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Review

Biologics in Pediatric Idiopathic Nephrotic Syndrome and Other Kidney Diseases—General Principles and Special Considerations

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Abstract: Idiopathic nephrotic syndrome (INS) and other pediatric kidney diseases represent significant challenges due to their complex pathogenesis, often involving dysregulated immune responses and renal injury. Biologic therapies, defined as targeted treatments derived from living organisms, have gained traction in managing these conditions, offering a potential shift in therapeutic paradigms. This review examines the current and emerging role of biologics in treating pediatric kidney diseases, focusing on indications, contraindications, adverse effects, therapeutic positioning, and a comparison with alternative immunosuppressive treatments.

Keywords: nephrotic syndrome; dysregulated immune responses; biologic therapies; adverse effects

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1. Introduction—Pathophysiology and Management Principles of Nephrotic Syndrome in Children and Role of Biologic Targets

Pediatric nephrotic syndrome (PNS), characterized by pronounced proteinuria (above 40 mg/h/m^2 in a 24 h urine collection or 200 mg protein/mmol creatinine in an early-morning spot urine), hypoalbuminemia (with consequent hyperlipidemia), and edema, is a clinical manifestation of several renal diseases, with enhanced protein leakage across the glomerular basement membrane. It is classified according to the underlying cause, such as primary NS, secondary NS, and congenital and infantile NS.

Primary NS is defined as NS without systemic disease and includes various diseases, such as idiopathic NS (the most common form), primary focal segmental glomerulosclerosis (FSGS, specific histologic lesion, present in some cases of INS in children), primary membranous nephropathy (MN), membranoproliferative glomerulonephritis, and Immunoglobulin A (IgA) nephropathy (IgAN). Secondary NS, on the other hand, is NS that is caused by systemic disease or another pathologic process causing glomerular dysfunction (due to medications or various noxious agents, for example). This is a consequence of MN (in the context of systemic lupus erythematosus (SLE), various infections or drug exposures), FSGS due to hyperfiltration as a consequence of decreased nephron number (due to kidney scarring, hypoplasia, or oligonephronia in children that were born preterm), postinfectious glomerulonephritis, lupus nephritis, vasculitides (IgA vasculitis and ANCA vasculitis, to name just two of them), and several other diseases.

Congenital NS occurs in children in the first three months and infantile NS between 3 and 12 months of age. Most children with NS presenting before one year of age have a genetic cause and a poor long-term prognosis. Family history of kidney disease and presence of extrarenal features, such as dysmorphic features or developmental delay,

suggest congenital NS, while symptoms and signs, such as rash, purpura, arthropathy, and recent group A streptococcal infection, suggest systemic disorder. Increased blood pressure (BP), various infections, thromboembolism, and pancreatitis may also be present in children with NS [1].

PNS can be classified according to response to treatment with corticosterids, which is correlated with long-term outcome. For children with signs and symptoms of typical PNS (between 1 and 12 years of age and without familial, extrarenal, or atypical signs and symptoms suggesting a secondary cause, including genetic mutation), treatment for minimal change disease (MCD) with corticosteroids is indicated without performing genetic testing or kidney biopsy (KB). Most of these children respond to corticosteroids. However, for the children who do not respond to corticosteroids, additional diagnostic procedures, such as genetic testing and/or KB, are necessary. This is supported by evidence from previous studies showing that age below 12 years, normal renal function, BP, and lack of macrohematuria were strongly associated with MCD on KB, which is now not necessary in the majority of these children [1]. For children above 12 years of age with no familial, extrarenal, or atypical signs and symptoms suggesting a secondary cause, however, KB is warranted in order to obtain a histologic diagnosis and to plan a treatment, but empirical treatment with corticosteroids is acceptable, especially in the presence of contraindications (which are rare) or parent's refusal of KB. Nevertheless, genetic testing and/or KB is necessary in cases of unresponsiveness to corticosteroids. Histologic examination of KB specimens reveals the underlying pathological process. Diffuse foot process effacement on electron microscopy (EM) is typical for PNS, most commonly MCD [1].

PNS primarily arises from immune dysregulation, often leading to podocyte injury and proteinuria. The interplay of several different cytokines, chemokines, and growth factors underpins the disease process. The identification of specific molecules implicated in the pathogenesis has paved the way for targeted biologic therapies aimed at modulating the immune response or preserving renal integrity. Biologic drugs are defined as drugs that are used for targeted treatments, derived from living organisms [1].

