteins form amyloid aggregates, which deposit in glomeruli and cause indirect podocyte injury. Others form crystals, fibrils, granules or microtubules that deposit in proximity to or inside podocytes. Treatment aims to suppress the plasma cell clone in the bone marrow responsible for their production.

Amyloid A amyloidosis

Chronic forms of systemic inflammation, for example, in hereditary fever syndromes or long-standing autoimmunity, can cause aggregation and deposition of serum amyloid A in various tissues, including the kidney. Glomerular deposits can cause indirect podocyte injury and nephrotic syndrome.

Metabolic storage diseases and drug-related pigment deposits

Genetic α-galactosidase deficiency in Fabry disease causes intracellular accumulation of globotriaosylceramide. In podocytes, such deposits cause damage associated with proteinuria and glomerulosclerosis. Glycogen storage disease or long-standing exposure to drugs such as hydroxychloroquine can have similar effects.

Box 2 |

Global variation in diagnosis and management

Clinical evaluation

Although a urinary dipstick result may be sufficient to diagnose nephrotic syndrome in a patient with massive oedema, the diagnosis may be easily missed in patients with mild or absent oedema that does not prompt urine analysis. Lack of access to HIV testing misses the opportunity to diagnose HIV infection and to institute anti-retroviral therapy. Failure to identify low nephron mass or single-nephron hyperfiltration as a cause for proteinuria and podocyte injury, as it frequently happens when patients are categorized by histopathological lesions only, may expose patients to unnecessary and ineffective immunosuppressive therapies.

Pathology

For children with idiopathic nephrotic syndrome, standard steroid or ciclosporin therapy will be available in most settings. However, in adults, the differential diagnosis is based on kidney biopsy findings; many parts of the world do not routinely provide access to kidney biopsy owing to cost and a lack of well-trained renal pathologists. Sometimes, biopsy samples are shipped from low-income countries to partner institutions abroad but turnaround time remains a problem. If the infrastructure for tissue processing and slide scanning are available, online slide review can be an option to obtain expert pathology reading with an acceptable turnaround time. A lack of access to immunoglobulin staining hinders the diagnosis of IgA nephropathy, membranous nephropathy or systemic immunological diseases that need different management to podocytopathies. A lack of access to electron microscopy compromises the diagnosis of certain glomerular disorders, including membranous nephropathy and Alport syndrome.

Genetic evaluation

A lack of access to genetic testing likely misses the diagnosis of >50 high-penetrance genetic causes of FSGS and may expose patients to unnecessary or ineffective immunosuppressive therapies. Family counselling is, therefore, not available and genetic disorders with systemic manifestations may be missed. Indeed, genetic testing as a key technology to personalized care for patients with podocytopathies is too dynamic to maintain equivalent availability and quality worldwide. Currently, few highly specialized centres regularly define new standards in terms of sequencing hardware and data analysis, which implies that many centres operate with different diagnostic algorithms. Globally, these modern diagnostic tools are not accessible to the majority of patients in low-income and middle-income countries for reasons of local availability and/or costs. Given the contributions of genetic factors to prognosis in certain regions of the world and the risk of progression to end-stage kidney disease, making certain diagnostics available either through raising awareness among local policymakers, through philanthropic initiatives or via research networks is warranted.

Treatment and renal replacement therapies

Cost may limit access to calcineurin inhibitors, mycophenolate mofetil and rituximab as therapies for primary FSGS. Not all patients will have access to dialysis or renal transplantation. A lack of access to renal replacement therapy or kidney transplant will result in premature death.

Chronic kidney disease

(CKD). Abnormalities in kidney structure or function (urine composition or impaired excretory function) lasting >3 months; progression is based on the cumulative degeneration of nephrons, the independent functional units of the kidney.

Glomerular filtration barrier

The parts of the nephron in which the filtration process of the blood takes place and the primary filtrate is formed; podocytes and their interdigitating foot processes, connected by the slit diaphragm, are essential components of the size-selective and charge-selective filtration barrier in the glomerulus

Nephrotic syndrome

A clinical syndrome defined by symmetrical oedema, hypoalbuminaemia, hyperlipidaemia and proteinuria of >3 g per day, caused by podocyte injury (from any cause) and leading to severe alterations of the glomerular filtration barrier

End-stage kidney disease

(ESKD) When nephron loss during chronic kidney disease reaches the point that homeostasis can no longer be maintained, presenting as renal failure (uraemia)

Glomerular filtration rate

(GFR) The central parameter of excretory kidney function that can be accurately measured as the clearance of injected tracers over time or can be estimated from a number of clinical and laboratory parameters, including creatinine and cystatin C

Podocyte shear stress

The hydrostatic pressure gradient across the glomerular filtration barrier that podocytes must withstand to avoid detachment and loss into the urine

Hyperfiltration

An elevated total glomerular filtration rate (GFR) is called hyperfiltration and implies hyperfiltration of every nephron; however, reduced total GFR implies compensatory hyperfiltration of the remnant nephrons, as a central mechanism for the progression of chronic kidney disease by promoting podocyte shear stress, podocyte detachment and adaptive focal segmental glomerulosclerosis

Oncotic pressure

The pressure resulting from the difference within the extracellular fluid between the protein contents of plasma and interstitial fluid

Syndromic disorders

Genetic diseases with manifestations in different organ systems due to the expression of the mutated gene in diverse tissues

Mitotic catastrophe

A type of cell death that occurs during mitosis, resulting from DNA damage or deranged spindle formation and linked to checkpoint failure

