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## Summary

Glomerular diseases are common causes of chronic kidney disease in childhood, adolescence, and adulthood. The epidemiology of glomerular diseases differs between different age groups, with minimal change disease being the leading cause of nephrotic syndrome in childhood, while membranous nephropathy and focal segmental glomerulosclerosis are more common in adulthood. IgA vasculitis is also more common in childhood. Moreover, there is a difference in disease severity with more children presenting with a relapsing form of nephrotic syndrome and a more acute presentation of antineutrophil cytoplasmic antibody–associated vasculitis and concomitant glomerulonephritis, as highlighted by the higher percentage of cellular crescents on kidney biopsy specimens in comparison with older patients. There is also a female preponderance in antineutrophil cytoplasmic antibody–associated vasculitis and more children present with tracheobroncholararyngeal disease. This article aims to summarize differences in the presentation of different glomerular diseases that are encountered commonly by pediatric and adult nephrologists and potential differences in the management.

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Glomerular diseases are a common cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in children and adults. The frequency of specific glomerular diseases varies across the lifespan. Minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and IgAN/IgA vasculitis (IgAV) are the leading glomerular diseases in children,<sup>1</sup> with some regional variance reported.

Although MCD and IgAV are more prevalent in children, most cases of IgAN and FSGS are diagnosed in adulthood. In adults, the regional difference in epidemiology becomes more obvious. In a large international study including 42,603 biopsy-proven cases, FSGS was the leading glomerular disease in the United States/Canada (4,462; 19.1%), whereas in Europe and Asia IgAN/IgAV were the leading glomerular diseases (3,318;

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22.1% and 636, 39.5%, respectively) and lupus nephritis (LN) (976 cases; 38.1%) was predominant in Latin America.<sup>2</sup> Frequencies of reported glomerular diseases also might depend on different approaches to screening for hematuria and proteinuria in different countries.<sup>3</sup>

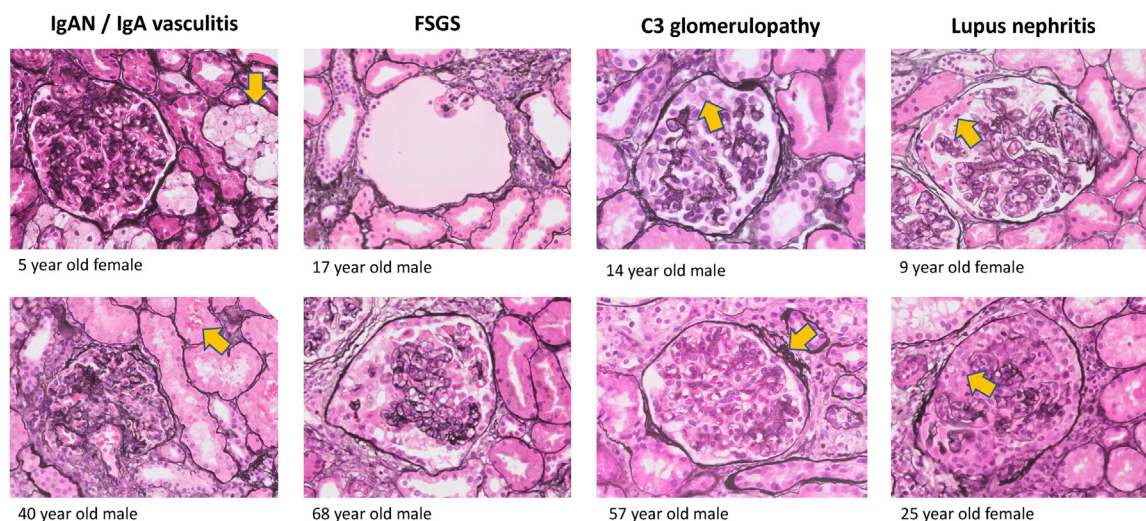
Glomerular diseases have distinct clinical features in childhood in comparison with adulthood, for example, the frequency of relapses of childhood nephrotic syndrome is higher compared with adults, and only a small proportion of adult survivors of childhood nephrotic syndrome will continue to relapse during their adult life.<sup>4</sup> With regard to histopathologic features on renal biopsy specimens, characteristic lesions do not seem to differ between children and adults, although it must be emphasized that in-depth, large group studies on this particular topic are scarce.

Nonspecific additional findings, mostly related to chronic changes, are more common in adults than in children, but they need not be disease-related. For instance, the number of globally sclerosed glomeruli increases with age, and interstitial fibrosis (IF) and tubular atrophy (TA), as well as arterial and arteriolar sclerosis, are present more often in renal biopsy specimens of adults, owing to a wide spectrum of comorbidities such as hypertension, obesity, and diabetes. Interestingly, a study that investigated which renal histopathologic lesions provided prognostic information beyond clinical and laboratory data found that exactly these chronic lesions were of

significant importance after adjustment for proteinuria and estimated glomerular filtration rate (eGFR).<sup>5</sup> Recent publications therefore suggest correction for age-related global glomerulosclerosis in antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN),<sup>6</sup> and nephrotic syndrome.<sup>7</sup> Figure 1 shows the similarity of glomerular lesions for some of the diseases described in this article, sometimes accompanied by subtle, additional findings most likely associated with age.

Glomerular diseases can be subclassified broadly into renal-limited diseases such as MCD, FSGS, and membranous nephropathy (MN), and systemic diseases with kidney involvement, for instance, ANCA-associated vasculitis (AAV) or systemic lupus erythematosus (SLE), in which kidney involvement is associated with increased mortality.

Pediatric glomerular diseases are usually less frequent, most therapeutic approaches reflect management of the respective adult glomerular disease. This does not include idiopathic nephrotic syndrome/MCD and IgAV, for which treatment regimens for adults mainly mirror pediatric experience. Of note, different classification criteria exist for children and adults for some entities, for instance, the European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society endorsed the Ankara 2008 criteria for IgAV and granulomatosis with polyangiitis (GPA).<sup>8</sup>



**Figure 1.** A selection of glomerular diseases in pediatric and adult ages. All glomeruli in silver staining at a magnification of 400 $\times$ . IgAN/IgA vasculitis: glomeruli show mesangial hypercellularity and expansion in both cases. The pediatric case shows foamy changes of tubular epithelial cells (arrow), related to nephrotic range proteinuria, which is more common at this age. The adult case has many erythrocytes in the tubular lumina (arrow), representative of hematuria, a more common manifestation in adults with IgAN. Both cases of focal segmental glomerulosclerosis (FSGS) are examples of collapsing FSGS. The pediatric case shows a relatively rare form with almost complete collapse of the capillary tuft, whereas the adult case has the more classic collapsing FSGS with podocytes surrounding the capillary tuft. There are relatively subtle changes in both cases of C3 glomerulopathy, with podocyte hypertrophy in the pediatric case (arrow) and mild mesangial hypercellularity in the adult case. The adult case also shows splitting of Bowman's capsule (arrow), which is most likely a result of ischemia adjacent to an area with interstitial fibrosis and tubular atrophy. Both cases of lupus nephritis are class IV lupus nephritis. In the pediatric case, the proximal tubular epithelial cells (arrow) are prominently present in the glomerulus, a feature often encountered in children and sometimes confused with crescent formation. In comparison, the adult case shows a real cellular and circumferential crescent (arrow).