This comprehensive review aims to provide a robust understanding of biologics in pediatric nephrology, bridging current knowledge with emerging therapeutic frontiers.

Materials and Methods

The author searched with appropriate terms, such as "nephrotic syndrome, children, dysregulated immune responses, biologic therapies, adverse effects", in various sources, including but not limited to PubMed, UpToDate, and a personal archive of medical articles and textbooks in the English language, available before the 10 December 2024.

2. Biologics in Clinical Practice

2.1. Rituximab

Rituximab (RTX) depletes B cells and reduces autoantibody production. Indications for its use are SDNS, FRNS, and refractory MCD. Contraindications are active infections, hypersensitivity to rituximab, or severe immunosuppression. The most common adverse effects are infusion reactions, risk of infections, and hypogammaglobulinemia. Regarding therapeutic positioning, it is increasingly used as a steroid-sparing agent, showing efficacy in reducing relapse rates in SDNS and FRNS compared to calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus [2].

It is, therefore, a treatment option in children with INS to achieve short- to medium-term disease remission and avoid adverse effects due to prolonged corticosteroid treatment. It is used in multidrug-resistant INS and in disease recurrence after kidney transplantation (KT) as well. According to available data, several patient characteristics, drug dosing,

and concomitant use of other immunosuppressive medications predict the effectiveness of this drug. Patients usually respond better with a longer time of remission if the drug is administered several times. Unfortunately, the RTX response is transient and additional courses of treatment are needed. For this reason, awareness of the long-term safety with repeated treatments is of utmost importance. Although it is considered generally safe, there are issues regarding long-term hypogammaglobulinemia. However, there are no available biomarkers to predict treatment outcome and the risk of side effects [3].

2.2. Tocilizumab

Tocilizumab is an anti-IL6 receptor monoclonal antibody that inhibits IL6-mediated inflammation. It is used in secondary forms of nephrotic syndrome (e.g., associated with autoimmune diseases) and in resistant cases of podocytopathies. Contraindications for its use are risk of severe infections and contraindication to immunosuppressive therapy. The most common adverse effects are hepatotoxicity, hyperlipidemia, and gastrointestinal perforation in at-risk populations. It has therapeutic potential in cases with elevated IL6 levels, such as autoimmune-related nephropathies. A pediatric case report was recently published with systemic onset juvenile idiopathic arthritis, presenting clinically with anasarca due to nephrotic syndrome and KB-confirmed amyloidosis deposits. Treatment with tocilizumab was initiated, followed by a decrease in proteinuria and normalization of kidney function [4].

2.3. Complement Inhibitors

Eculizumab is a complement C5 inhibitor, preventing the formation of the membrane attack complex. It is used for the therapy of aHUS as well as complement-mediated glomerulopathies, such as C3 glomerulopathy (C3G). Contraindications for its use are known hypersensitivity or inadequate meningococcal vaccination status. Increased susceptibility to meningococcal infections is the main adverse effect. However, there are cost implications as a limiting factor for its wider use. It is considered the first-line treatment for aHUS, often reversing renal dysfunction when administered early [5,6].

Dysregulation of the complement system is the main cause of C3G, as well as some other diseases with complement involvement, such as IgAN, nephritis in the context of SLE, and primary MN. Pegcetacoplan, a drug with selective inhibition of C3 and C3b components of the complement system, can decrease renal injury in C3G and other glomerulopathies inflicted by the activated complement system. This biologic agent has been proven safe and effective in these diseases, especially in terms of proteinuria reduction and estimated glomerular filtration rate (eGFR) preservation [7].

Complement system activation has pathogenic involvement and also carries a worse prognosis in patients with hematopoietic stem cell transplant (HSCT), especially in those with accompanied thrombotic microangiopathy (TMA). A recent study on such patients, with associated multiorgan failure, proved an increased survival rate with eculizumab treatment, even to 66% one year post-HSCT, compared to prior reports of untreated children with the same clinical features, with only 16.7% survival one year post-HSCT. Treatment, with a median of 11 doses of eculizumab, was continued until TMA resolved, which occurred in about two months. Children with increased plasma terminal lytic complex at the initiation of therapy responded worse, had a worse prognosis, and needed more doses of eculizumab, especially those with intestinal bleeding. It is of note that the majority of survivors had proteinuria and slightly decreased eGFR (compared to pre-HSCT eGFR) on long-term follow-up. According to these results, eculizumab is an effective drug in these patients; however, early intervention and a search for additional targetable endothelial injury pathways would be useful [8].

