UK Kidney Association

Clinical Practice Guideline:
The initial immunosuppressive treatment for children and young people with immune mediated glomerular diseases

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Conflicts of interest statement

All authors made declarations of interest in line with the policy in the UK Kidney Association Clinical Practice Guidelines Development Manual. Further details can be obtained on request from The UK Kidney Association.

Endorsements

The British Association for Paediatric Nephrologists (BAPN) have agreed to endorse this guideline.

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Executive summary

There is a wealth of progress being made to advance the outcomes of immune mediated glomerular diseases (IM-GD), such that clinical trials are plentiful and adults with immune mediated glomerular diseases are on the edge of many, hopefully transformative, treatments coming to the clinical setting. These treatments are beginning to start the research journey to gain high quality evidence to support their use in children too. Discrepancies in the current management of patients can hinder improvements in outcomes or they can be a barrier to implementation of new treatments when they do reach the clinical setting.

Aligning the initial clinical management over the first 12 months after diagnosis for patients with immune mediated glomerular diseases, through the use of nationally agreed best practice recommendations, aims to reduce the variation in care across the UK. This document offers evidence-based practice guidelines, with research recommendations, to support consistency in management for children and young people.

The dedication of the multi-professional group that included lay members volunteering their time to create this guideline is greatly appreciated. It is positively anticipated that these guidelines will require perpetual updates as new treatments reach patient benefit over the coming years.

Prof. Louise Oni, Chair of the IM-GD Guideline Development Group.

Aims and objectives

The primary aim of the clinical practice recommendation is to create a united, paediatric-specific clinical approach for immune mediated glomerular diseases (IM-GD) nationally that is aligned with existing international guidelines and the latest evidence. This will aspire to improve the quality of care and reduce unwarranted variation across the UK in the treatment administered to children and young people (CYP) with IM-GD through these agreed standard treatment plans.

The objectives of the programme of work were:

- To review existing practice to provide nationally and internationally accepted speciality guidelines.
- To systematically summarise the current evidence relating to the treatment of IM-GD in children and young people.

To generate and agree on best practice recommendations for the immunosuppressive treatment following confirmation of IM-GD diagnosis in children and young people with the primary aim at achieving disease remission (termed ‘induction treatment’) and long term immunosuppressive treatment aimed at consolidating disease remission (termed ‘consolidation treatment’) within the first 12 months following diagnosis.

Background

Immune mediated glomerular diseases is the major clinical and pathological term used to categorise diseases that cause glomerular disease in the setting of systemic autoimmune disease, infection, drugs or malignancy affecting individuals of all ages. Although deemed a rare disease, after congenital anomalies of the kidney and urinary tract, GN is the second most common contributor of all cause chronic kidney disease (CKD) in children and the young [3]. Children and young adults who experience IM-GD then have a lifetime of disease and/or subsequent morbidity. IM-GD encompasses several diseases, each of which possess their own pathophysiology and clinical course, and collectively they have a population incidence of approximately 5.5 per 100,000 people [1].

GD outcomes remain poor; in most kidney failure registries, glomerular diseases account for 20-25% of prevalent cases and a large retrospective consortium study evaluating outcomes in children with IM-GD who had severe crescentic histological features on kidney biopsy, demonstrated a rate of end stage kidney disease (ESKD) of 12% at just one year and in patients with severe crescentic features the median time to reach ESKD was only 100 days [1]. Although hopefully these outcomes are improving, it is recognised that chronic kidney disease (CKD) due to GD progresses to ESKD at a faster rate than other forms of kidney disease, a group referred to as 'fast progressors'[2]. Kidney failure is life changing for children and young people and preventing them from embarking on the journey to reach this end point is a priority. The rate of complete disease remission in IM-GD, across all ages, remains suboptimal, for example the complete response rate of lupus nephritis at six and 12 months was reported to be 65 and 20%, respectively [2]. Prescribing of novel treatments is often challenging in CYP due to the few trials conducted in this population and a lack of paediatric specific evidence. Consensus agreement in the approach to management is an initial step towards improving evidence generation. Children typically have a more acute, potentially reversible disease process, when compared to adults, where paediatric nephrologists aspire to achieve complete renal response with very minimal residual proteinuria and normal kidney function to provide the optimal lifelong outcome for this population. These differences require guidance specifically adapted for children. Several clinical international guidelines already exist in this field, including those by reputable global organisations such as the kidney disease improving global outcomes (KDIGO) and the International Paediatric Nephrology Association (IPNA), and this project aims to translate them for implementation in UK practice, where applicable.