Overfill scenario

Nephrotic syndrome associated with oedema secondary to a positive sodium balance, mainly due to sodium retention; patients present with intravascular hypervolaemia (hypertension) and interstitial hypervolaemia (oedema)

Acute kidney injury (AKI)

An abrupt decrease in kidney function, resulting in the retention of urea and other nitrogenous waste products in the blood and in the dysregulation of extracellular volume and electrolytes

Underfill scenario

Nephrotic syndrome associated with oedema secondary to a rapid fall in blood oncotic pressure with volume shifts into the interstitial compartments; patients present with intravascular hypovolaemia and interstitial oedema

Renin–angiotensin system

The hormone system that regulates blood pressure, volume and electrolyte balance, and systemic vascular resistance

Anasarca

General swelling of the whole body that can occur when the tissues of the body retain too much fluid

Cushingoid features

Weight gain, hypertension, cutaneous striae rubrae and easy bruising

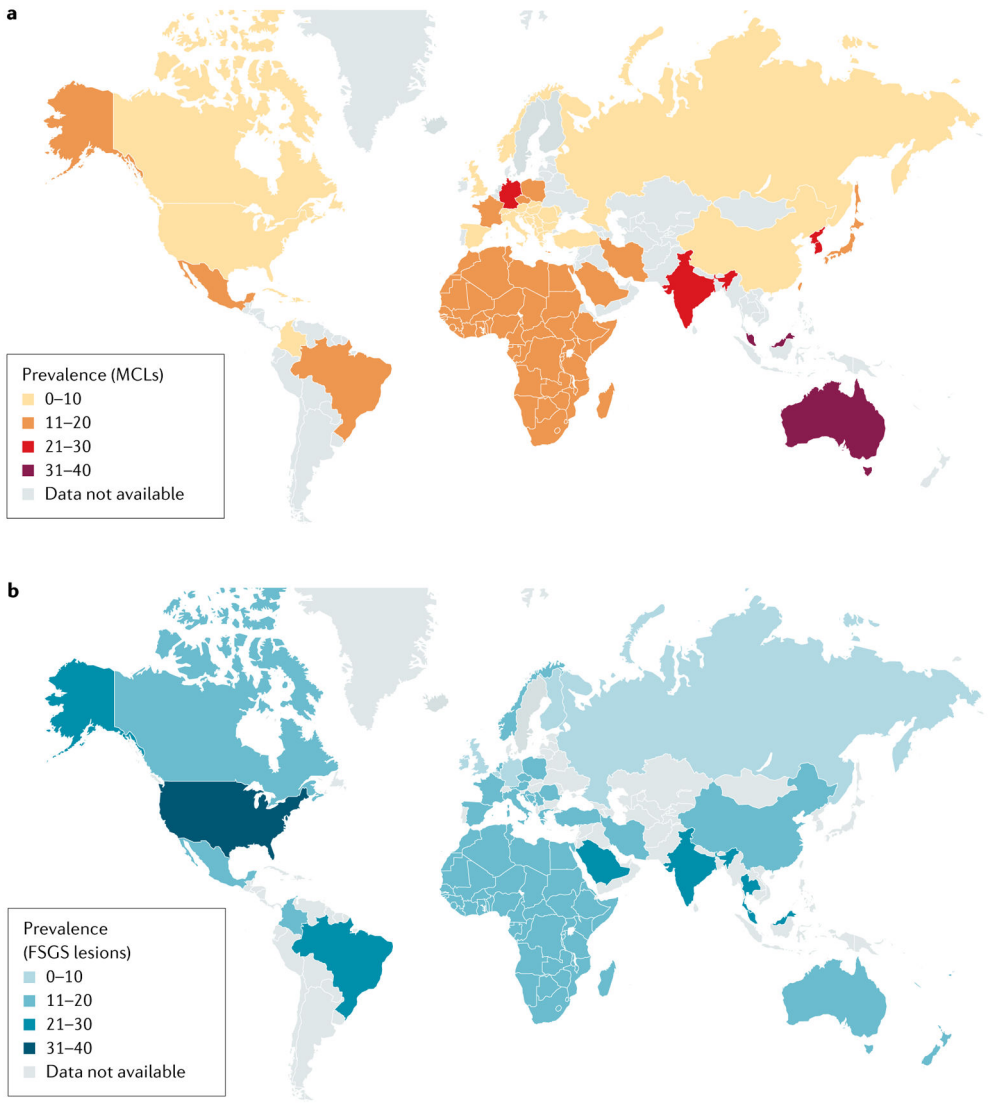

Fig. 1 |. Worldwide prevalence of podocytopathies.

a | Worldwide prevalence of podocytopathy with minimal change lesions (MCLs). **b** | Worldwide prevalence of podocytopathy with focal segmental glomerulosclerosis (FSGS) lesions. Data are expressed as a percentage of total kidney biopsies and were obtained from international registries[8,9,254-262].