2.4. Abatacept (B7-1 Inhibitor)

Abatacept, a B7-1 inhibitor, is indicated for use in selected cases of FSGS with podocyte expression of B7-1. Its role is in potentially stabilizing podocyte function; however, its efficacy is restricted to a subset of patients, which is a limitation for widespread use. A published report described the successful use of abatacept, mostly in patients with FSGS recurrence post-KT, especially in the presence of B7-1 immunostaining of podocytes in KB tissues. B7-1 could, therefore, be used as a biomarker to predict response to therapy in patients with B7-1-positive glomerular disease, mainly by stabilizing β1-integrin activation in podocytes [9].

In addition, previous reports described the B7 expression on podocytes of patients with various kidney diseases, presenting as proteinuria, such as lupus nephritis, MN, and diabetic nephropathy. According to them, B7 blockade seems to protect podocytes and subsequently reduce proteinuria [10]. A case report of a male teenager with NS recurrence post-KT and unresponsiveness to RTX and plasmapheresis (PF) treatment achieved good long-term response to abatacept treatment, with a follow-up period of more than four years [11]. According to results of another pediatric study, treatment with abatacept, according to B7-1 immunostaining in KB tissues, was successful in cases of recurrent NS post-KT and unresponsiveness to combined therapy with PF and RTX. According to these results, the authors proposed B7-1 podocyte staining as useful to identify patients who might respond to abatacept. However, more similar studies are needed [12].

2.5. Daratumumab

Daratumumab (DTM), an anti-CD38 monoclonal antibody, has been, at the research stage, combined with RTX in clinical trials targeting comprehensive B-cell suppression. For this purpose, a combined treatment with RTX (given in a single dose of 375 mg/m^2) and DTM (given in a single dose of 16 mg/kg) is planned, in order to maintain remission, without use of medications, in patients with multi-drug-resistant NS (MRNS, defined as the need for two or more oral drugs, including corticosteroid, mycophenolate mofetil, and calcineurin inhibitors), SRNS, and post-transplant NS recurrence. After the combined treatment with RTX and DTM, other immunosuppression is being planned to be withdrawn. As the main aim, time-free remission of MRNS will be evaluated [10].

2.6. Ofatumumab

Ofatumumab (OFM) is anti-CD20 monoclonal antibody with affinity for the CD20 molecule, at a different epitope than RTX [13]. Ofatumumab is able to induce disease remission in children with steroid-dependent nephrotic syndrome (SDNS), according to recent reports [14,15]. The authors of a single-center randomized clinical trial in children with calcineurin-dependent SDNS found non-superiority of a single dose of OFM over RTX in maintaining remission. But after two years, 34% of patients in the RTX group were in remission compared to only 24% in the OFM group. In addition, OFM produced better results in children over 16 years of age compared to younger patients [16]. However, the optimal dosing of OFM for kidney diseases in children has not been established yet. In addition, reported studies were based mainly on case reports and case series. Some of these studies proved that fully humanized OFM could be more effective compared to chimeric OFM in MRNS. The safety of these novel drugs is a critical concern, especially regarding the need for very high doses, particularly for OFM, in cases of MRNS. Previous studies with a standard dose of OFM (1500 mg/1.73 m^2) pointed towards an increased rate of respiratory infections compared to RTX [13]. However, RTX and OFM have been proven to be safe in SDNS patients [16]. In general, the clinical use of human and humanized antiCD20 monoclonal antibodies has emerged as a very useful treatment option for kidney diseases

with proteinura, especially those that are resistant or only partially responsive to RTX. There are still challenges to be addressed regarding the selection of the most appropriate anti-CD20 antibody and its dose [13].

3. Emerging Biologics in Research

3.1. Molecules Under Investigation

3.1.1. MMP12 (Macrophage Metalloelastase)

Inhibition of MMP12 may protect against podocyte injury by reducing extracellular matrix degradation. The authors of a published study investigated the kidneys of experimentally induced glomerulonephritis in mice and confirmed a large amount of MMP-12 in mouse kidney, predominantly in podocytes, that progressed to NS, providing evidence of MMP-12's role in the pathogenesis of NS in animal models [17].