Universal kidney care (for example blood pressure control and/or proteinuria management) is also an important aspect of the basic standard of care as an adjunct to management and therefore the group generated helpful agreed guidance is included as an appendix in this document.

Guideline development group

The guideline development group (GDG) was formed and is referred to as the UK Children's IM-GD GDG. An advert was sent out using the British Assocation of Paediatric Nephrology (BAPN) and UK Kidney Association (UKKA) networks requesting expressions of interest to contribute. Kidney Voices for Research and kidney themed patient association groups were used to assist with finding lay contributors. The group consisted of a Chair, a clinical lead, an experienced UKKA guideline representative, clinical expert members representing all 13 UK paediatric nephrology centres, an adult nephrologist, a general paediatrician, paediatric nephrology trainee representatives, a paediatric renal pharmacist, a specialist paediatric nephrology nurse, a paediatric rheumatologist, a paediatric pathologist, and lay patient/parent representatives (for list of members please see appendix 5). Advice was sought from relevant paediatric subspecialists as needed, e.g. paediatric endocrinology and immunology.

Methodology

The guideline was developed according to the UK Kidney Association (UKKA) *Clinical Practice Guideline Development Manual* (Originally published by the Renal Association in September 2016) and in accordance with the *Appraisals of Guidelines for research and evaluation II* instrument [4]. The guideline followed standard developmental stages. The Children's IM-GD GDG defined the topic areas and key questions for the scope document. The scope included the population, setting, target audience, intended users, and key clinical questions. It was distributed during a period of open consultation to request wider feedback at the initial stages. The key questions provided a framework for the literature review that included using pre-defined methodology and working in partnership with stakeholders. Agreed treatment plans were derived from topic areas and key questions were developed by the UK Children's GN GDG. The recommendations were designed to take into consideration the findings of the existing international guidelines, systematic review of the latest evidence, existing local protocols and practices, clinical experts and the consensus of the GDG. To ensure wider agreement, following peer review from the GDG members, a period of open consultation at the end took place to gather further feedback. In line with the recommended wording, the terminology used for each clinical recommendation reflected the strength of the evidence supporting the recommendation. The working group committed to monthly virtual meetings, face to face events took place in April 2023, Oct 2023 and March 2024 to formulate and agree the clinical recommendations. The guidelines were disseminated via UKKA once completed and a lay summary included. Amendments were made after open consultation prior to the final endorsement.

Generation and grading of recommendations

To achieve group agreement, discussions took into account existing clinical practice and national or international guidelines where evidence was limited or lacking. The modified GRADE system was used to evaluate the strength of the recommendation, with grade 1 being a strong recommendation (depicted by 'we recommend'), and grade 2 being a weaker recommendation (depicted by 'we suggest'). The quality of evidence was graded A-D with grade A being high-quality evidence, grade B moderate-quality, grade C low-quality evidence from observational studies, or controlled trials with very serious limitations, grade D evidence was generally case studies or expert opinion. Studies were downgraded if there was evidence of bias, indirectness, imprecision or inconsistency of results and the strength of the recommendation could be adjusted taking into context the balance of benefit or harms to patients.

Populations that will be covered

- Children and young people aged 0-18 years presenting with IM-GN will include the following subtypes;
    1. Idiopathic nephrotic syndrome (INS)
    2. Immunoglobulin A (IgA) related glomerulonephritis (including IgA nephropathy (IgAN) and IgA vasculitis nephritis (IgAVN) also known as HSP nephritis)
    3. Primary membranous nephropathy (MN)
    4. Lupus nephritis (LN)
    5. Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis
    6. Anti-glomerular basement membrane (GBM) GN
    7. Immunoglobulin and complement mediated GN with membranoproliferative GN (MPGN) pattern
    8. Post infectious GN

Populations that will not be covered

The guideline will not include:

- Children with an identified mono-genetic cause or disease where no obvious immune driver is recognised
- Non glomerular diseases
- Patients aged >18 years

- Diseases not yet covered in the KDIGO glomerular diseases guideline such as atypical haemolytic uraemic syndrome.

