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EDITORIAL

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# Antibody-mediated podocytopathies: a disease entity that implies immunotherapy

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Podocytopathies are kidney diseases in which injury to podocytes, either direct or indirect, leads to proteinuria [1]. The phenotypic characterization of podocytopathies usually reveals the presence of minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) on kidney biopsies. These patterns of injury differ in terms of onset of disease, treatment responsiveness and subsequent long-term renal survival [2, 3]. Convincing evidence suggests that MCD and FSGS are manifestations of one disease and a transition from MCD to FSGS is often found on repeat kidney biopsies in cases with progressive disease, presenting with decline in kidney function or non-responsiveness to commonly used immunosuppressive therapies [4]. Response rates in 90% of patients with MCD and a therapeutic effect in ≈50% of patients with FSGS are seen in response to B cell–depleting therapy with rituximab [3]. This, in conjunction with a significant recurrence rate of 30–40%, and depending on patient selection even ≥50%, for FSGS after kidney transplantation [4], hints at an autoimmune response in a substantial proportion of patients with podocytopathies.

Several circulatory markers have been identified and proposed to be causative of FSGS lesions in primary cases, but without convincing and reproducible evidence. The discovery of circulating antibodies targeting nephrin, an essential structural component of the slit diaphragm of podocytes, marked a landmark discovery in nephrology. The use of enzyme-linked immunosorbent assays (ELISAs) and immunoprecipitation of full-length nephrin revealed a positive finding in 29% of the 62 analyzed samples [5]. Confocal microscopy indicated that nephrin co-localized with a punctate immunoglobulin G (IgG) pattern on renal biopsies, suggesting a causative role of these antibodies in the development of nephrotic syndrome. A subset of patients with detectable circulating nephrin antibodies had sequential samples ($n = 11$) during remission, and all were antibody negative as defined by the threshold of the ELISA test [5]. A Japanese multi-institutional study tested the value of anti-nephrin antibodies in children with recurrent FSGS after transplantation. They compared the antibody levels of 14 cases with a primary form with those of 8 patients with a genetic FSGS. Of the 14 children with a proposed non-genetic form, 11 (78.6%) had recurrent FSGS and were found to have circulating anti-nephrin antibodies above the threshold for positivity (231 U/ml), with a median antibody level of 899 U/ml. Responders to therapy had a significant decrease in antibody levels, while non-responders had persistently high titers. Patients with genetic forms of FSGS had a median anti-nephrin antibody level of 113 U/ml [6]. A single-center study from Russia investigated levels of anti-nephrin antibodies in individuals with presumed primary and secondary FSGS, MCD and membranous nephropathy

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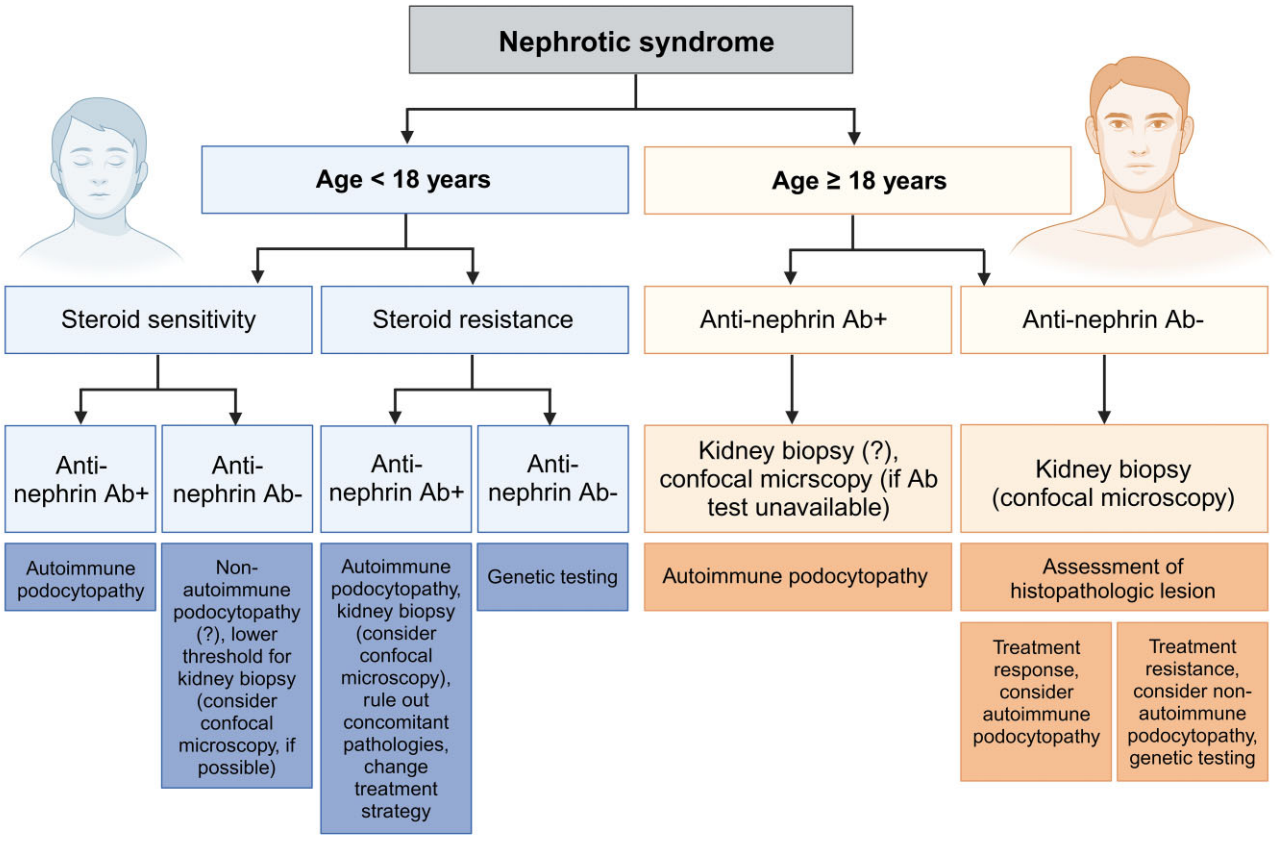