Supportive measures, such as vaccinations or prophylactic antimicrobials to reduce the infectious risk inherent to all immunosuppressants, management of edema, and maintaining bone health by using antiresorptive agents during high-dose glucocorticoid therapy, are important in all age groups. Certain treatment-related side effects, such as cosmetic effects, weight gain, need for contraception, and infertility, usually have greater significance for younger individuals and always should be addressed thoroughly.

This review provides an update on common glomerular diseases occurring during childhood and adult life, highlighting differences (and similarities) in presentation forms (particularly the frequency of kidney involvement), long-term outcomes, and emphasizes current principal management differences.

### PODOCYTOPATHIES: MCD/FSGS

The proportion of the various causes of nephrotic syndrome (NS) differs between pediatric and adult patients, also impacting nomenclature. In childhood, MCD is considered by far the most common cause. Therefore, young patients usually do not undergo a biopsy, but receive empiric treatment with glucocorticoids (steroids) for what, in the absence of histology, is called *idiopathic nephrotic syndrome* (INS).<sup>9</sup> In the majority of cases, there is quick and complete remission; this course is called steroid-sensitive NS.<sup>10</sup> Consequently, although not strictly identical, the terms steroid-sensitive NS and MCD usually are used interchangeably in pediatric nephrology. Only if a remission is not achieved after sufficiently long treatment (steroid-resistant nephrotic syndrome [SRNS], defined as lack of complete remission after 4 weeks of steroids at a standard dose),<sup>11</sup> is a tissue diagnosis warranted, leading to selection bias of diagnoses based on biopsy findings. A notable exception to this approach is congenital NS, in which a monogenetic cause can be established in 70% to 85% of cases.<sup>9</sup> In this age group, a genetic diagnosis usually is pursued at the onset, as discussed later. Likewise, in cases of SRNS, early genetic testing is indicated, especially in children but also in adults.<sup>12</sup> If a FSGS pattern is present, histopathologic assessment (collapsing variant; chronic tubulointerstitial damage  $\geq 25\%$  or segmental sclerosis) predicted worse renal outcome, defined as a 50% or greater decline in eGFR, ESKD, or death.<sup>13</sup>

Because the causes of NS are more heterogeneous in adulthood, a biopsy is recommended in all cases. In addition, in adults, it is important to exclude secondary causes of MCD resulting from infection, drugs, autoimmune disease, and malignancy.<sup>14</sup> MCD is one of the few glomerulopathies in which NS can be accompanied by acute kidney injury at presentation, which is attributable mainly to age, extent of proteinuria, hemodynamics, and

lesions seen on kidney biopsy<sup>15,16</sup>; on average, such patients are older and more likely male.<sup>17</sup>

Treatment recommendations for MCD are based mainly on pediatric data and, for many years, have been extrapolated to adult patients. High-dose glucocorticoids remain the first-line therapy, with calcineurin inhibitors (CNI), mycophenolate mofetil (MMF), levamisole, and cyclophosphamide representing established alternative agents. Because of its recognized toxicity, the latter increasingly is abandoned. B-cell depletion, mainly with rituximab (RTX), has emerged as an attractive treatment option in this indication<sup>18</sup> and its use is increasing rapidly, as discussed later. Trial evidence for MMF is limited in pediatric nephrology, but this knowledge gap is likely to close in the near future.<sup>19-21</sup> In an adult cohort, the Myfortic pour Syndrome Nephrotique study (combining low-dose prednisone with MMF) showed encouraging results.<sup>22</sup> Although pediatric protocols contain detailed tapering instructions for glucocorticoid schedules,<sup>11</sup> albeit with substantial variability, such data are scarce for adult patients.<sup>23,24</sup> This is particularly problematic because adults show treatment response later and less frequently, with an overall risk of steroid overexposure and its well-established adverse effects. On the other hand, the clinical course more often is relapsing in younger individuals. Approximately 80% of children with an initially steroid-sensitive course will experience at least one relapse and, in a significant minority, such relapses continue into adulthood.<sup>9</sup> The definition of frequently relapsing courses (FRNS), defined as two or more episodes of NS within 6 months or more than 4 episodes within 1 year,<sup>25</sup> are also more common in childhood and underline the importance of continuous immunosuppression. In the recently published International Pediatric Nephrology Association clinical practice guidelines, the definition of childhood FRNS was changed to “include children with two or more relapses in the first 6 months of the disease, or three or more relapses in any 12-month period,” to prevent steroid overexposure.<sup>11</sup>

The need for additional treatment options for patients with multiple relapses or resistance to steroids is widely acknowledged.<sup>10</sup> Anti-CD20 monoclonal antibodies are used increasingly in both childhood and adult MCD and show promise for providing long-term remission. RTX, the chimeric prototype, has been in use for more than a decade in this indication.<sup>26</sup> Although newer, fully humanized antibodies such as ofatumumab hold theoretical advantages, a recent study found no clinical benefit with regard to maintenance of remission at 1 year in a cohort with steroid-dependent nephrotic syndrome (SDNS), defined as relapse within 2 weeks after reduction or discontinuation of steroids, or CNI-dependent NS when compared with rituximab (n = 140; age, 2-24 y).<sup>27</sup> Notably, a Japanese study, using a combined approach with RTX, followed by MMF, reported a reduced risk of

relapse in a cohort of children with FRNS/SDNS (n = 39).<sup>21</sup> A global anti B-cell strategy (the combination of obinutuzumab and daratumumab) appeared promising in a small study of children with severe NS (n = 14).<sup>28</sup>

In parallel, existing treatment regimens are being refined constantly, with the overall aim of a reduction of cumulative steroid dose. Although the question of optimal treatment duration largely has been settled for children, with steroid schedules now limited to 2 to 4 months, shortened steroid regimens are not yet well established for adult patients and there is an overall impression that many adults are treated for too long (ie, frequently for up to 6 months).<sup>9,29</sup> Ozeki et al<sup>30</sup> prospectively compared the effectiveness of a short-term steroid regimen (n = 35; median age, 51 y) with a historical control group treated conventionally. Although relapses occurred earlier in the short-term group, no difference in the occurrence of frequent relapses was noted. Response-adapted protocols represent another interesting approach. In a recent nonrandomized study, among 59 children with a first episode of INS, early responders at 8 weeks (n = 27) received a rapid tapering schedule (8 compared with 24 weeks in the standard protocol), resulting in a 50% lower cumulative steroid dose with no differences in the rates of relapses, FRNS, or SDNS.<sup>31</sup> In all, high-quality evidence from clinical trials for the treatment of adult MCD remains scarce, with notable exceptions. Recently, the acrolimus vs prednisolone for the treatment of nephrotic syndrome secondary to minimal change disease: A Randomised Control Trial study (n = 52; median age, 43 y) improved the foundation for tacrolimus monotherapy for incident MCD. Notably, with a duration of only 26 weeks, the relapse rate was high in both arms.<sup>32</sup>