3.1.2. VEGFA (Vascular Endothelial Growth Factor A)

Anti-VEGF therapies aim to mitigate vascular endothelial damage, particularly in glomerular diseases like FSGS. VEGF enhances angiogenesis and permeability in the kidney. A study in adults in Taiwan revealed that patients who received the anti-VEGF antibody bevacizumab had a significantly increased risk of getting chronic kidney disease (CKD) compared to patients without this treatment [18]. A case report was published where a 15-year-old boy developed NS and thrombotic microangiopathy about two years after anti-VEGF treatment and after its discontinuation NS went into remission in several weeks [19]. The authors of a published study confirmed that anti-VEGF therapy can decrease tumor growth in an animal model, with a greater than 95% reduction in tumor weight as well as prevention of the formation of lung metastases. However, termination of treatment resulted in rebound tumor growth [20].

3.1.3. CSF1 (Colony-Stimulating Factor 1)

Targeting CSF1 could potentially reduce macrophage-mediated inflammation and glomerular injury. Macrophages have many other crucial roles during development and tissue homeostasis due to their plasticity. CSF-1 seems to promote kidney regeneration after birth in mouse models of hypoxemia-induced injury. In addition, CSF-1 therapy rapidly promoted kidney regeneration, a decrease in interstitial fibrosis, and resolution of inflammatory injury [21].

3.1.4. Other Molecules

Oher molecules, such as IL17F and IL4 (Interleukins), whose modulation showed some potential in balancing pro-inflammatory and anti-inflammatory responses [22,23] and EGF (Pro-epidermal Growth Factor), whose enhanced signaling could promote renal recovery and reduce fibrosis [24], have the potential to be therapeutic targets in the future.

Table 1 summarizes the mechanisms of action, indications, contraindications, and adverse effects of some biologic drugs. Table 2 summarizes some biologic drugs used in reported studies in the management of idiopathic nephrotic syndrome and some other kidney diseases in the pediatric population [2–10,13–16].

Table 1. Summary of some biologic drugs and their mechanisms of action [2–10,13–16].

Name of the Biologic Drug	Mechanism of Action	Indications	Contraindications	Adverse Effects
Rituximab	monoclonal antibody against CD20 on B cells—depletes B cells and reduces autoantibody production	SDNS, FRNS, refractory MCD	active infections, hypersensitivity, severe immunosuppression	infusion reactions, risk of infections, hypogammaglobulinemia
Tocilizumab	anti-IL6 receptor monoclonal antibody—inhibits IL6-mediated inflammation	secondary forms of NS (associated with autoimmune diseases), resistant podocytopathies	Risk of severe infections, contraindication to immunosuppressive therapy	hepatotoxicity, hyperlipidemia, gastrointestinal perforation
Eculizumab	complement C5 inhibitor—prevents the formation of the membrane attack complex	aHUS, complement-mediated glomerulopathies	Hypersensitivity, inadequate meningococcal vaccination	Increased susceptibility to meningococcal infections
pegcetacoplan	selective inhibition of C3 and C3b components of complement system	C3 glomerulopathy	Hypersensitivity, inadequate meningococcal vaccination	Increased susceptibility to meningococcal infections
abatacept	B7-1 inhibitor—stabilizes podocyte function, especially those with expression of B7-1	FSGS (with podocyte expression of B7-1), lupus nephritis, membranous nephropathy, diabetic nephropathy	Hypersensitivity	Anemia, hypertension, headache, pyrexia
Daratumumab	anti-CD38 monoclonal antibody; influences T-cell function (mainly CD4+ and CD8+ T cells)	Lupus nephritis, multidrug-resistant NS, combined with rituximab	Hypersensitivity	infusion reactions, lymphopenia, neutropenia, anemia, fatigue
Ofatumumab	anti-CD20 antibody, determines its immune effect through the Fc domain	SDNS, MRNS, post-transplant FSGS relapse	Hypersensitivity	increased rate of respiratory infections (especially if compared to rituximab), bronchospasm, allergic reactions, anemia

Abbreviations: SDNS—steroid-dependent NS; FRNS—frequently relapsing NS; MCD—minimal change disease; NS—nephrotic syndrome; aHUS—atypical hemolytic uremic syndrome; FSGS—focal segmental glomerulosclerosis; MRNS—multidrug-resistant nephrotic syndrome.

Table 2. Summary of some biologic drugs used in reported studies in the management of idiopathic nephrotic syndrome and some other kidney diseases in the pediatric population [2–10,13–16].