Target audience

The guideline is aimed at healthcare professionals working within secondary and tertiary care who manage CYP during the initial 12 months of IM-GD. This will mostly be UK paediatric nephrologists working within the BAPN network and specialist nursing staff working in paediatric nephrology units, although some conditions may be treated by general paediatricians, adult nephrologists or other specialists depending on the specific disease, resources, and local services. The guideline has been developed for use within the UK clinical healthcare environment (National Health Service, NHS). Although the guideline has not been directly aimed at patients, parents or carers managing CYP with IM-GD, their needs have been considered throughout and a lay summary is included.

Clinical issues that were included

The purpose of the guideline is to outline immunosuppressive treatment for CYP with IM-GD.
This includes:

- Induction immunosuppressive treatment following diagnosis, including the use of extracorporeal treatment such as plasmapheresis where appropriate.
- Consolidation immunosuppressive treatment over the first 12 months and treatment intensity according to specific characteristics.

Clinical issues that were not covered

- Immunosuppressive treatment beyond the first 12 months following diagnosis.
- Specific treatment of hypertension, active infections, or proven thrombosis.
- Management of transition into adult services.
- Management of organ involvement beyond the kidney (relevant for multi-systemic diseases).
- Management of chronic kidney disease or the use of kidney replacement therapy.
- Management of glomerular diseases post kidney transplantation.

Evidence synthesis

The latest literature was extracted using pre-defined methods to generate an evidence synthesis. Relevant international guidelines were retrieved, and local guidelines were used to reflect current clinical practice especially in situations where there was limited evidence. The literature was kept up to date until 21st May 2024. Concepts were combined using Boolean operators (AND, OR and NOT) and general search concepts were used for the population (“pediatric”, “paediatric”, “child*”, “adolescen*”) and treatment (“treatment”, “medication”, “immunosuppress*”).

Disease subtype searches were as follows;

1. INS: (“nephrotic syndrome”, “idiopathic nephrotic syndrome”) then subdivided as
    - Idiopathic NS that has responded to steroid
    - Idiopathic NS that has not responded to steroid treatment
2. Immunoglobulin A related GN:

- IgAV nephritis ("immunoglobulin A vasculitis nephritis", "immunoglobulin A vasculitis-nephritis", "IgA vasculitis nephritis", "IgA vasculitis-nephritis", "IgAV", "Henoch Schonlein purpura", "Henoch Schonlein purpura nephritis", "HSP", "HSPN").
- IgA nephropathy ("IgA nephropathy", "Immunoglobulin A nephropathy", IgAN")

3. Primary MN: ("membranous nephropathy", "membranous nephritis", "MN")
4. LN: ("lupus nephritis", "SLE nephritis", "lupus glomerulo*", "SLE glomerulo*", "LN")
5. ANCA associated vasculitis: ("anti-neutrophil cytoplasmic antibody associated vasculitis", "ANCA associated vasculitis", "AAV",
6. Anti-GBM: ("anti glomerular basement membrane", "anti-GBM", "anti GBM", "
7. Ig and complement mediated GN: ("C3 GN", "complement 3 glomerulo*", "C3 glomerulo*, "MPGN", "membranoproliferative")
8. Post infectious GN: ("infection" AND "glomerulo*", "nephritis", "streptococcal")

Three bibliographic databases were searched; Medline (https://www.nlm.nih.gov/medline), Embase (https://www.embase.com) and Cochrane central register of controlled trials (https://www.cochranelibrary.com/central). The process was performed according to the Cochrane Handbook for Systematic reviews of interventions. The results were merged, and duplicates were removed by title. Each article was independently screened for full text review according to the eligibility criteria. Two members synthesized the literature and discussed areas of disagreement. An updated search was performed and then the evidence was closed. Searching of reference lists was permitted and an evidence narrative summary was produced for members of the GDG.