Although there is compelling evidence for an autoimmune origin of MCD, with the recent discovery of anti-nephrin antibodies in a selected cohort of adults and children,<sup>33</sup> the picture is more diverse for FSGS. Furthermore, there is ongoing debate whether a proportion of FSGS cases represent MCD at a later stage. The term *FSGS* originally was descriptive, indicating that a segmental form of glomerulosclerosis occurs in fewer than 50% of glomeruli in the biopsy specimen, but later became used as a pattern of disease for which, consequently, different phenotypes were distinguished as represented in the histologic classification. Distinguishing so-called primary FSGS from secondary FSGS has always been cumbersome because of the lack of consistent relations based on histologic, clinical, serologic, genetic, and other factors. A change to a terminology based more on pathophysiology is gathering momentum, with the umbrella term primary podocytopathy increasingly being used.<sup>34</sup> A better understanding of the underlying cause(s) will allow for a more personalized treatment approach, for instance, avoidance of immunosuppression in genetic or secondary forms of INS.

If, after therapy with glucocorticoids, remission does not occur, non-immune-mediated causes of FSGS need to be considered. The proportion of hereditary causes of FSGS correlates inversely with age. Screening for genetic FSGS generally is recommended for all children presenting with SRNS and this approach is mirrored increasingly in adult nephrology.<sup>35</sup> Notably, apart from the well-described genes encoding proteins of the slit membrane or podocytes, such as nephrin and podocin, adult genetic FSGS is much more heterogenous and it now is recognized, that Alport genes (*COL4*) represent the most common hereditary subgroup of FSGS.<sup>36</sup> On principle, genetic cases portend a poor prognosis. *APOL1* gain-of-function variants have been associated with severe FSGS. Inaxapalin, an APOL1 channel function inhibitor, was found to be effective in 13 patients and therapy reduced the proteinuria at week 13 by -47.6%.<sup>37</sup>

By and large, primary FSGS in adults follows a similar treatment path as MCD, with CNI and RTX representing the main nonsteroid immunosuppressants. Novel treatment concepts for adults were summarized in a recent article.<sup>38</sup> Sparsentan, a dual endothelin angiotensin-receptor antagonist, failed to provide evidence that it is superior to irbesartan in slowing the progression of kidney disease, but led to an 18% greater reduction in proteinuria in individuals with FSGS.

## Membranous Nephropathy

Membranous nephropathy, with an estimated incidence of 10 to 12 per million in North America and 2 to 17 per million in Europe, is the most common form of nephrotic syndrome in adults, but some cases are encountered in early childhood.<sup>39</sup> Our understanding of membranous nephropathy improved during the past 2 decades, with the identification of pivotal antigens leading to the onset of nephrotic syndrome (Table 1). Antenatal membranous nephropathy with placental transfer of antineutral endopeptidase antibodies was reported as a cause of nephrotic syndrome, with co-localization of fetal/child neutral endopeptidase with maternal IgG in subepithelial deposits.<sup>40</sup> In 2009, the discovery of the M-type phospholipase A2 receptor (PLA2R) antibodies in 70% of patients with idiopathic (primary) membranous nephropathy was a major breakthrough, PLA2R colocalizes with IgG4 in immune deposits.<sup>41</sup> Testing for PLA2R antibodies is widely available. Immunologic remission, characterized by a negative PLA2R antibody test, in PLA2R-associated MN predicts reduction of proteinuria, and measurement of PLA2R antibody titers at regular intervals (initially every 2-3 months) is recommended by current guidelines.<sup>25</sup> In rituximab-treated individuals, a 50% PLA2R antibody titer reduction preceded an equivalent reduction in proteinuria by 10 months.<sup>42</sup> In those with PLA2R antibody negativity, the reappearance of

**Table 1. Antigens Identified in Membranous Nephropathy**

Antigen	PLA2R	THSD7A	PCDH7	NELL-1	EXT1/ EXT2	NCAM-1	SEMA3B	HTRA1	TGFBR3	FAT1	CNTN1	Neirin G1	FCN3	CD206	EEA1	SEZ6L2	NPR3	MST1	VASN	NDNF
Age V Ig subclass (dominant) diseases	55-60 IgG4	60 IgG4	60 IgG1, other subclasses	65 IgG1	35-40 IgG1	35 IgG1 (+other subclasses)	7/35 IgG1	65-70 IgG4	40 All subclasses	50-70 IgG4	65-70 All subclasses	50-60 IgG4	25-55 All subclasses	65 -	20-70 All subclasses	65-80 IgG4	60 -	20-70 All subclasses	20-85 All subclasses	45 IgG1
Associated diseases	No	Malignancy (around 10%)	Malignancy (around 10%)	30% (malignancy), drug-induced (some cases)	SLE (30%), other autoimmune	SLE (6.6%)	Pediatric (pre-dominant), potential familial	No	SLE	HSCT	CIDP	No	SLE	No	Cutaneous SLE	Cerebellar ataxia	No	No	No	Syphilis
Frequency	70%-80%	2%-3%	1%-3%	3%-4%	30%-35% (LN)	2% (LN 6.6%)	1%	1%	6% (LN)	0.9%	Rare	0.24%	0.2%	0.2%	1.1%	0.2%	0.1%	0.9%	1.2%	0.3%

Several antigens were identified in membranous nephropathy, some were assumed to be primary and some secondary, which led to the reclassification of the disease based on the presence of the antigen. Most of the antigens are rare, and thus frequencies of detection might differ between cohorts. Some of these antigens are associated with specific diseases. Although PLA2R-associated membranous disease can be associated with other diseases (ie, diabetic kidney disease, presence of hepatitis B), it usually is considered a primary cause of membranous nephropathy. Other antigens, such as EXT1/EXT2, are associated with autoimmune disorders, especially systemic lupus erythematosus. Abbreviations: CD206, cluster of differentiation 206; CIDP, Chronic inflammatory demyelinating polyneuropathy; CNTN1, contactin-1; EEA1, early endosome antigen 1; EXT1/EXT2, exostosin 1/exostosin 2; FAT1, protocadherin FAT1; FCN3, ficolin 3; HSCT, hematopoietic stem cell transplantation; HTRA1, high-temperature recombinant A1; LN, lupus nephritis; MST1, macrophage stimulating 1; NCAM-1, neural cell adhesion molecule 1; NDNF, neuron-derived neurotrophic factor; NELL-1, neural epidermal growth factor like-1 protein; NPR3, natriuretic peptide receptor 3; PCDH7, protocadherin 7; PLA2R, M-type phospholipase A2 receptor; SEMA3B, semaphorin 3B; SEZ6L2, seizure-related 6 homolog-like 2; SLE, systemic lupus erythematosus; TGFBR3, transforming growth factor  $\beta$ -receptor 3; THSD7A, thrombospondin type-1 domain-containing 7A; VASN, vasorin.