**Figure 1:** A proposed diagnostic algorithm in patients with nephrotic syndrome and suspected podocytopathy. In children, testing might be performed in all patients at the time of initial presentation. In the case of steroid sensitivity, an autoimmune podocytopathy needs to be considered. In those with anti-nephrin antibody negativity, other causative factors might be considered, but in general a histological assessment of the podocytopathy might help to further classify the underlying pattern of injury. In steroid resistance and antibody positivity, a kidney biopsy is helpful to rule out other pathologies leading to persistent proteinuria. Persistent positivity of antibodies might be helpful to guide therapy. In adults with nephrotic syndrome, antibody positivity might be sufficient to make a diagnosis and remove the need for a kidney biopsy. An autoimmune podocytopathy can be diagnosed based on the presence of anti-nephrin antibodies. In those with antibody negativity, a kidney biopsy is required to assess the histopathologic lesions leading to nephrotic syndrome. If patients respond to therapy, an autoimmune podocytopathy can be considered. If antibodies are not detectable and resistance to therapy is present, genetic testing should be considered. Confocal microscopy and the co-localization of punctate IgG and nephrin might be helpful to diagnose an autoimmune podocytopathy when there is limited access to antibody testing by conventional means. Figure created with BioRender.com.

(MN). The identified levels were highest in MCD, followed by primary and secondary FSGS, MN and controls [7]. An obvious issue arising from these studies is the difference in the techniques used to detect antibodies to nephrin and the different thresholds to define antibody positivity; all used an arbitrary level to define positivity.

The relevance of anti-nephrin antibodies was recently confirmed in a large study analyzing samples from paediatric and adult cases with glomerulonephritides. The presence of antibodies was determined by the use of a new hybrid technique combining immunoprecipitation with ELISA. In total, 46 of 105 (43.8%) adults with MCD had detectable antibodies, while 7 of 74 (9.5%) with primary FSGS tested positive for anti-nephrin antibodies. In nephrotic patients not exposed to immunosuppression, 68.6% (24/35) had anti-nephrin antibodies in their serum. In childhood nephrotic syndrome, 94 of 182 (51.6%) patients tested positive. This number increased to 89.7% (35/39) when analysis was restricted to children with nephrotic syndrome and not currently taking immunosuppression. A positive test was more frequently found in those patients with higher proteinuria, lower serum albumin and higher serum cholesterol.

As previously shown in the initial discovery paper, the disappearance of antibodies indicated a response to immunosuppressive therapy and antibody negativity seemed to correspond to a reduction of protein excretion to negligible levels. Further extensive mechanistic studies have shown *in vivo* pathogenicity of autoantibodies against nephrin. In a murine experimental model, immunization with nephrin induced autoantibodies to nephrin, leading to the onset of nephrotic syndrome within 3 weeks of follow-up. Mouse IgG was present at the slit diaphragm in areas of podocyte effacement and co-localization of punctate IgG and nephrin was reported [8].

However, several questions remain unanswered and arise from the recent discovery of anti-nephrin antibodies as a cause of podocytopathies.

**Who should be tested for anti-nephrin antibodies? How frequently should these tests be performed?** While it seems clear that the presence of anti-nephrin antibodies can identify autoimmune podocytopathies, the prognostic value offered by phospholipase A2 receptor (PLA2R) antibodies in predicting a future reduction of proteinuria is not seen. In PLA2R-associated MN, a 50% reduction of antibodies precedes remission by ≈10 months

[9]. This is in contrast to antibody-positive podocytopathy, as most patients achieve remission weeks after immunosuppression is started and this associates with becoming antibody negative. However, some patients reported in the landmark studies also achieved clinical remission despite the ongoing presence of antibodies [8].