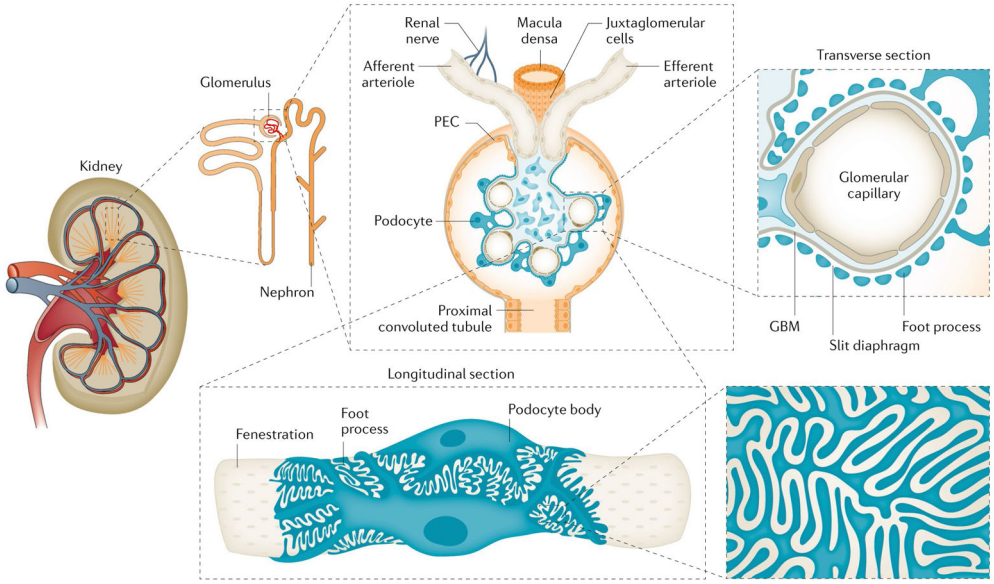

Fig. 2 |. Structure of the nephron, the glomerulus and the filtration barrier.

The kidney is comprised of functional units, nephrons, each of which is made of a glomerulus and a tubule. In healthy humans, the average number of nephrons is ~1 million (range 250,000 to <2.5 million). The glomerulus is composed of a tuft of capillaries covered by visceral epithelial cells — the podocytes — and surrounded by a capsule lined on the inner surface by parietal epithelial cells (PECs). The latter cell population contains podocyte progenitors, which are motile and progressively differentiate into podocytes in the region near the vascular pole of the glomerulus. The vascular pole of the glomerulus includes both the afferent and efferent arterioles (transverse section). The outermost layer is composed of podocytes adhering to the glomerular basement membrane (GBM) and interdigitating (longitudinal section), with the slit diaphragm spanning each gap between pairs of foot processes. The innermost layer is constituted by fenestrated endothelial cells.

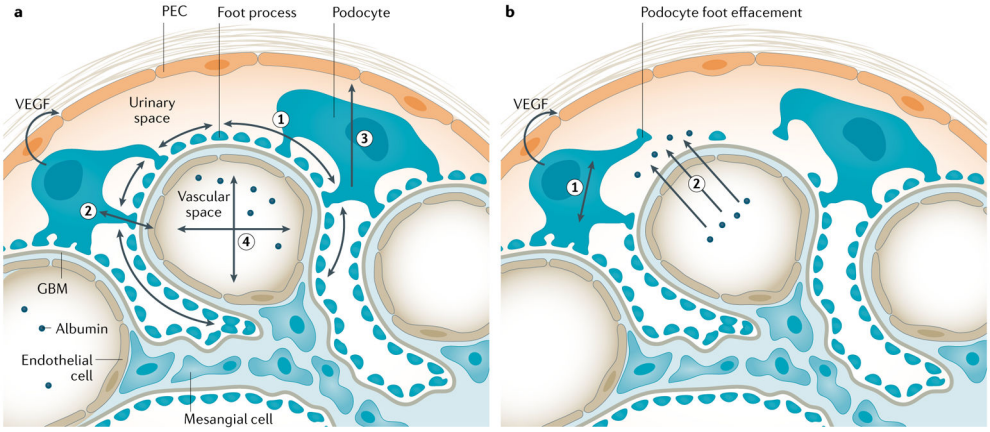

Fig. 3 | Mechanical podocyte stress.

a | Under normal conditions, several kinds of physical stress are present in the glomerulus[46,47]. The hydrostatic pressure gradient across the glomerular capillary and the Bowman (urinary) space outside the capillary creates circumferential stress on the podocyte foot processes (**1**). Fluid filtration across the glomerulus generates shear stress on the lateral aspects of the foot processes (**2**). Filtrate flow laterally across the podocyte cell body in the Bowman space confers shear stress (**3**). Podocyte-derived vascular endothelial growth factor (VEGF) acts on intravascular endothelial cells and is needed for maintaining the glomerular filtration barrier and keeping serum proteins such as albumin inside the vasculature (**4**). **b** | Numerous medical conditions increase the filtration load to the kidneys, which translates into increasing filtration pressure at the level of individual glomeruli. As a trade-off, horizontal podocyte stress (**1**) increases as the number of podocytes remains constant. Such podocyte stretching ultimately leads to compromise of the filtration barrier, podocyte detachment and loss, and proteinuria. Proteinuria also increases oncotic pressure acting on podocytes (**2**), as protein in the Bowman space further increases the amount of fluid passing the filtration barrier, which defines single-nephron filtration. This mechanism is common to most forms of progressive chronic kidney disease, as the total effective glomerular filtration surface declines. Hyperfiltration is present early in some forms of chronic glomerular disease, including diabetes mellitus. GBM, glomerular basement membrane; PEC, parietal epithelial cell.