Inclusion criteria for literature review

All systematic reviews of randomized controlled trials (RCTs), prospective uncontrolled trials, observational studies, and registry studies restricted to human studies and only those available in full text in English were retrieved. It was agreed that the inclusion criteria and search methodology used for the IPNA guidelines were acceptable for this project's ambitions to allow an update of the literature for certain subtypes of IM-GD.

IPNA guidelines were available for INS and IgA related GN where a thorough literature search had been performed, meaning the updated literature search inclusion period was limited from January 2022 to May 2024 for these subtypes.

The literature search inclusion period was from September 2013 to May 2024 for all other subtypes as follows;

- Primary membranous nephropathy
- Lupus nephritis
- ANCA associated vasculitis
- Anti-glomerular basement membrane (GBM) GN
- Ig and complement mediated GN with membranoproliferative GN (MPGN) pattern
- Post infectious GN

Clinical questions for literature review

The questions about treatment interventions were framed in PICO (Patient, Intervention, Comparator, Outcome) format.

- Population: CYP under the age of 18 years of age with IM-GD
- Intervention: immunosuppressive treatment including medication and plasmapheresis
- Comparison: no treatment or different treatments where different regimens exist
- Outcome: estimated glomerular filtration rate (eGFR), CKD stage, need for kidney replacement therapy, proteinuria, infection rates, drug-related adverse effects, patient reported outcome measures.

The framework used was: In CYP under 18 years of age with [IM-GD subtype] is treatment with [immunosuppressive agent] associated with improved clinical outcomes [inclusive of eGFR, CKD, need for kidney replacement therapy, proteinuria, infection rates, drug-related side effects, QOL] compared to [alternative immunosuppressive agent or no treatment]?

The guideline was developed with consultation and input from relevant patient-support groups and allied professional bodies, known as stakeholders. Relevant stakeholders were identified by the GDG and were directly invited to formally review the scope document and contribute throughout the development process. A list of stakeholders is provided in Appendix 6.

Results

The results yielded several relevant international published guidelines, access to unpublished international guideline and pooled local practice guidelines.

Existing international guidelines

- IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome, 2020 [3].
- IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome, 2023 [4].
- KDIGO 2021 Clinical Practice Guideline for the management of Glomerular Diseases, 2021[5].
- KDIGO 2024 Clinical Practice Guideline for the management of Lupus Nephritis, 2024 [6].
- The KDIGO 2024 Clinical Practice Guideline for Antineutrophilic Cytoplasmic Antibody (ANCA)-associated Vasculitis, 2024 [7].
- Chung SA, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol. 2021 Aug;73(8):1366-1383 [8].
- IPNA Clinical Practice Recommendations for the Diagnosis and Management of Children with IgA Nephropathy and IgA Vasculitis Nephritis [9].

Existing local guidelines

- NHS Greater Glasgow and Clyde. Guideline on the classification and management of glomerulonephritis in general paediatrics.
- UK Kidney Association commentary on the KDIGO 2021 clinical practice guideline for the management of glomerular diseases, 2023
- Leeds Children's Hospital. Regional Guideline for the management of idiopathic nephrotic syndrome in childhood, 2022
- The Newcastle upon Tyne Hospitals NHS Foundation Trust. Management of childhood Nephrotic syndrome in children, 2022
- The Newcastle upon Tyne Hospitals NHS Foundation Trust. Cyclophosphamide therapy for Paediatric Rheumatology and Renal patients, 2013.
- Bristol Royal Hospital for Children. Clinical guideline management of vasculitis in children, 2019.

Literature search

The literature search discovered 104 papers for consideration of inclusion. This included 28 papers on INS with 26 papers focused on steroid sensitive nephrotic syndrome [10–33], and 4 on steroid resistant nephrotic syndrome since the IPNA evidence synthesis [34–37]. One paper Tu, J., et al., *Clinical assessment of moderate-dose glucocorticoid in the treatment of recurrence of primary nephrotic syndrome in children: a prospective randomized controlled trial* was excluded because it was not available in full text in English [38].