circulating antibodies predicted disease relapse. The age at presentation of PLA2R-associated membranous nephropathy is approximately 55 to 60 years, and is in line with other identified antigens with either no distinctive disease association, chronic inflammatory demyelinating polyneuropathy-associated MN, or malignancy-associated MN. Exostosin-1/exostosin-2 positivity is present in approximately 33% of cases with LN, further subdivided into 75% with pure class V (membranous LN) and 25% with mixed classes. These patients are younger, present more frequently with proteinuria levels of 3.5 g/d or greater, and have less-extensive chronic damage on kidney biopsy specimens.<sup>43</sup> A further antigen, semaphorin 3B-associated MN, has been identified predominantly in pediatric cases (8 of 11), mostly in patients younger than 2 years of age.<sup>44</sup> Similarly, circulating cationic bovine serum albumin (BSA) and anti-BSA antibodies may be causative in early childhood-onset (age, <5 y) MN, BSA could be detected in subepithelial granular deposits.<sup>45</sup> Testing for most of these antigens, except for PLA2R and thrombospondin type 1 domain containing 7A, currently is not available in most centers.

Because childhood-onset MN is rare, most children younger than age 10 to 12 years will receive high doses of oral steroids for 4 to 8 weeks owing to suspected INS.<sup>39</sup> Initiation of therapy depends on the risk classification of patients with MN (Supplementary Table 1). In patients with low-to-moderate risk, the likelihood of spontaneous remission without immunosuppression is high. In those with high-to-very high risk, specific considerations should be taken into account and early initiation of immunosuppression may be necessary. Notably, response to rituximab may be suboptimal in those patients with heavy proteinuria because it is lost via the urine and redosing or higher doses might be considered.<sup>46</sup> In the very-high-risk setting, defined as those presenting with impaired or deteriorating kidney function attributed to MN, cyclophosphamide might be preferred over rituximab.<sup>25</sup> Trials with sufficient power comparing the efficacy of B-cell-depleting agents (ie, rituximab) versus alkylating agents (ie, cyclophosphamide) are required to guide therapy in such scenarios.<sup>25</sup> Specific therapeutic approaches do not differ between children and adults, but, in general, management of childhood MN does not include the use of cyclophosphamide as first-line therapy.<sup>47</sup>

**Lupus Nephritis**

SLE usually manifests within the first decades of life, with a median age at onset in childhood of approximately 12 years,<sup>48</sup> and the early 30s in adulthood.<sup>49</sup> Analysis of the US Medicaid claims data indicated a prevalence of 9.73 per 100,000 in children, with SLE being more common in Asians, Blacks, Hispanics, and

Native Americans, than among Whites. Among 2,959 children, 37% were considered to have LN.<sup>50</sup> The prevalence in adults was almost 15-fold higher, and again lowest in Whites in the United States. Among the 34,339 patients with SLE, 7,388 (21.5%) presented with LN.<sup>51</sup> The frequency of LN depends not only on age at diagnosis (more frequent among children than in adults), but also is influenced by other factors, such as impact of genetic background. In a Hungarian analysis, 39.2% of children and 26.4% of adults presented with LN, and the difference was driven mainly by prepubertal children.<sup>49</sup> In Southeast Asia the prevalence of LN was higher in males (76% of 25 patients) than in females (45.2% of 261 patients)<sup>52</sup> (Table 2). A small study focusing on pediatric LN (n = 23) versus late-onset LN (n = 13; age,  $\geq 50$  y) found that children presented with more severe acute lesions than adults, having more crescents on biopsy specimens, a higher disease activity index, but a lower percentage of IF.<sup>53</sup> Notably, ESKD only occurred in pediatric cases. In patients who did not develop ESKD, the eGFR increased from  $86 \pm 66$  to  $116 \pm 62$  mL/min per  $1.73 \text{ m}^2$  in children compared with an increase from  $70 \pm 18$  to  $78 \pm 20$  mL/min per  $1.73 \text{ m}^2$  in adults at 12 months,<sup>53</sup> showing greater recovery potential in children, indicating that the recovery

potential is higher in pediatric cases. Survival rates without advanced CKD, ESKD, or death seem to have improved, with 16.8% of children with LN reaching this composite end point at 20 years. Predictors of worse outcome are severe kidney failure requiring kidney replacement therapy, nonresponse to therapy at 12 months, and multiple nephritis flares.<sup>54</sup> These risk factors are, as a similarity, also reported in adult LN cases.<sup>55,56</sup> In children and adults with no response to immunosuppression, nonadherence to the prescribed medication should be considered. Noncompliance to treatment emerged as the strongest predictor of poor outcome, defined as failure to achieve remission among children with LN in China.<sup>57</sup>

Treatment approaches in children and adults are similar. Recommendations for pediatric LN were issued by the Single Hub and Access point for pediatric Rheumatology in Europe initiative in 2017.<sup>58</sup> These recommendations do not cover novel therapies such as belimumab, which recently was approved by the Food and Drug Administration for management of children with LN aged 5 to 17 years. Likewise, the 2019 EULAR/European Renal Association recommendations<sup>59</sup> for the management of LN do not cover recently approved therapies for LN in adults, such as belimumab and voclosporin. Updates to these guidelines also should indicate which

**Table 2.** Key Differences in the Presentation of Children and Adults With Systemic Lupus Erythematosus

	Tarr, <sup>47</sup> Children*	Fiorot, <sup>48</sup> Children	Tarr, <sup>49</sup> Adults*	Lee, <sup>52</sup> Adults
Patients	79	1,537	342	286
Countries	Hungary	Brazil	Hungary	China, Malaysia, India
Female:male ratio	7.8:1	6.16:1	10:1	10.44:1
Age at diagnosis, y	$12.02 \pm 2.89$	12.1	$32.5 \pm 7.93$	–
ANA	100%	93.4%	100%	–
dsDNA antibodies	82%	59.5%	85%	–
Lupus nephritis	39.2% (prepubertal, 72%; postpubertal, 24%)	40.9%	26.4%	47.9%
	Class II: 21.4% (more frequently than in adults)	Biopsy at time of diagnosis (n = 143): Class I: 7%	Class II: 2.5% (less frequently than in children)	LN classes not reported
	Class IV: 42.9% (less frequently than in adults)	Class II: 16.8%	Class IV: 68.4% (more frequently than in children)	
	No difference between classes III and V between the groups	Class III: 13.3%	No difference in occurrence of classes III and V	
		Class IV: 46.2%		
		Class V: 16.1%		
		Class VI: 0.7%		
Butterfly rash	61%	53%	35.5%	38.1%
Photosensitivity	20%	45%	9%	19.6%
Oral ulcers	11.4%	32.9%	4%	21.3%
Hematologic manifestations	57%	41.8% <sup>†</sup>	36.5%	81.1%
Polyarthritis	68%	–	87%	61.9%
Neurologic symptoms	6.3%	11%	17.3%	10.8%
Serositis	26.6%	26.9%	35.7%	18.9%

Different frequencies of lupus nephritis have been reported, although studies using similar databases report a higher frequency of lupus nephritis in childhood systemic lupus erythematosus.