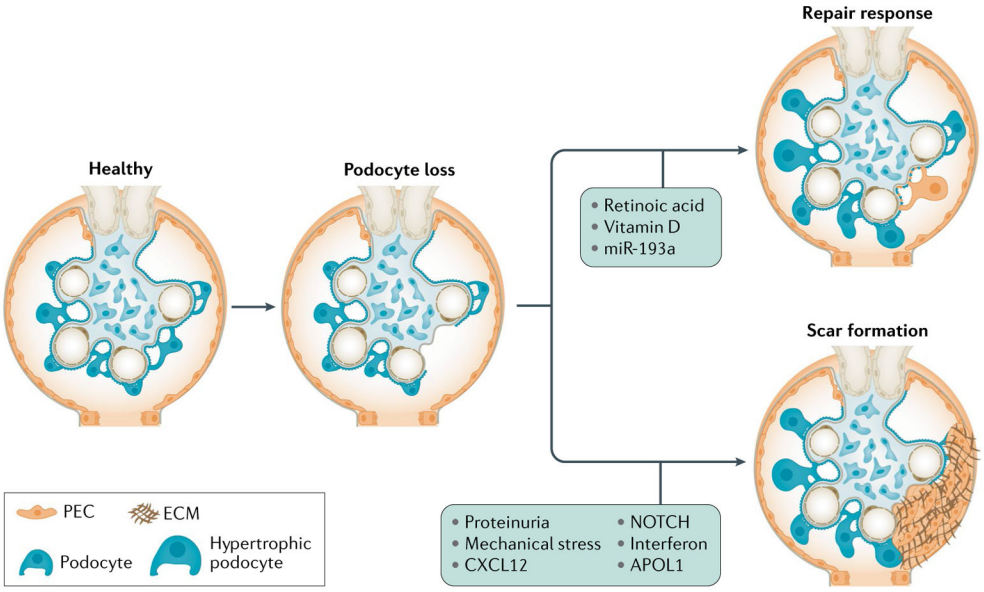

Fig. 4 |. Consequences of podocyte loss.

Following injury, podocyte loss can occur that can trigger two responses. First, the remaining podocytes adapt by increasing their size to cover the newly denuded glomerular basement membrane (podocyte hypertrophy). Second, parietal epithelial cells (PECs) along the Bowman capsule, which include a population of resident podocyte progenitors, supply new podocytes after injury and loss. These mechanisms contribute to podocyte functional recovery and reduce proteinuria following injury but can be inefficient or become maladaptive. Indeed, hypertrophic podocytes may be unable to maintain a normal foot process structure, leading to a further increase in local shear stress that triggers further podocyte detachment. In addition, differentiation of PECs into podocytes can be hampered by mechanical stress and proteinuria, leading to inefficient podocyte regeneration and scar formation. ECM, extracellular matrix.

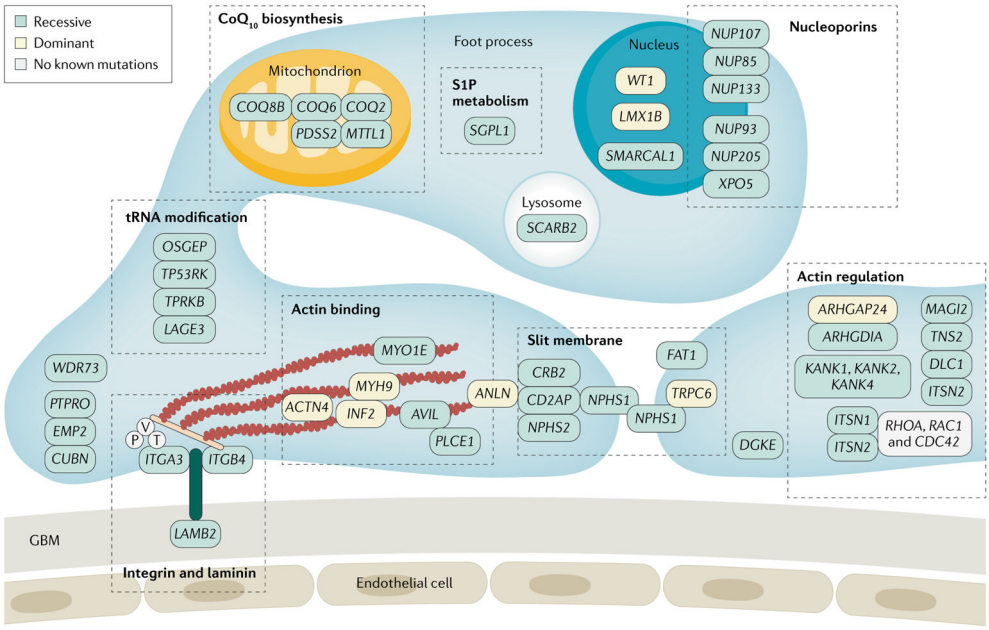

Fig. 5 |. Monogenetic diseases and SRNS.

Identification of single-gene causes of steroid-resistant nephrotic syndrome (SRNS) placed the podocyte at the centre of SRNS pathogenesis because most of the implicated genes are expressed in podocytes. Foot processes interdigitate with those from neighbouring podocytes, forming the glomerular slit membrane, which is critical for filtering and retention of protein in the bloodstream. Its integrity is lost in nephrotic syndrome. Proteins encoded by genes that, if mutated, cause monogenic SRNS localize to specific subcellular sites of podocytes depicted here. CoQ_{10}, coenzyme Q_{10}; GBM, glomerular basement membrane; P, paxillin; T, talin; V, vilin. Adapted with permission from REF.[263], Oxford University Press.