Following the completion of the IPNA evidence synthesis, there were 13 further papers on IgA related GN this included 8 papers on IgAV [39–46] and 5 papers based on IgAN [47–51]. Using the period for the literature review, there were 5 MN [52–56], 28 LN [57–85], 13 ANCA [86–98], 1 anti-GBM study [99], 12 C3 GN [100–112], 3 post infectious [113–115], and 2 papers on crescentic GN [116,117] were obtained during the inclusion period to help inform these guidelines. The evidence synthesis summary did not include a summary of KDIGO, IPNA guidelines or adult guidelines as these were reviewed and used as a foundation for each domain to construct the recommendations to support existing evidence or in situations where any paediatric data was lacking. The final included literature used for the evidence synthesis was distributed to the GDG and consisted of 24 papers on SSNS, 4 on SRNS, 5 on IgAN, 8 on IgAV-N, 5 on MN, 28 on LN, 13 on ANCA, 1 anti-GBM, 12 C3GN, 2 post infectious GN and 2 crescentic GN.

General recommendations for CYP with IM-GD

Number	RECOMMENDATION	Grade
Initial assessment		
General 1.0	We suggest kidney involvement should be assessed with clinical and laboratory findings in all children using a minimum of: measurement of blood pressure; documentation of peripheral oedema; urine dipstick analysis, measurement of serum kidney function to calculate eGFR; full blood count, and serum albumin. Depending on the clinical history, a more extended glomerular disease screen may be applicable, including; complement C3, C4, anti-streptococcal antibody titres, immunoglobulins, genetic testing, and immune profiling (ANA, dsDNA, ANCA, Anti-GBM, membranous auto-antibodies such as PLA2R, TSHD7A or a suitable panel). Differential diagnoses should also be considered according to the clinical history.	**2D**
Definitions		
General 1.1	We suggest defining complete response to treatment for IM-GD according to low or no detectable levels of proteinuria (urine protein/creatinine <20 mg/mmol on first morning void), or stable levels of proteinuria if proven to have chronic kidney damage, no haematuria (negative dipstick for blood and/or <5 red blood cells/high-power microscopic field) and stable (no worse than 15% from baseline if related to chronic changes) or normal eGFR (>90 ml/min/m^2).	**2C**
Management strategy		
General 1.2	We recommend that the treatment goal should be to achieve complete remission in children and young people with acute onset IM-GD.	**1C**
General 1.3	We suggest a maximum dose of intravenous methylprednisolone at 500mg for 3 days for routine use, to be aligned with the maximum dose used for adult patients.	**2C**
General 1.4	We suggest that in cases of IM-GD with histological evidence of chronic damage complete response may be an unrealistic goal when the aim should be to achieve nephroprotection by reduction of residual proteinuria and maintaining a stable eGFR.	**2C**

General 1.5	We suggest the use of intravenous cyclophosphamide or high dose mycophenolate mofetil (MMF) , together with intravenous methylprednisolone, and consideration of additional rituximab in children with IM-GD and rapidly progressive disease where there is deteriorating kidney function.	**2D**
General 1.6	We suggest repeating a kidney biopsy for histological analysis if there is uncertainty regarding whether the clinical features of IM-GD are due to active disease.	**2D**
Research and follow up		
General 1.7	We recommend that all children and their primary caregivers, should be offered the opportunity to participate in research. This includes registries (such as the National registry of rare kidney disease, RaDaR), contributing to biosampling, clinical trials, and any other advances to improve the future understanding of these diseases.	**1D**
General 1.8	We suggest that patients who have had IM-GD should be followed up for at least 5 years; the frequency of these assessments should be individualised according to the response to treatment and the local infrastructure which is likely to vary across the UK. Follow up may be conducted in partnership with primary or secondary care colleagues. A suggested frequency of follow up is approximately monthly for the first 3 months, 3-4 monthly until 12 months or whilst taking immunosuppression, then 6 monthly thereafter progressing to annual reviews once disease stability has been achieved. If the patient develops secondary CKD then follow up should be according to the CKD stage.	**2D**
General 1.9	We suggest that children and young people with IM-GD are managed by clinicians with suitable expertise.	**2D**
General 2.0	We suggest that more research is needed to understand the long term impact of treatment adverse effects in the management of children and young people with IM-GD, for example fertility.	**2D**

The assessment of a patient with IM-GD has been outlined in a succinct recommendation using extracted information from existing guidelines. The complete response definition uses a combination of the international guidelines and the threshold of proteinuria accepted by the regulatory authorities. There is a 'dose' effect of proteinuria in the causal relationship with CKD progression and this threshold has been described to preserve kidney health in the long term and used to align clinical practice goals [(118)].