Abbreviations: ANA, anti-nuclear antibodies; dsDNA, double-stranded DNA.

\*Patients with childhood systemic lupus erythematosus were compared with patients with adult-onset disease.

<sup>†</sup>The percentage of leukopenia/lymphopenia is given.

patients should receive these agents and when (ie, early in the disease course or in cases with persistent proteinuria). Such information also largely is missing in the current Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases,<sup>25</sup> but an update of the KDIGO guideline and the EULAR recommendations incorporating these newer therapies is on its way. Refinement of therapy and a tailored approach will be possible with the recently approved therapeutics and others that currently are under investigation.

### ANCA-Associated Vasculitis

AAV presents most frequently in adulthood, with a distinct age at presentation among the clinical phenotypes. Patients with GPA and eosinophilic GPA typically present in their 50s, while microscopic polyangiitis (MPA) presents a decade later. Because kidney involvement is relatively rare in eosinophilic GPA (25%-30%), the following section focuses on GPA and MPA with reported kidney involvement in adults of 58.6% and 82.3%, respectively.<sup>60</sup> Reports of frequencies of clinical phenotypes and organ involvement likely are biased by whether rheumatologists or nephrologists contribute to the data collection. Childhood-onset AAV is much rarer and usually manifests between age 10 and 15 years. Among 231 cases collected by pediatric rheumatologists, there was a preponderance of GPA,<sup>61</sup> although a case series from Italy reported 85 children with kidney involvement and found that MPA was more frequent.<sup>62</sup> Although both females and males are affected in a similar proportion during adulthood, females are predominantly affected in childhood. Kidney involvement seems to be more common in childhood, especially in cases with GPA, whereas other manifestations such as cardiovascular and ear, nose, and throat involvement seem to be less common (Table 3).<sup>60-63</sup> In GPA, laryngotracheobronchial disease is much more frequent in children with AAV, and is present in approximately a third at initial presentation. Approximately 15% develop laryngotracheobronchial disease even after immunosuppressive treatment is initiated.<sup>64</sup> This is reflected in the EULAR/PRINTO/PRES criteria for childhood GPA,<sup>8</sup> whereas laryngotracheobronchial disease is missing in several classifications of GPA focusing on adults.<sup>65</sup> Notably, no specific criteria for childhood MPA exist. The Birmingham Vasculitis Activity Score in its third version<sup>66</sup> and the Pediatric Vasculitis Activity Score<sup>67</sup> comprising 56 and 64 items (22 redefined and 8 added, in comparison with the Birmingham Vasculitis Activity Score) are established tools to assess disease manifestations, severity, and activity at initial presentation and at follow-up visits.

Most children with AAV and kidney involvement present with crescentic class (50.6%), defined as the

presence of 50% or more cellular crescents on biopsy specimens.<sup>62</sup> The median eGFR in these children was 23 mL/min per 1.73 m<sup>2</sup> and improved to 68 mL/min per 1.73 m<sup>2</sup> at 6 months. The prognosis of those with a sclerotic class (15.3%) was poor, with a decrease in eGFR from 21 to 10 mL/min per 1.73 m<sup>2</sup> at 6 months. Most patients with kidney failure during follow-up evaluation belonged to these two groups, whereas those patients in the focal ( $\geq 50\%$  normal glomeruli) and mixed class (not classified according to other classes) had a good long-term prognosis.<sup>62</sup> Among 145 adult patients with ANCA glomerulonephritis, crescentic class was present in 25.5% of patients.<sup>68</sup> At 1 year, eGFR had increased by 21 mL/min per 1.73 m<sup>2</sup> in those with a crescentic class, whereas eGFR remained stable in the sclerotic class. In contrast to children, there was also a proportion of mixed-class patients contributing to the group with kidney failure during follow-up evaluation. Taken together, the frequency of crescentic class and the recovery in eGFR in children exceeds those reported in adulthood, indicating that children present with more acute kidney involvement at baseline but show a higher potential to recover eGFR once immunosuppression is initiated. Nonetheless, those with a sclerotic class at presentation have a poor outcome, highlighting that early diagnosis is essential to prevent CKD progression and ESKD.

Therapeutic options between children and adults do not differ. Although studies including patients from the prirituximab era still report a high frequency of cyclophosphamide use, most children and adults with a serum creatinine concentration less than 4 mg/dL (353.6  $\mu$ mol/L) nowadays would receive rituximab alongside corticosteroids and/or avacopan (in adults<sup>69</sup>). Cyclophosphamide is an alternative, especially in those with more severe kidney dysfunction,<sup>25,62,68</sup> and may be combined with rituximab and steroids. In patients with a serum creatinine concentration of 5.7 mg/dL (500  $\mu$ mol/L) or greater, plasma exchange (PLEX) might be added to the other induction therapies, and patients with acute lesions (high percentage of crescents) in particular might benefit from the addition of PLEX.<sup>25</sup>

In children younger than 12 years of age, coatomer protein complex subunit alpha gene mutations are a relevant differential diagnosis. These children present with lung disease, including alveolar hemorrhage in 50%, joint pain, and some with kidney disease. ANCA is positive in some, whereas a concomitant presence of antinuclear antibodies and rheumatoid factor are common in coatomer protein complex subunit alpha syndrome. Kidney biopsy specimens usually show the presence of immunoglobulins or complement on immunofluorescence,<sup>70</sup> a rather unusual finding in ANCA glomerulonephritis, where absence of immunoglobulins and complement are common characteristics of pauci-immune glomerulonephritis.