Detection of anti-nephrin antibodies aid in diagnosing an antibody-mediated podocytopathy and a test should be performed in patients presenting with nephrotic syndrome and the presence of diffuse foot process effacement on electron microscopy and clinical/laboratory signs of primary nephrotic syndrome (low serum albumin, high cholesterol, nephrotic-range proteinuria), independent of the age of presentation. Current standard practice in childhood aims to avoid a diagnostic kidney biopsy in steroid-sensitive nephrotic syndrome [2]. Thus the detection of anti-nephrin antibodies before initiation of immunosuppression will help to classify their disease as an autoimmune podocytopathy (Fig. 1). In the scenario of clinical remission, testing for the presence of anti-nephrin antibodies is of limited value. While those with persistent nephrotic syndrome might remain antibody positive, and in such cases the ongoing presence of antibodies inform a change in the immunosuppressive strategy earlier in the disease course, such patients might also benefit from a kidney biopsy to exclude concomitant pathologies.

**What are the consequences of the presence of anti-nephrin antibodies?** In PLA2R-associated MN, it has been proposed that a diagnostic kidney biopsy is not required when the estimated glomerular filtration rate (eGFR) is ≥60 ml/min/1.73 $m^2$, as it does not alter diagnosis or management [10]. However, anti-nephrin antibodies in podocytopathies seem to predict a primary nephrotic syndrome rather than a specific disease per se, so a kidney biopsy is needed to make a diagnosis of either a podocytopathy or an alternative. This is important information that should be included in future diagnostic algorithms for podocytopathies.

**Is genetic testing required when anti-nephrin antibodies are present?** In patients with an immediate response to therapy, testing will not be required to exclude genetic forms of nephrotic syndrome. This is also true in patients with a response when antibodies to nephrin are not detectable and the cause of podocytopathy is unknown. These patients might have other circulatory factors causing podocyte injury and subsequent proteinuria. In patients presenting with persistent nephrotic syndrome despite immunosuppressive therapy and anti-nephrin antibody positivity, genetic testing needs to be considered. However, the role of genetic testing needs to be defined and requires further study.

**What about patients at risk of recurrent FSGS after kidney transplantation?** Data from Japan [6] indicate that a significant proportion of patients with recurrent FSGS will have detectable anti-nephrin antibodies. Pre-transplant positivity for antibodies indicates a higher risk for immediate post-transplant recurrence. This should be assessed prior to transplantation and a management strategy identified. Adjustment of pre-transplant strategies to avoid recurrence might be required and therapies such as B cell depletion with rituximab to achieve antibody negativity might be considered in such individuals. In patients with recurrent FSGS after kidney transplantation, long-term extracorporeal therapy is often required to reduce proteinuria [11]. Achieving antibody negativity might allow a reduction in the frequency of plasma exchange or immunoadsorption.

The discovery of anti-nephrin antibodies in a substantial number of children and adults with podocytopathies is a major milestone in nephrology research. Antibody positivity hints at not only an antibody-mediated pathogenesis in these individuals, but also reinforces the rationale behind the use of B cell–depleting agents as the predominant management strategy.

The potential of anti-nephrin antibodies as a prognostic tool seems limited based on the published experience. In specific circumstances it might be possible to use these antibodies in lieu of a kidney biopsy to diagnose a podocytopathy, and there may also be a role in individuals refractory to treatment.

The frequency of antibody positivity in recurrent FSGS cases outside of Japan needs to be established. Similarly, whether the antibody can serve as a prognostic tool to predict the recurrence of disease in a transplant patient and whether it could serve as a therapeutic monitoring tool after recurrence is unclear. In the first instance, a priority should be the development of an accessible commercial test that requires approval by regulatory agencies and will allow global testing of patients for the presence of anti-nephrin antibodies. At the moment, the tests that are used are assays on a research level, with variable sensitivity and specificity. The key publications have used in-house ELISA tests [5, 8] and immunoprecipitation to determine anti-nephrin antibodies [5, 8]. Development of commercial tests will require easy applicability. An ELISA test, similar to established methods to detect PLA2R antibodies, would be easy to implement in a non-research setting. However, low titers of anti-nephrin antibodies as reported might impact the development of such a commercial test. If access to a test for circulating anti-nephrin antibodies is not available, anti-nephrin-positive disease can also be diagnosed by the performance of confocal microscopy, where a clear overlap of punctate IgG with nephrin can be considered as a positive test [5].

In Fig. 1, the Immunonephrology Working Group (IWG) of the European Renal Association (ERA) proposes a diagnostic algorithm for patients with nephrotic syndrome and a suspected podocytopathy, with the caveat that prospective studies are required to confirm the validity of these proposals.

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## AUTHORS' CONTRIBUTIONS

A.K., C.B., A.M. and P.G. wrote the first draft of the manuscript. All authors significantly contributed to the content and reviewed the manuscript.

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