GN subtype 1: Idiopathic nephrotic syndrome (INS)

Definitions

To align terminology, we suggest that the following definitions for idiopathic nephrotic syndrome (INS) are used. Definitions are taken from the IPNA SSNS guidelines (4) and SRNS guidelines (3) with minor modifications for standard UK practice.

Initial presentation and steroid sensitivity	
a	A 'typical' or uncomplicated initial presentation of childhood idiopathic nephrotic syndrome (INS) is defined by: i. Onset in early childhood with a typical age of 18 months to 3 years with a range up to 12 years, although it can occur at any age. ii. Nephrotic range proteinuria with urine protein:creatinine ratio >200 mg/mmol, hypoalbuminaemia and clinically detectable oedema.

	iii. Exclusion of atypical features such as faltering growth, fatigue, chronic kidney disease, macroscopic haematuria, systemic symptoms including rash, joint pain or swelling, sustained hypertension, abnormal autoantibody profile or complement (if measured). iv. Normal renal function (in the absence of acute hypovolaemia) or failure of renal function to normalise after hypovolaemia is corrected
b	Nephrotic syndrome in complete response is defined as a negative or trace of protein on urine dipstick for 3 consecutive days.
c	Steroid sensitive nephrotic syndrome (SSNS) is defined as nephrotic syndrome which enters complete response within 4 weeks of taking prednisolone at standard dose (60 mg/m^2 daily, maximum dose 60 mg).
d	Late response SSNS is defined as nephrotic syndrome which enters complete response between 4-6 weeks after taking prednisolone, assuming there has been adequate compliance, and this may include the use of 3 doses of intravenous methylprednisolone (500 mg/m^2/day, max dose 500 mg).
e	In patients unable to attain complete response to treatment, partial response is defined as: i. Urine protein creatinine ratio between 20 and 200 mg/mmol from a first morning void, and/or ii. Serum albumin >30 g/l
Relapsing disease	
f	Nephrotic syndrome relapse is defined as: i. 3 consecutive days of 3+ protein measured on early morning urine dipstick. ii. 5 consecutive days of 2+ protein confirmed with either a urine protein:creatinine ratio >200 mg/mmol and/or a serum albumin <30 g/l iii. Occurring in children with clinically detected oedema without reported proteinuria on home testing who have either a urine protein:creatinine ratio >200 mg/mmol and/or a plasma albumin <30 g/l.
g	An infrequent relapse within the first 12 months from initial presentation is defined as: i. not preceded by two or more relapses (or one relapse within the first 6 months following presentation), and ii. occurring at least 2 weeks after stopping prednisolone for any previous relapse.
h	Frequently relapsing SSNS (FRSSNS) is defined as disease in which there are ≥2 relapses within the first 6 months, or ≥3 relapses within any 12 months of the course of SSNS.
i	Steroid dependent SSNS (SDNS) is defined as disease in which there is failure to wean steroid medication as manifest by: i. two consecutive relapses on prednisolone treatment for the first episode or a relapse within 14 days of stopping prednisolone, or ii. two or more relapses within a 6-month period whilst taking maintenance prednisolone of at least 15 mg/m^2 per 48 hours (given as a daily or alternate day dose).
j	A complicated relapse is defined as a relapse requiring hospitalisation due to one of the following indications: a. severe oedema b. symptomatic hypovolemia or AKI requiring IV albumin infusions c. thrombosis d. significant infection such as sepsis, peritonitis, pneumonia, cellulitis
Steroid resistant disease	
k	Steroid resistant nephrotic syndrome (SRNS) is defined as nephrotic syndrome which has not entered complete remission by 6 weeks, having taken prednisolone at standard dose for at least 4 weeks that may have included 3 doses of intravenous methylprednisolone (500 mg/m^2/day, max dose 500 mg)).
l	CNI (calcineurin inhibitor)-resistance is defined as absence of at least partial remission after 6 months of treatment within target CNI ranges.

m	Multi-drug resistant SRNS is defined as absence of complete remission after 12 months of at least two mechanistically distinct steroid sparing agents at standard doses that may be given sequentially or in combination.
n	Secondary steroid resistance is defined as disease which is initially steroid sensitive but becomes steroid resistant in subsequent relapses.