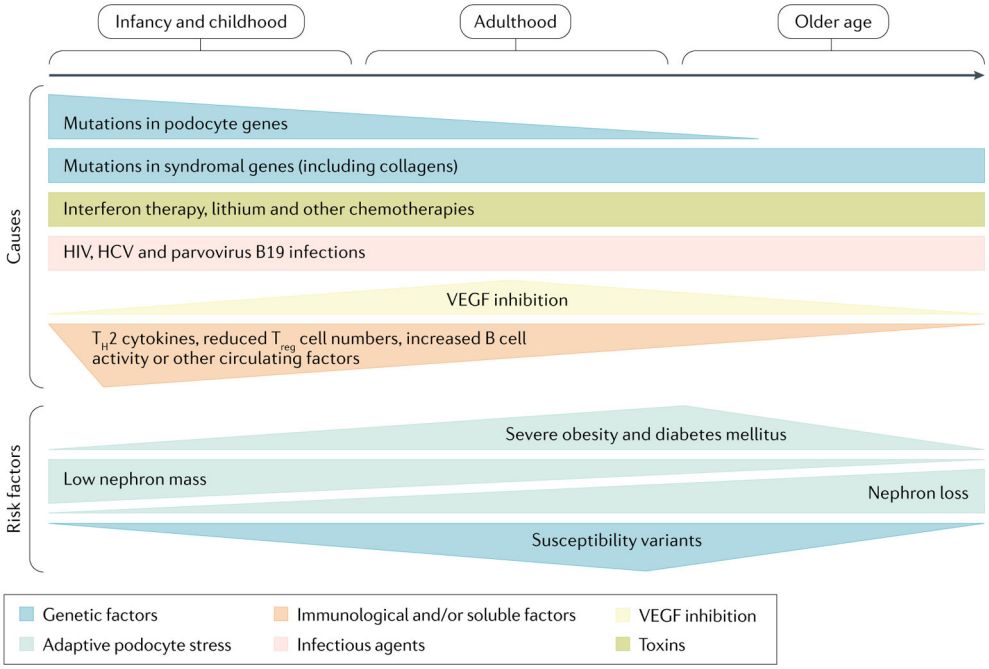

Fig. 6 | Causes and risk factors underlying podocytopathies across the lifespan.
Patient age and sex are associated with an increased probability of different types of podocytopathies related to different causes or risk factors that can frequently even combine in the same patient. For example, genetic causes are more frequent in children and young adults, whereas immunological causes are more frequent in male children. On the other hand, podocytopathies related to inhibition of vascular endothelial growth factor (VEGF) are observed during pre-eclampsia and are, therefore, more prevalent in pregnant women. Major risk factors for the development of a podocytopathy, such as increased single-nephron glomerular filtration rate for obesity or diabetes, are more frequently observed in adult middle-age patients, whereas a low nephron mass endowment can cause a podocytopathy during adolescence or early adulthood. Finally, a susceptibility gene, such as *APOL1*, is prevalent in Black adult patients. HCV, hepatitis C virus; T_H, T helper; T_{reg} cell, regulatory T cell.

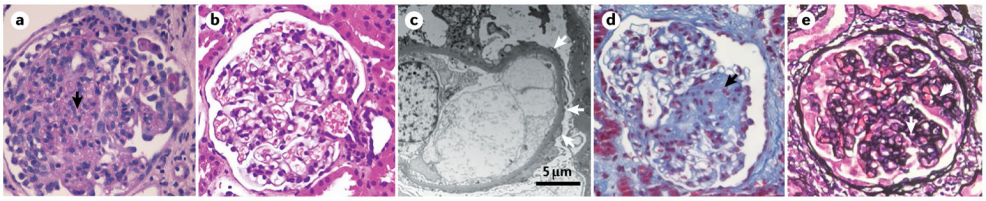

Fig. 7 | Pathology of podocytopathies.

a | The lesion pattern of diffuse mesangial sclerosis occurs only in young children and is usually associated with severe nephrotic syndrome. The glomerulus shows diffuse mesangial sclerosis (arrow) with prominent mesangial consolidation, closure of the capillary loops and overlying prominent immature podocytes. Periodic acid–Schiff staining; magnification ×400. **b** | The lesion pattern of minimal changes on light microscopy shows a normal glomerulus. Haematoxylin and eosin staining; magnification ×200. **c** | On electron microscopy, minimal change disease foot process effacement (arrows) is visible. Minimal change lesions are usually associated with steroid-sensitive nephrotic syndrome but can also be associated with isolated proteinuria or, rarely, with steroid-resistant nephrotic syndrome, particularly in the early phases of the disease. **d** | The lesion pattern of focal segmental glomerulosclerosis (FSGS) is associated with diverse clinical presentations but most frequently with isolated proteinuria or steroid-resistant nephrotic syndrome. FSGS lesions (arrow) have been distinguished into five subtypes but the lack of accuracy to predict a specific cause of disease or outcome limits their clinical relevance[264]. In addition, particularly in maladaptive FSGS, lesions typically start in juxtamedullary nephrons, which are sensitive to haemodynamic injury and harbour fewer podocyte progenitors, which explains why FSGS starts and is more frequently observed in juxtamedullary glomeruli[53]. Perihilar and cellular variants share an intermediate prognosis and the former is associated with maladaptive (secondary) causes[265]. Coarse segmental staining for IgM and C3 can occur with minimal or FSGS lesions. At electron microscopy, limited effacement with narrow foot processes is frequent in maladaptive podocytopathy with secondary FSGS lesions[197], whereas diffuse foot process effacement is typical of primary podocytopathies and virus-related or drug-related podocytopathy[266-268]. Masson’s trichrome staining; magnification ×200. **e** | The lesion pattern of collapsing glomerulopathy is less common and usually associated with severe steroid-resistant nephrotic syndrome. Traditionally, collapsing glomerulopathy has been associated with people of African descent and a fast rate of progression to end-stage kidney disease, whereas tip lesions (which are the result of proliferation of parietal epithelial cells at the urinary pole) are associated with white ethnicity, a low histological score at presentation and a better response to therapy. The collapse of the tuft is evident by the circular black lines (capillaries) and loss of the urinary space (arrows). Jones methenamine silver staining; magnification ×200.