Biologic Drug	Disease in Which It Was Used	Study Design	Number of Patients
Rituximab	SDNS, FRNS	A retrospective multicentric international cohort study	346
	SRNS, SDNS, signs of calcineurin inhibitor toxicity	Multicentric cohort study	57

Table 2. *Cont.*

Biologic Drug	Disease in Which It Was Used	Study Design	Number of Patients
Tocilizumab	Systemic onset JIA, presenting with anasarca due to NS, KB-confirmed amyloidosis deposits	Case report	1
Eculizumab	CaHUS	Observational cohort study	243
Pegcetacoplan	C3G in patients at least 16 years old	Single-arm, open-label, phase 2, 48-week study	8
Abatacept	Post-KT FSGS that failed conventional therapy	Case series	12
	FSGS recurring post-KT, resistant PF and RTX	Case report	1
Ofatumumab	SDNS, SRNS	Case series	2
	1 patient with post-KT recurrent FSGS, resistant to plasmapheresis and several immunosuppressive drugs, 4 patients with SRNS	Case series	5
	Young patients with NS in remission with corticosteroids and calcineurin inhibitors	Single-center study	140

Abbreviations: SDNS—steroid-dependent NS; FRNS—frequently relapsing NS; NS—nephrotic syndrome; SRNS—steroid-resistant NS; JIA—juvenile idiopathic arthritis; KB—kidney biopsy; CaHUS—complement-mediated atypical hemolytic uremic syndrome; C3G—C3 glomerulopathy; KT—kidney transplantation; RTX—rituximab; PF—plasmapheresis.

3.2. Comparison with Conventional Therapies

Biologics offer a more targeted approach compared to broad-spectrum immunosuppressants such as corticosteroids, calcineurin inhibitors (CNIs), and alkylating agents such as cyclophosphamide (CYPH). The selectivity of biologics reduces systemic side effects but is often accompanied by high costs and a risk of immunodeficiency-related complications [1,2,5]. Table 3 highlights key differences.

Table 3. Comparison of biologics with conventional therapies.

Aspect	Traditional Therapies	Biologics
Mechanism	Broad immunosuppression and immune modulation	Target-specific pathways
Side Effects	Systemic: infections, diabetes, hypertension, nephrotoxicity	Target-specific, systemic infections, hypersensitivity
Efficacy in SRNS	Variable	Higher in certain refractory cases
Cost	Moderate	High
Administration	Oral, intravenous	Intravenous, subcutaneous

3.3. Role in Therapeutic Schemata

Biologics are typically integrated into therapy after the failure of conventional agents:

- Corticosteroids: remain the cornerstone for initial treatment.
- Second-line immunosuppressants: include CNIs, mycophenolate mofetil, or alkylating agents, often combined with corticosteroids.
- Biologics: used for resistant cases to achieve remission or as steroid-sparing agents.

3.4. Other Special Clinical Conditions with Kidney Involvement

Vasculitis is a term describing inflammation in blood vessels and presents clinically with numerous and varying symptoms and signs. Many different organs can be affected.

Quick recognition and therapy initiated as soon as possible are both very important regarding the management of these children because many of these diseases can have very severe and life-threatening courses without appropriate treatment [25].

Regarding the treatment of children with vasculitis, it is crucial to distinguish primary vasculitis from other conditions presenting in a similar way and also from other diseases, such as various infections, pharmacological agents, or systemic diseases (such as SLE and juvenile dermatomyositis) that can cause secondary vasculitis where treatment is directed to the underlying disease. In the latter, administration of immunosuppressive therapy may have very severe adverse consequences; however, it is appropriate in patients with primary vasculitis. Making an accurate diagnosis is, therefore, vital in order to begin appropriate treatment. In order to understand the treatment principles of pediatric vasculitis, the phases of disease activity on which they depend are shown in Table 4 [25].

Table 4. Treatment principles in childhood vasculitis.