Management of INS at disease presentation

Number	RECOMMENDATION	Grade
INS 1.1	We recommend that children with a 'typical' first presentation of nephrotic syndrome commence treatment with prednisolone 60 mg/m^2 per day or 2 mg/kg/day (maximum dose 60 mg) for 4 weeks.	**1A**
INS 1.2	We suggest that for children under the age of 5 years, prednisolone should be dosed according to body surface area, preferably using the Mosteller formula: $$BSA = \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}}$$ This should be based on an estimated dry weight for the child rather than their oedematous weight.	**2C**
INS 1.3	We recommend that a kidney biopsy prior to treatment should be considered in children who present with atypical features such as macroscopic haematuria, abnormal kidney funtion (in the absence of hypovolaemia), hypertension with a euvolaemic state or low complement factor C3 or C4.	**1B**
INS 1.4	We recommend that children with typical newly-presenting nephrotic syndrome should not routinely be commenced on steroid-sparing drugs at the point of initial remission.	**1A**
INS 1.5	We suggest that in children aged >5 years prednisolone may be dosed by either body surface area or weight with a maximum dose of 60mg per day.	**2C**
INS 1.6	We suggest that prednisolone should be given as a single daily dose in the morning.	**2B**
INS 1.7	We recommend that children who have not entered remission after 4 weeks of prednisolone 60 mg/m^{2}per day are discussed with a paediatric nephrologist as they may require 3 consecutive daily doses of high dose intravenous methylprednisolone (500 mg/m^2, maximum dose 500 mg) to test steroid-responsiveness and may need a kidney biopsy.	**1C**
INS 1.8	We recommend that children who enter remission within 4 weeks of commencement of prednisolone at 60 mg/m^2 per day, continue to receive prednisolone at that dose for a total of 4 weeks, then reduce the dose to 40 mg/m^2 (maximum dose 40 mg) given on alternate days for a further 4 weeks, then stop.	**1A**
INS 1.9	We suggest that children who are late responders (i.e. only enter remission within 6 weeks of presentation) receive a more prolonged taper of prednisolone over at least 8 weeks and commence tacrolimus as a steroid-sparing agent.	**2D**
INS 1.10	We suggest consideration of a kidney biopsy and/or genetic testing in children who are late or partial responders.	**2D**

Rationale

INS responding to corticosteroids is referred to as steroid sensitive nephrotic syndrome (SSNS). It is a relapsing disease in more than 80% of children, with a disease course that is commonly declared in the first year following the initial presentation. Disease control cannot always be achieved without maintenance immunosuppressive treatment when drug toxicity becomes a concern and the management aim should be to use the lowest amount of therapy required

to minimise both relapse rate and side effects. The recent IPNA definitions, including "SSNS controlled on therapy" place a numerical value on the number of acceptable relapses per year which have been incorporated. For disease that is resistant to the initial steroid course, long-term registry studies show that the risk of end-stage kidney disease is dependent on the extent of proteinuria, the risk being lowest when complete response is achieved which continues to be the therapeutic goal [119].

The original corticosteroid regimen to treat newly presenting nephrotic syndrome in children was a consensus agreement from the ISKDC [120]. Four more recent well-designed RCTs have shown that shorter initial courses are equally effective [121]. The four RCTs used a combination of the ISKDC 4 weeks + 4 weeks regimen and the German paediatric nephrology group, Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) regimen of 6 weeks + 6 weeks as standard treatment and the 2021 KDIGO [5] and 2023 IPNA guidelines [4] do not distinguish between them due to little difference in outcomes by 24 months [122]. Studies comparing dosing regimens have not found any consistent difference between weight or body surface area regimens [123–125]. For very small children, body surface area dosage calculation are more precise [126].