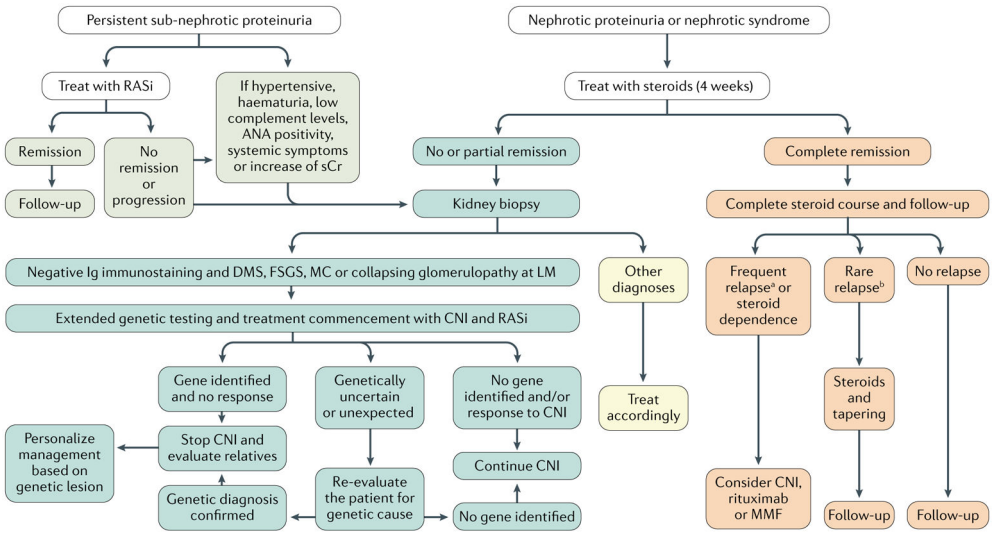

Fig. 8 |. Diagnosis and management of paediatric patients with proteinuria or nephrotic syndrome.

In children with podocytopathies, persistent sub-nephrotic proteinuria of >0.5 g per day is treated with a renin–angiotensin system inhibitor (RASi), maximally titrated. Patients are longitudinally followed up. If the proteinuria is associated with other symptoms, such as hypertension, kidney biopsy is required to exclude other glomerular disorders, which are treated accordingly. The length and frequency of the follow-up is determined for each patient based on renal function and residual proteinuria but, at a minimum, yearly evaluation should be performed even in patients with long-standing complete remission and normal renal function. Paediatric patients with idiopathic nephrotic-range proteinuria or nephrotic syndrome are treated with steroids, the response to which defines further management. Steroid-resistant patients should undergo biopsy and genetic testing; treatment with second-line immunosuppressive agents can be started while awaiting the results of genetic testing and should be continued only if these tests are unrevealing. Uncertain or unexpected genetic diagnosis should be confirmed with re-evaluation of the patient and their family. When a genetic diagnosis is ascertained, management should be personalized on the gene identified. By contrast, paediatric patients with nephrotic-range proteinuria or nephrotic syndrome who achieve complete or partial remission should be followed up and re-treated with steroids in case of relapse. Steroid-sparing immunosuppressive agents should be considered only for frequently relapsing and steroid-dependent patients. Based on guidelines from Kidney Disease Improving Global Outcomes (KDIGO)[241] and the International Pediatric Nephrology Association[242], updated and modified based on recent literature. ANA, antinuclear antibody; CNI, calcineurin inhibitor; DMS, diffuse glomerulosclerosis; FSGS, focal segmental glomerulosclerosis; Ig, immunoglobulin; LM, light microscopy; MC, minimal changes (with foot process effacement); MMF, mycophenolate mofetil; sCr, serum creatinine. [a]≥2 relapses in 6 months or ≥4 relapses in 12 months. [b]<2 relapses in 6 months or <4 relapses in 12 months.