Phase of Disease Activity	Main Characteristics
Induction treatment	Its aim is to stop inflammation in a patient with disease onset and to achieve remission
Maintenance treatment	After achieving remission, treatment should continue in order to preserve it. In diseases that are usually acute and self-limiting (Mb. Kawasaki, for example), the patient usually stays in remission without drugs
Treatment of relapse	Treatment, necessary to decrease the inflammation
Refractory treatment	Increased treatment requirement for patients unresponsive to standard treatment, which may include alternative or additional immunosuppressive drugs or biologic response modifiers

Therapy of rare forms of chronic vasculitis should be conducted by clinicians that have enough experiences in dealing with these diseases, the drugs needed for treatment, and their effects in a specific pediatric population. Some vasculitis types, such as IgA vasculitis (IgAV), are acute and often have a self-limiting course and potent pharmacological treatment is usually not necessary. Other types of vasculitis, on the other hand, have a chronic course with exacerbations, associated with severe morbidity and mortality due to renal and/or pulmonary disease. These diseases as well as their treatment can have adverse somatic, psychosocial, and other non-medical sequelae, which is very important to consider in a developing and growing child [25].

In pediatric chronic vasculitis, immunosuppressive treatment is necessary in order to achieve and maintain remission. Corticosteroids are the cornerstone of treatment, with no need for additional medications, especially in milder forms. But in children with a severe course of a disease, additional immunosuppressants or biologic agents are usually necessary. Rtx is indicated in severely affected pediatric patients with ANCA vasculitis, after initial (induction) treatment. Other biologic drugs are treatment options in children with Takayasu disease [25,26]; however, their description would be beyond the scope of this article.

In contrast to IgAV and Mb. Kawasaki, other primary forms of chronic systemic vasculitis have a remitting course. Corticosteroids and cyclophosphamide (CYPH, in more severe cases) are the main drugs for these diseases. Other immunosuppressive medications and biologics, such as TNF inhibitors, Rtx, and some others, turned out

to be effective in small pediatric studies and they are being increasingly used [25]. In more severely affected children with these diseases, several drugs can induce remission; however, over 50% of them suffer from relapses that may affect other organs in the long-term course with consequent significant morbidity. Repeated applications of CYPH can increase morbidity, which demands a search for alternative drugs. In this context, several trials have confirmed Rtx (given twice a year) to be successful in maintaining disease remission in ANCA-associated vasculitis (AAV), with minimal adverse effects, besides hypogammaglobulinemia [25,27].

In addition, maintenance treatment with anti-TNF drugs and anti-IL 6 antibodies in patients with other forms of vasculitis (such as Takayasu arteritis) can provide a useful alternative treatment option, compared to more traditional immunosuppressant drugs. However, no similar studies have been conducted on these diseases of childhood. Nevertheless, several biologics are used for treatment of these children at an increased rate, especially in those with no response to traditional therapy (such as corticosteroids or CYPH) or those with a remitting course [25,28].

4. Challenges and Future Directions

- **Accessibility:** The high costs of biologics limit their use, particularly in low-resource settings.
- **Long-term Safety:** Limited data on pediatric populations necessitate further research.
- **Personalized Medicine:** Advances in biomarker discovery could optimize biologic use, tailoring therapies to individual patients.

Emerging technologies such as RNA-based therapies and engineered antibodies hold promise for next-generation biologics, potentially expanding treatment options [2–5,10,11,15].

5. Conclusions

Biologics have revolutionized the landscape of pediatric nephrology, offering targeted and effective treatment options for refractory kidney diseases. While challenges remain in accessibility and safety, ongoing research into novel molecules and pathways continues to expand the therapeutic arsenal. Comparative studies with conventional therapies will further refine their role in clinical practice. While agents like rituximab and eculizumab are now established in clinical practice, emerging biologics targeting various molecules hold promise for future interventions. Ongoing research should focus on optimizing these therapies, minimizing adverse effects, and addressing cost barriers. The integration of biomarkers for patient stratification and response monitoring will further enhance the efficacy of biologics in pediatric kidney diseases.

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References

1. Niaudet, P. Clinical Manifestations, Diagnosis, and Evaluation of Nephrotic Syndrome in Children. UpToDate. Available online: https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-evaluation-of-nephrotic-syndrome-in-children?csi=9a79419c-f527-4dc8-b081-93037b53d73b&source=contentShare (accessed on 10 December 2024).