**Table 3.** Key Differences in Presentation of Patients With Childhood-Onset and Adult-Onset Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

	Cabral <sup>61</sup> Children	Sacri <sup>63</sup> Children	Calatroni*, <sup>62</sup> Children	Kronbichler <sup>60</sup> Adults
Patients	231	66	85	999
Specialty	45 pediatric rheumatologists	–	–	Nephrologists and rheumatologists (mainly)
Recruitment	United States (34), Canada (6), Europe (3), and Asia (2)	France	Italy and Canada	31 countries
MPA:GPA ratio	1:3.81	1.36:1	1.66:1	1:2.08
Female:male ratio	1.56:1	4.99:1	1.83:1	1:1
Average age at diagnosis of MPA versus GPA, y	11-11.5 versus 13.5			64 versus 53
Constitutional/general, MPA versus GPA	76-85% versus 75-88%			86% versus 78%
Renal, MPA versus GPA	75%-100% versus 78%-100%			83% versus 59%
Pulmonary, MPA versus GPA	29%-44% versus 66%-74%			63% versus 63%
ENT, MPA versus GPA	0%-17% versus 53%-75%			26% versus 82%
Eyes, MPA versus GPA	0%-31% versus 21%-43%			13% versus 38%
Skin, MPA versus GPA	25%-52% versus 25%-47%			30% versus 35%
Gastrointestinal, MPA versus GPA	11%-58% versus 18%-36%			22% versus 19%
Nervous system, MPA versus GPA	5%-21% versus 4%-20%			37% versus 31%
Musculoskeletal, MPA versus GPA	3%-52% versus 4%-65%			49% versus 63%
Cardiovascular, MPA versus GPA	0%-6% versus 0%-5%			15% versus 11%

The different cohorts with childhood antineutrophil cytoplasmic antibody–associated vasculitis differed (ie, the study by Cabral et al reported a preponderance of GPA cases, while it generally was assumed that most children with antineutrophil cytoplasmic antibody–associated vasculitis would present with MPA. Of note, the presence of distinct disease features often is influenced by the specialties recruiting patients for observational studies or clinical trials; thus, there is a recruitment bias toward, for instance, more frequent kidney involvement (and subsequently more cases with myeloperoxidase–antineutrophil cytoplasmic antibody/MPA) in cohorts recruited by nephrologists versus rheumatologists. Abbreviations: ENT, ear, nose and throat; GPA, granulomatous polyangiitis; MPA, microscopic polyangiitis.

\*This study focused specifically on children with kidney involvement.



## Anti–Glomerular Basement Membrane Disease

Anti–glomerular basement membrane (GBM) disease is rare in childhood, nevertheless it is responsible for 20% of all rapidly progressive glomerulonephritis (RPGN) cases in children,<sup>71</sup> predominantly in toddlers.<sup>72,73</sup> In adults, bimodal peaks in incidence occur in the third and sixth decades.<sup>74</sup> Although males are affected mostly at earlier adult ages, there is a predominance of females in childhood and the elderly. A strong association between HLA-DRB1\*1501<sup>75</sup> and disease susceptibility has been reported, although a protective role of HLA-DR7 and DR1<sup>76</sup> alleles has been found. Environmental factors may precipitate disease onset. Data from Ireland have shown spatial and temporal clustering of disease incidence, supporting environmental influences.<sup>77</sup> In addition, infections (ie, influenza A and severe acute respiratory syndrome coronavirus 2) may contribute to disease onset, however, a causative role remains unclear.<sup>78</sup> More direct evidence exists on smoking as an environmental trigger because pulmonary hemorrhage occurs in almost all smokers but is uncommon in nonsmokers.<sup>79</sup>

The detection of anti-GBM antibodies either in serum or histologically in the presence of kidney and/or lung disease is the basis of the diagnosis. Affected patients present mostly with both RPGN and alveolar hemorrhage, but kidney involvement also may occur alone, which is more prevalent before puberty<sup>73</sup> and in the elderly.<sup>80</sup> Atypical cases such as isolated lung involvement with IgG4 subtype levels of anti-GBM or overlap with vasculitis or membranous nephropathy can occur,<sup>74</sup> however, data on these entities in children are missing. Outcome data in children are very limited and encompass predominantly case reports.<sup>72,81</sup> Williamson et al<sup>82</sup> reported four patients with anti-GBM disease aged 0 to 19 years, of which only one patient had kidney function recovery. This patient had a shorter time from symptom onset to hospital admission, suggesting that earlier intervention might be associated with improved outcomes. A survey involving pediatric centers from different countries showed that most children present with cellular crescents greater than 50% on the initial biopsy specimen, which is associated with poor prognosis (16% with complete renal recovery).<sup>73</sup> Similarly, data from adult populations showed poor kidney outcomes, which depends mainly on the severity of kidney disease (ie, presence of oligoanuria at baseline, percentage of crescents, and extent of interstitial infiltrates in kidney biopsy specimens or need for dialysis).<sup>83–85</sup> Interestingly, patients with atypical presentation of anti-GBM disease on a biopsy specimen (linear diffuse GBM staining for immunoglobulins without histologic presence of crescentic and necrotizing GN) may have a less-aggressive clinical course and might have better overall and kidney outcomes,<sup>86</sup> whereas patients with double seropositivity

for ANCA and anti-GBM antibodies may have a relapsing-remitting disease course and should be followed up more closely.<sup>87</sup>

Because the disease course often is aggressive and the outcome is poor, immediate initiation of immunosuppressive therapy is necessary. The rapid elimination of pathogenic autoantibodies using PLEX along with glucocorticoids (GC) and cyclophosphamide is the standard treatment in both pediatric and adult patients, as recommended by KDIGO 2021.<sup>25</sup> The addition of rituximab to standard therapy resulted in high remission rates<sup>88</sup> in a small case series of adult patients; nevertheless, data from larger cohorts are lacking. In patients with ESKD, kidney transplantation is the preferred option in both children and adults. In adults, long-term patient (0.03 per 100 person-years) and graft survival (6.2 per 100 person-years) is comparable with patients with IgAN.<sup>89</sup>

## IgAN/Vasculitis

IgAN is the most prevalent primary glomerulopathy in adults, with an estimated incidence of 2.5 per 100,000 per year.<sup>90</sup> IgAV (formerly known as Henoch-Schönlein purpura), its systemic form, represents the most common pediatric vasculitis. Although rarer in adults, it can occur at any age.<sup>91</sup> The natural history of IgAN is variable and determined by clinical findings at presentation and features on histopathology. The original Oxford Classification's scoring system of mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, and TA/IF, and its 2016 update, which added the presence of crescents as a predictive marker, is valid for adults and children.<sup>92,93</sup> However, because of the limited number of patients included, its prognostic value in pediatric cases remains debated.<sup>92,93</sup> Barbour et al<sup>94</sup> addressed this shortcoming by presenting a predictive tool in a large international cohort of more than 1,000 children. Although many cases of childhood IgAN resolve spontaneously, approximately 10% to 20% of children require KRT after 20 years.<sup>93</sup> Specific therapies with positive trial results in adults, such as sparsentan<sup>95</sup> or target-release budesonide,<sup>96</sup> remain untested in children with IgAN.