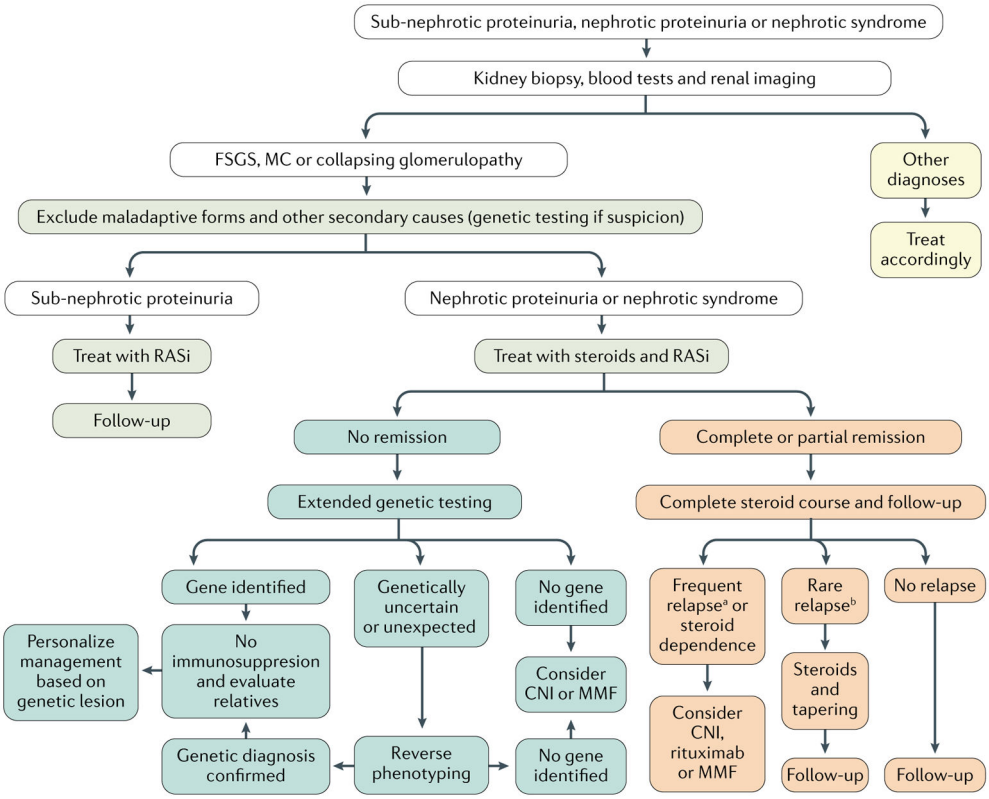

Fig. 9 |. Diagnosis and management of adults with proteinuria or nephrotic syndrome.
Renal biopsy, laboratory examinations and renal imaging (and, potentially, genetic testing) exclude other glomerular disorders and rule out secondary aetiologies of podocytopathies, which are treated according to the cause. Sub-nephrotic proteinuria is generally treated with a renin–angiotensin system inhibitor (RASi), maximally titrated; patients are longitudinally followed up based on renal function and residual proteinuria; a yearly evaluation should be performed even in patients with long-standing complete remission and normal renal function. Patients with idiopathic nephrotic-range proteinuria and nephrotic syndrome are treated with a course of steroids and with RASi. Response to steroids defines further management: steroid-resistant patients should undergo genetic testing and treatment with second-line immunosuppressive agents should be considered only if these tests are unrevealing. When a genetic diagnosis is ascertained, management should be targeted to the gene identified. Conversely, patients who achieve complete or partial remission should be followed up and re-treated with steroids in case of relapse. Steroid-sparing immunosuppressive agents should be considered only for frequently relapsing and steroid-dependent patients. Based on Kidney Disease Improving Global Outcomes (KDIGO) guidelines[241], updated and modified based on recent literature. CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis; MC, minimal changes (with foot process effacement); MMF, mycophenolate mofetil. [a]≥2 relapses in 6 months or ≥4 relapses in 12 months. [b]<2 relapses in 6 months or <4 relapses in 12 months.

Table 1 |

Clinical definitions

Condition	Adults	Children
Proteinuria	Proteinuria of 300–3,400 mg per day or urinary protein to creatinine ratio <300 mg/g (or<300 mg/mmol)	Urinary protein to creatinine ratio >0.2 or proteinuria >100 mg/m^2 per day or ≥4 mg/m^2 per hour or positive urine dipstick[149]
Nephrotic range proteinuria	Proteinuria of ≥3.5 g per day or urinary protein to creatinine ratio ≥3,000 mg/g (or ≥300 mg/mmol) with normal serum albumin	Urinary protein to creatinine ratio ≥200 mg/mmol (2 mg/mg) in first morning void or 24-hour urine sample ≥1,000 mg/m^2 per day corresponding to 3+ or 4+ by urine dipstick or ≥40 mg/m^2 per hour
Nephrotic syndrome	Proteinuria of ≥3.5 g per day or urinary protein to creatinine ratio of ≥3,000 mg/g (or ≥300 mg/mmol) with oedema, serum albumin of <3.0 g/dl and hypercholesterolaemia	Urinary protein to creatinine ratio ≥200 mg/mmol (2 mg/mg) in first morning void or 24-hour urine sample ≥1,000 mg/m^2 per day corresponding to 3+ or 4+ by urine dipstick and either hypoalbuminaemia (serum albumin of <30 g/l) or oedema when serum albumin level is not available
Partial remission	Proteinuria of 0.3–3.5 g per day or urinary protein to creatinine ratio of 300–3,500 mg/g (or 30–350 mg/mmol) with >50% decrease from baseline and stable renal function	Urinary protein to creatinine ratio >20 mg/mmol but <200 mg/mmol and, if available, serum albumin ≥30 g/l
Complete remission	Proteinuria of <0.3 g per day or urinary protein to creatinine ratio of <300 mg/g (or <30 mg/mmol), stable renal function and normal serum albumin	Urinary protein to creatinine ratio ≤20 mg/mmol (0.2 mg/mg) or negative or trace dipstick on 3 or more consecutive occasions
Relapse	Proteinuria of >3.5 g per day or urinary protein to creatinine ratio of >3,500 mg/g (or >350 mg/mmol) after achievement of remission	Urinary protein to creatinine ratio of ≥200 mg/mmol (2 mg/mg) on a first morning urine sample or ≥3+ protein on urine dipstick for 3 consecutive days
Frequently relapsing nephrotic syndrome	Two or more relapses within 6 months (or >4 relapses within 12 months)	Two or more relapses within 6 months (or >4 relapses within 12 months)
Steroid-dependent nephrotic syndrome	Two or more relapses during or within 14 days of completing steroid therapy	Two consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy
Steroid-resistant nephrotic syndrome	Failure to achieve remission after 16 weeks of corticosteroid therapy	Failure to achieve remission after 4–6 weeks of corticosteroid therapy[a]

Definitions are from Kidney Disease Improving Global Outcomes (KDIGO)[241] for adults and from the International Pediatric Nephrology Association[242] for children, unless otherwise stated.