2. Chan, E.Y.; Yu, E.L.M.; Angeletti, A.; Arslan, Z.; Basu, B.; Boyer, O.; Chan, C.Y.; Colucci, M.; Dorval, G.; Dossier, C.; et al. Long-Term Efficacy and Safety of Repeated Rituximab to Maintain Remission in Idiopathic Childhood Nephrotic Syndrome: An International Study. *J. Am. Soc. Nephrol.* **2022**, *33*, 1193–1207. [CrossRef] [PubMed]
3. Chan, E.Y.; Yap, D.Y.; Colucci, M.; Ma, A.L.; Parekh, R.S.; Tullus, K. Use of Rituximab in Childhood Idiopathic Nephrotic Syndrome. *Clin. J. Am. Soc. Nephrol.* **2023**, *18*, 533–548. [CrossRef] [PubMed]
4. Singhal, J.S.; Pande, N.; Sharma, J. A child with systemic onset juvenile idiopathic arthritis and nephrotic syndrome. *Pediatr. Nephrol.* **2024**, *40*, 381–383. [CrossRef] [PubMed]
5. Brocklebank, V.; Walsh, P.R.; Smith-Jackson, K.; Hallam, T.M.; Marchbank, K.J.; Wilson, V.; Bigirumurame, T.; Dutt, T.; Montgomery, E.K.; Malina, M.; et al. Atypical hemolytic uremic syndrome in the era of terminal complement inhibition: An observational cohort study. *Blood* **2023**, *142*, 1371–1386. [CrossRef] [PubMed]
6. Loirat, C.; Fakhouri, F.; Ariceta, G.; Besbas, N.; Bitzan, M.; Bjerre, A.; Coppo, R.; Emma, F.; Johnson, S.; Karpman, D.; et al. HUS International. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr. Nephrol.* **2016**, *31*, 15–39. [CrossRef]
7. Dixon, B.P.; Greenbaum, L.A.; Huang, L.; Rajan, S.; Ke, C.; Zhang, Y.; Li, L. Clinical Safety and Efficacy of Pegcetacoplan in a Phase 2 Study of Patients with C3 Glomerulopathy and Other Complement-Mediated Glomerular Diseases. *Kidney Int. Rep.* **2023**, *8*, 2284–2293. [CrossRef] [PubMed]
8. Jodele, S.; Dandoy, C.E.; Lane, A.; Laskin, B.L.; Teusink-Cross, A.; Myers, K.C.; Wallace, G.H.; Nelson, A.; Bleesing, J.; Chima, R.S.; et al. Complement blockade for TA-TMA: Lessons learned from a large pediatric cohort treated with eculizumab. *Blood* **2020**, *135*, 1049–1057. [CrossRef]
9. Greka, A.; Weins, A.; Mundel, P. Abatacept in B7-1-positive proteinuric kidney disease. *New Engl. J. Med.* **2014**, *370*, 1263–1266. [CrossRef] [PubMed]
10. Angeletti, A.; Bruschi, M.; Kajana, X.; La Porta, E.; Spinelli, S.; Caridi, G.; Lugani, F.; Verrina, E.E.; Ghiggeri, G.M. Biologics in steroid resistant nephrotic syndrome in childhood: Review and new hypothesis-driven treatment. *Front. Immunol.* **2023**, *14*, 1213203. [CrossRef]
11. Muhlbacher, T.; Amann, K.; Mahling, M.; Nadalin, S.; Heyne, N.; Guthoff, M. Successful long-term management of recurrent focal segmental glomerulosclerosis after kidney transplantation with costimulation blockade. *Clin. Kidney J.* **2021**, *14*, 1691–1693. [CrossRef] [PubMed]
12. Burke, G.W., 3rd; Chandar, J.; Sageshima, J.; Ortigosa-Goggins, M.; Amarapurkar, P.; Mitrofanova, A.; Defreitas, M.J.; Katsoufis, C.P.; Seeherunvong, W.; Centeno, A.; et al. Benefit of B7-1 staining and abatacept for treatment-resistant post-transplant focal segmental glomerulosclerosis in a predominantly pediatric cohort: Time for a reappraisal. *Pediatr. Nephrol.* **2023**, *38*, 145–159. [CrossRef] [PubMed]
13. Basu, B.; Angeletti, A.; Islam, B.; Ghiggeri, G.M. New and Old Anti-CD20 Monoclonal Antibodies for Nephrotic Syndrome. Where We Are? *Front. Immunol.* **2022**, *13*, 805697. [CrossRef] [PubMed]
14. Vivarelli, M.; Colucci, M.; Bonanni, A.; Verzani, M.; Serafinelli, J.; Emma, F.; Ghiggeri, G. Ofatumumab in Two Pediatric Nephrotic Syndrome Patients Allergic to Rituximab. *Pediatr. Nephrol.* **2017**, *32*, 181–184. [CrossRef] [PubMed]
15. Wang, C.S.; Liverman, R.S.; Garro, R.; George, R.P.; Glumova, A.; Karp, A.; Jernigan, S.; Warshaw, B. Ofatumumab for the Treatment of Childhood Nephrotic Syndrome. *Pediatr. Nephrol.* **2017**, *32*, 835–841. [CrossRef]
16. Ravani, P.; Colucci, M.; Bruschi, M.; Vivarelli, M.; Cioni, M.; DiDonato, A.; Cravedi, P.; Lugani, F.; Antonini, F.; Prunotto, M.; et al. Human or Chimeric Monoclonal Anti-CD20 Antibodies for Children With Nephrotic Syndrome: A Superiority Randomized Trial. *J. Am. Soc. Nephrol.* **2021**, *32*, 2652–2663. [CrossRef] [PubMed]
17. Uchio, K.; Sawada, K.; Manabe, N. Expression of macrophage metalloelastase (MMP-12) in podocytes of hereditary nephrotic mice (ICGN strain). *J. Vet. Med. Sci.* **2009**, *71*, 305–312. [CrossRef]
18. Lye, L.F.; Chou, R.H.; Wu, T.K.; Chuang, W.L.; Tsai, S.C.; Lin, H.J.; Tsai, F.J.; Chang, K.H. Administration of Bevacizumab and the Risk of Chronic Kidney Disease Development in Taiwan Residents: A Population-Based Retrospective Cohort Study. *Int. J. Mol. Sci.* **2023**, *25*, 340. [CrossRef] [PubMed]
19. Yılmaz, S.; Özçakar, Z.B.; Taktak, A.; Kiremitçi, S.; Ensari, A.; Dinçaslan, H.; Yalçınkaya, F. Anti-VEGF-related thrombotic microangiopathy in a child presenting with nephrotic syndrome. *Pediatr. Nephrol.* **2016**, *31*, 1029–1032. [CrossRef] [PubMed]
20. Rowe, D.H.; Huang, J.; Kayton, M.L.; Thompson, R.; Troxel, A.; O'Toole, K.M.; Yamashiro, D.; Stolar, C.J.; Kandel, J.J. Anti-VEGF antibody suppresses primary tumor growth and metastasis in an experimental model of Wilms' tumor. *J. Pediatr. Surg.* **2000**, *35*, 30–32; discussion 32–33. [CrossRef] [PubMed]
21. Alikhan, M.A.; Jones, C.V.; Williams, T.M.; Beckhouse, A.G.; Fletcher, A.L.; Kett, M.M.; Sakkal, S. Colony-stimulating factor-1 promotes kidney growth and repair via alteration of macrophage responses. *Am. J. Pathol.* **2011**, *179*, 1243–1256. [CrossRef] [PubMed]
22. Yang, J.; Sundrud, M.S.; Skepner, J.; Yamagata, T. Targeting Th17 cells in autoimmune diseases. *Trends Pharmacol. Sci.* **2014**, *35*, 493–500. [CrossRef] [PubMed]