Although IgAN is by definition limited to the kidneys, IgAV (included in the Chapel Hill classification criteria as a small-vessel vasculitis with deposition of IgA-dominant immune complexes),<sup>97,98</sup> is characterized by multi-organ involvement, including the skin, gastrointestinal tract, and the kidneys; the latter constellation is termed IgAV with nephritis (IgAVN).<sup>99</sup> Kidney involvement is present in approximately one third of pediatric cases, but is more common in adults.<sup>91</sup> Apart from the differences in extrarenal manifestations, IgAVN also has a higher rate of macroscopic hematuria and nephrotic-range proteinuria than IgAN.<sup>91</sup> Histopathology cannot distinguish

these entities, with mesangial IgA deposition as a shared feature, but crescents are more frequent in IgAVN.<sup>91</sup>

IgAV is considered a disease of childhood and indeed, age at onset younger than 20 years is one of the four classification criteria of the American College of Rheumatology.<sup>100</sup> This classification, however, is of limited utility for adults.<sup>101</sup> Although kidney involvement increases with age, IgAVN also ranks among the most common biopsy-verified kidney diseases in the pediatric population. A recent retrospective long-term, follow-up study from the *Norwegian Kidney Biopsy Registry* assessed the frequency of the various causes of glomerulopathies in children. Among 575 biopsy specimens, IgAN and IgAV accounted for almost a quarter of all cases (11% and 13.2%, respectively).<sup>102</sup>

Recently, the Single Hub and Access point for pediatric Rheumatology in Europe initiative published recommendations for the diagnosis and treatment of IgAV.<sup>99</sup> As stated in KDIGO, criteria of comparable quality do not exist for adults. Therefore, in this population, diagnosis usually is established by applying childhood criteria.<sup>103</sup>

Unsurprisingly, the severity of kidney involvement and age at diagnosis determines the long-term prognosis of IgAVN.<sup>101,104</sup> Although outcomes in children with IgAVN generally are favorable, a small subset of patients will require kidney replacement therapy in their early 20s.<sup>102</sup> A retrospective analysis applied the Oxford Classification to a small pediatric cohort with IgAVN (n = 32) and found that S1 (ie, the presence of glomerulosclerosis) performs well in predicting renal outcomes.<sup>105</sup> In adults, kidney involvement portends a poorer prognosis. In a retrospective analysis of 250 adults with IgAVN, approximately one-third developed CKD at a median follow-up period of approximately 15 years, and 11% reached ESKD.<sup>106</sup>

There is a dearth of high-quality evidence for the management of IgAVN.<sup>107</sup> Supportive therapy for IgAN and IgAV does not differ substantially in individuals with mild and moderate kidney involvement. For cases with more severe forms, treatment regimens frequently are extrapolated from trials for IgAN. However, patients with a diagnosis of IgAV, compared with IgAN, are more likely to receive immunosuppressive therapy.<sup>108</sup> For IgAN and IgAVN, treatment with glucocorticoids for kidney involvement should be limited to individuals with crescentic glomerulonephritis.<sup>109</sup> The only randomized trial for severe adult-onset IgAVN (n = 54) found no benefit of the addition of cyclophosphamide (6 pulses, adjusted for kidney function) to steroids alone.<sup>110</sup> PLEX remains a last-resort option for refractory cases in all age groups.<sup>111</sup>

An observational study in a small pediatric cohort with IgAVN and nephrotic-range proteinuria (n = 12; mean age, 7.5 y; range, 4–15 y) reported a benefit of an MMF-based immunosuppressive regimen. All but one

patient attained long-term remission (mean follow-up period, 33.5 mo).<sup>112</sup> However, a retrospective survey of an adult cohort (including 67 patients with a follow-up period >6 months) found no response to MMF at 1 year.<sup>101</sup>

Lastly, a small uncontrolled case series suggested benefit of anti-CD20 therapy in the treatment of severe forms of IgAV, refractory to other lines of therapy.<sup>113,114</sup> A recent systematic review found 35 patients with IgAV treated with RTX, including 16 patients with pediatric onset.<sup>115</sup> The role of RTX in this indication currently is being investigated by the French Evaluation of Glucocorticoids Plus Rituximab Compared to Glucocorticoids Plus Placebo for the Treatment of Patients With Newly-Diagnosed or Relapsing IgA Vasculitis study (NCT05329090).

### C3 Glomerulopathies

The C3 glomerulopathies (C3G) are a group of rare kidney diseases caused by the dysregulation of the alternative complement pathway. The definition of C3G consists of two different entities, namely C3 glomerulonephritis (C3GN) and dense deposit disease with characteristic C3 complement accumulation in the absence or minimal presence of immunoglobulin staining on kidney biopsy specimens.<sup>116</sup> Both subgroups have overlapping histopathologic and clinical features; nevertheless, a distinct ultrastructural appearance using electron microscopy is seen.<sup>117</sup> Unique genetic variants (ie, in convertase and complement regulator genes or *CFHR5*) have been described in 25% to 43% of the patients, while abnormalities of acquired anticomplement autoantibodies (ie, C3 and C5 nephritic factors) frequently are observed and analysis thereof might be considered a part of the diagnostic work-up.<sup>118–120</sup>

Epidemiologic data show an incidence rate between 0.2 to 5 cases per 1 million,<sup>118</sup> however, data on childhood-onset C3GN are lacking. The clinical presentation may vary on a wide scale from asymptomatic hematuria and proteinuria to the appearance of RPGN. Importantly, postinfectious glomerulonephritis may present with a predominance of C3 deposits in the kidney biopsy specimen, and thus needs to be considered as a potential differential diagnosis, especially in patients with persistent proteinuria, possible microhematuria, and low serum C3 levels. In addition, patients older than 50 years should be evaluated for monoclonal gammopathy, which is observed in 60% to 80% of this patient population with predominantly C3GN.<sup>121</sup> Rare cases with extrarenal manifestations causing retinal abnormalities<sup>122</sup> or acquired partial lipodystrophy<sup>123</sup> also can occur.

C3G can lead to ESKD within 10 years after diagnosis in nearly 70% of the affected children and in 30% to 50% in adults.<sup>118</sup> A recent study that looked into associations between histologic parameters and outcome