[a]Recommendations and definitions vary slightly among different guidelines.

Table 2 |

Potential adverse events associated with immunosuppressive treatment

Treatment	Possible adverse effects	Measures to reduce toxicity
Steroids	Cataracts[233]; excessive weight gain, obesity or Cushingoid features[243]; suppression of the hypothalamic–pituitary–adrenal axis[244]; behaviour disturbances (such as hyperactivity or depression); hypertension[243]; osteopenia[243]; statural growth impairment (in children)[232]	Alternate-day therapy or low dose (<1 mg) whenever possible[234]
Ciclosporin	Nephrotoxicity[229,230,245,246]; hyperlipidaemia; hypertrichosis; gum hypertrophy	Blood trough level should not exceed 200 ng/ml (REF.[247]); once remission is achieved, decrease the dose to <5 mg/kg (REF.[248])
Tacrolimus	Nephrotoxicity[249]; glucose intolerance; headache; seizures	If possible, target lower trough concentrations (3–5 ng/ml)[250]
Mycophenolate mofetil	Gastrointestinal disturbances (abdominal pain and diarrhoea); haematological abnormalities and infections; teratogenic effects	Monitoring to target area under the curve (>45 μg·h·ml)[251]; recommend contraception in women with child-bearing potential[252]
Rituximab	Infusion-related reactions; leukopenia and/or hypogammaglobulinaemia; neutropenia; hepatitis induced by hepatitis B virus reactivation; progressive multifocal leukoencephalopathy; pulmonary fibrosis	If anaphylaxis is suspected, discontinue treatment; regular monitoring of complete blood count; recommend G-CSF and antibiotics administration if severe neutropenia with infection occurs; discontinue treatment
Levamisole	Neutropenia; vasculitis; flu-like symptoms	Regular monitoring of complete blood count; discontinue treatment if neutropenia or vasculitis occur
Cyclophosphamide	Neutropenia and infection[253]; gonadal toxicity; malignancy; alopecia; haemorrhagic cystitis	Discontinue treatment if the WBC count falls <3,000/mm^3 (until the count rises); maximum daily dose and cumulative dose should not exceed 2.5 mg/kg and 300 mg/kg, respectively

G-CSF, granulocyte colony-stimulating factor; WBC, white blood cell.

Table 3 |

Clinical trials for new drugs in podocytopathies

NCT number	Drug	Mechanism of action	Status	Phase	Population	Completion
NCT03970122	GFB-887	Transient receptor potential channel 5 inhibitor	Completed	Phase I	Healthy volunteers	April 2020
NCT03598036	Voclosporin	High potency and stability calcineurin inhibitor	Recruiting	Phase II	FSGS	December 2020
NCT03649152	Propagermanium	CC-chemokine receptor 2 inhibitor	Active, not recruiting	Phase II	FSGS	June 2020
NCT03422510	CXA-10	Anti-inflammatory and antifibrotic	Recruiting	Phase II	FSGS	April 2021
NCT03448692	PF-06730512	SLIT2 antagonist	Recruiting	Phase II	FSGS	January 2023
NCT02921789	Bleselumab	Anti-human CD40 antibody	Active, not recruiting	Phase II	FSGS	April 2021
NCT03703908	CCX140-B	CC-chemokine receptor 2 inhibitor	Recruiting	Phase II	FSGS	March 2021
NCT03536754	CCX140-B	CC-chemokine receptor 2 inhibitor	Active, not recruiting	Phase II	FSGS	March 2020
NCT04009668	Adalimumab	Anti-human TNF antibody	Recruiting	Phase II	FSGS, MC	January 2021
NCT02592798	Abatacept	T cell inhibitor	Completed	Phase II	FSGS, MC	January 2020
NCT03366337	Bardoxolone	Nuclear factor erythroid 2-related factor activator and NF-κB inhibitor	Completed	Phase II	FSGS	January 2019
NCT03493685	Sparsentan	Dual endothelin type A and angiotensin II type 1 receptor antagonist	Recruiting	Phase III	FSGS	December 2022
NCT04340362	VX-147	APOLl antagonist	Recruiting	Phase II	APOL1-associated FSGS	May 2021
NCT02585804	Dapagtiflozin	SGLT2 inhibitor	Completed	Phase IV	FSGS	April 2017
NCT02639260	*N*-acetyl mannosamine	Sialic acid precursor	Completed	Phase 1	FSGS	June 2018

Trials were selected by using, as key words, FSGS, MC, minimal change disease, DMS and collapsing glomerulopathy. Only trials that have been completed in the past 3 years or that have yet to be completed have been included. Search of clinicaltrials.gov was performed on 12 June 2020. DMS, diffuse mesangial sclerosis; FSGS, focal segmental glomerulosclerosis; MC, minimal changes; SGLT, sodium/glucose cotransporter.