23. Peroumal, D.; Biswas, P.S. Kidney-Specific Interleukin-17 Responses During Infection and Injury. *Annu. Rev. Immunol.* **2024**, *42*, 35–55. [CrossRef]
24. Tang, M.J.; Lin, Y.J.; Huang, J.J. Thyroid hormone upregulates gene expression, synthesis and release of pro-epidermal growth factor in adult rat kidney. *Life Sci.* **1995**, *57*, 1477–1485. [CrossRef] [PubMed]
25. Cabral, D.; Morishita, K. Vasculitis in Children: Management Overview. UpToDate. Available online: https://www.uptodate.com/contents/vasculitis-in-children-management-overview?csi=470bff0a-c8c0-4729-aa8c-004aacf6fe2a&source=contentShare#H11 (accessed on 5 December 2024).
26. Morishita, K.; Brown, K.; Cabral, D. Pediatric vasculitis: Advances in treatment. *Curr. Opin. Rheumatol.* **2015**, *27*, 493. [CrossRef]
27. Guillevin, L.; Pagnoux, C.; Karras, A.; Khouatra, C.; Aumaître, O.; Cohen, P.; Maurier, F.; Decaux, O.; Ninet, J.; Gobert, P.; et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *New Engl. J. Med.* **2014**, *371*, 1771. [CrossRef] [PubMed]
28. Singer, O.; McCune, W.J. Update on maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis. *Curr. Opin. Rheumatol.* **2017**, *29*, 248. [CrossRef] [PubMed]