**Table 4.** Primary Glomerular Disease: Differences in Clinicopathologic Features and Treatment Response

Disease	Minimal Change Disease	Primary FSGS	Membranous Nephropathy	IgAN/IgA Vasculitis	C3GN
Age/ characteristics	Peak: Children: 1-12 years Adults: 45 years Preponderance: Children: male Adults: female	Peak: Children: 9 years Adults: 30-35 years Percentage of nephrotic diseases: Children: 6% Adults: 20%-25%	Peak: Children: 7-15 years Adults: 50-60 years Comment: Much less common in children	Peak: IgA nephropathy: equally common in children and adults IgA vasculitis: more common in children (mean age, 6 y)	Peak: Adults: 41 years
Clinicopathologic differences	Presentation: Nephrotic syndrome Elderly: acute kidney injury/hypertension (age, >50 y) Adults: thromboembolic complications more common Children: infections common because of low IgG Histology: IF/TA (in the absence of sclerosis) could be a consequence of hypertension (elderly); in children indicative of a sampling error (FSGS)	Presentation: Children: nephrotic syndrome, normal eGFR, no IF/TA Adults: often subnephrotic proteinuria, more frequently hypertension and impaired kidney function	Presentation: Nephrotic syndrome, preserved eGFR, normal blood pressure (majority of children and adults) Thromboembolic events common, especially in adults	Presentation: Hematuria and proteinuria (similar in children and adults) eGFR (normal to ESKD at presentation; more commonly impaired in adults) Children: less severe skin involvement (IgAV); GI involvement more common Adults: more frequent progression to CKD Histology: Children: mesangial and endocapillary hypercellularity more common Adults: focal glomerulosclerosis, IF/TA	Presentation: Hematuria and proteinuria Increase in serum creatinine concentration common Adults: nephrotic syndrome more common
Disease association/secondary forms	Malignancy, drugs, infection, and autoimmune disease (common in adults)	Low nephron mass, viral infections, genetic, drugs, obesity	Adults: malignancy, infection, and autoimmune diseases Children: sema-phorin 3B and BSA-related MN	Infections, malignancy, inflammatory bowel disease, familial Mediterranean fever, spondyloarthropathies, drugs	Adults: monoclonal gammopathy common Adolescents: alternative complement pathway abnormalities
Immunosuppressive treatment	GC RTX (CNI, other agents)	GC CNI (RTX, other agents)	Stratified based on risk category: RTX GC + CYC GC + CNI RTX + CNI	Individual decision: GC CYC RTX (dapsone)	GC MMF (Eculizumab)
Treatment response	Remission: Children: early (8 d) Adults: late (2 mo) Relapse risk: high in both groups, but occurs more rapidly in children	Response: faster response in children	Response: better treatment response in children	Response: Proteinuria: reduction similar in both groups eGFR improvement greater in children	Outcome: Relapses: more common in children CKD and ESKD: more common in adults
Post-transplant recurrence	Uncommon, rarely progresses to ESKD	30%-40% after first transplantation, ≥80% if recurrence occurred before	10%-30%	10%-30%	67%-84%

Abbreviations: BSA, bovine serum albumin; CKD, chronic kidney disease; CNI, calcineurin inhibitor; CYC, cyclophosphamide; C3GN, C3 glomerulonephritis; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal and segmental glomerulosclerosis; GC, glucocorticoid; GI, gastrointestinal; IF, interstitial fibrosis; IgAV, IgA vasculitis; MMF, mycophenolate mofetil; MN, membranous nephropathy; RTX, rituximab; TA, tubular atrophy.

indicated that cellular and fibrocellular crescents and IF/TA scores were significant determinants of deterioration in kidney function.<sup>120</sup> The disease frequently recurs in kidney transplants (approximately 66%), especially early after transplantation, and is associated with a high rate of graft loss.<sup>124</sup> The progression to CKD and ESKD is similar in patients with C3GN and dense deposit disease<sup>125</sup>; nevertheless, individual differences can be observed,<sup>126</sup> and pediatric patients seem to achieve clinical remission<sup>127</sup> more often. According to data<sup>128</sup> from the National Registry of Rare Kidney Diseases from the United Kingdom, pediatric patients with crescentic disease (>50% on the initial biopsy specimen) and an eGFR less than 90 mL/min per 1.73 m<sup>2</sup> had the highest risk of developing ESKD. An analysis from Turkey found that nephrotic syndrome and eGFR at diagnosis and a low serum C3 level at the last follow-up evaluation were associated with a high ESKD risk.<sup>129</sup> Moreover, lower remission rates were observed in children with a serum albumin level less than 2.5 g/dL at diagnosis and persistently low C3 serum levels.<sup>130</sup> A retrospective analysis involving both pediatric and adult patients with C3G found that clinical (worse kidney function, advanced age) and histologic (ie, glomerulosclerosis and IF) markers of chronicity were associated with the worst kidney outcomes.<sup>125</sup> Using complement biomarker profiles, distinct combinations of C3 and sC5b-9 levels (normal C3/high sC5b-9 and low C3/normal sC5b-9) were described to be predictors of ESKD in a cohort of 165 patients from the French national cohort.<sup>127</sup> Notably, this approach was not applicable in pediatric patients. Pediatric patients with rare, disease-predicting variants in complement genes might have a higher risk of developing ESKD<sup>127</sup>; nevertheless, existing data are scarce. In male patients older than age 50 years carrying a *CFHR5* mutation, a higher risk of developing CKD and ESKD was shown as compared with female patients (80% versus 21% and 78% versus 22%, respectively).<sup>131</sup>

There are no established therapeutic regimens and treatment approaches are similar in both pediatric and adult patients with C3G. The most treatment evidence exists with MMF. A Spanish study found that patients treated with MMF in combination with GCs had better renal remission and survival rates compared with those receiving other immunosuppressive therapies (ie, only GCs or GCs plus cyclophosphamide).<sup>132</sup> However, another small study by Avasare et al<sup>133</sup> showed that the combination of MMF with GCs led to remission only in 67% of the patients with C3G. In accordance, further data suggest a variable response to immunosuppressive therapy with MMF in patients with different triggering factors,<sup>134-137</sup> and clinical features suggest the need for individualized therapy approaches. In addition, the response to eculizumab, a monoclonal antibody against the complement protein C5, varied in patients with C3GN,<sup>138,139</sup> and it remains unclear which patients

might benefit from this treatment option. It should be noted that several clinical studies on different complement-targeted therapies currently are ongoing and showed promising preliminary results as already reviewed elsewhere.<sup>140</sup> Of importance, a recent, large-scale, whole-genome analysis of data revealed a substantial proportion of patients without rare complement genetic variations, but with a common variant locus overlapping the HLA locus, indicating that these patients might have underlying autoimmune mechanisms and might benefit from immunosuppressive therapies.<sup>141</sup>

## CONCLUSIONS

Although glomerular diseases share similarities across all age groups including disease- and treatment-related complications such as infections, there are important differences in frequency, presentation, and outcome (including relapse, comorbidity, and complications) (see Table 4 for a summary). Traditionally, because of the rarity of the respective entities, trial results have been extrapolated in both directions (ie, from childhood to adults [eg, INS and IgAV] and from adults to pediatric cohorts [eg, ANCA-associated vasculitis]). Obviously, first-hand experience from adequately powered trials in the respective age groups would be worthwhile, eventually resulting in more individualized treatment regimens. Encouragingly, major developments over the past decades have ushered in an era of precision medicine (ie, establishing the correct diagnosis in genetic FSGS and the subdivision of MN according to various target antigens) in pediatric as well as in adult nephrology.

More generally, modern treatment strategies pursue the concept of steroid minimization, a formidable task, impeded by small case numbers and frequent off-label use of alternative agents. Lastly, because many patients will undergo the process of care transition, a strict dichotomy between childhood and adulthood is neither feasible nor desirable for chronic diseases such as glomerulopathies. Multicenter initiatives such as the Cure Glomerulonephropathy study are underway and already provide more data on these important entities, which still account for substantial morbidity and mortality for the young and the old.

## APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.semnephrol.2023.151435>.

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