Endocrinologists have strongly advocated for the avoidance of abrupt discontinuation of corticosteroids after this treatment course due to the risk of acute adrenal insufficiency reported in adults with other diseases [127]. These concerns have led to national guidance from the Neonatal and Paediatric Pharmacists Group (NPPG) providing caution against abrupt discontinuation for all indications. Despite the ISKDC regimen being in use for more than 50 years, these concerns are not well-described in children with SSNS and in the PREDNOS trial where corticosteroid adverse effects were systematically recorded there were no cases of adrenal insufficiency [128], suggesting it is not a common phenomenon. A British Paediatric Surveillance Unit (BPSU) survey on acute adrenal insufficiency between 2020 and 2022 is due to be published soon and this topic has been highlighted as a priority area for research. In the meantime, children should be issued with a steroid card and advised about this risk. Recent studies comparing whether prednisolone should be given as a single or divided dose for an initial episode of nephrotic syndrome [129] and in relapse [30] do not add convincing evidence to change practice. Single daily dosing is therefore suggested in line with IPNA guidance and maintaining alternate day dosing for consolidation was felt to be most aligned with UK practice in the absence of data to prove adrenal insufficiency.

Studies using the addition of non-steroid-based immunosuppression in the initial presentation are emerging however to date these have been small, single-centre, and inadequately powered. RCT's evaluating MMF and levamisole as initial therapy are underway and may provide evidence for future updates [130,131]. Children who are late to respond to treatment (>2 weeks) or who relapse whilst taking the initial course are highly likely to develop early steroid dependent disease [132] and considering how best to stratify this higher risk population is a much needed area for future development.

Management of INS that responds to steroids (SSNS) and has a first relapse

Number	RECOMMENDATION	Grade
INS 1.11	We recommend that children who experience a first relapse of nephrotic syndrome more than 2 weeks after stopping prednisolone receive prednisolone 60 mg/m^2/day (maximum dose 60 mg once daily) until remission followed by 40 mg/m^2 (maximum dose 40 mg) on alternate days for 4 weeks and then stopped.	**1B**
INS 1.12	We suggest that children who experience a first relapse of nephrotic syndrome whilst taking the initial corticosteroid course or within 2 weeks of stopping could be treated with prednisolone 60 mg/m^2 per day (maximum dose 60 mg) once daily until remission followed by 40 mg/m^2 (maximum dose 40 mg) on alternate days for 4 weeks and then tapered over at least a further 8 weeks, and commence on either tacrolimus or mycophenolate mofetil as a steroid-sparing agent.	**2D**

Rationale

In recent years, there have been small RCTs suggesting equivalent efficacy using smaller doses of prednisolone and the duration has been challenged too. Kainth et al showed potential efficacy from a 2-week duration compared to standard 4-weeks, however, unfortunately, the study was underpowered [133]. The Italian PROPINE study showed no benefit from longer durations [134]. Children who experience frequent relapses are often prescribed individualised tapering courses of corticosteroid though the evidence for this is also lacking. The clinical course of children who relapse early (within 2 weeks of stopping steroids), is usually frequently relapsing disease [4].

Management of INS that responds to steroids (SSNS) and has subsequent relapses

Number	RECOMMENDATION	Grade
INS 1.13	We recommend that children with frequently relapsing or steroid dependent nephrotic syndrome commence a maintenance drug to prevent further relapses.	**1D**
INS 1.14	We suggest review of maintenance treatment to consider an alternative agent if there is more than one relapse in the 6 months following commencement.	**2D**
INS 1.15	We suggest that for children with frequently relapsing, but not steroid dependent nephrotic syndrome, the maintenance treatment should use a personalised approach to conside one of the following treatments: 1. Levamisole 2. Mycophenolate mofetil 3. Tacrolimus (preferred calcineurin inhibitor)	**2C**
INS 1.16	We suggest that for children with steroid dependent nephrotic syndrome, where there are no contra-indications, the first choice of a steroid-sparing agent should either be mycophenolate mofetil or tacrolimus.	**2D**
INS 1.17	We suggest that for children with frequently relapsing INS or steroid dependent disease, a course of oral cyclophosphamide may be another therapeutic option with consideration of its side effect profile including the risk of infertility.	**2D**

Rationale

The 2022 IPNA guidelines clearly stated that on-going frequently relapsing disease should signal the need for a review of regular maintenance treatment. There are few direct comparators of steroid-sparing agents. A trial evaluating children in India, compared levamisole with mycophenolate mofetil [135] and found no difference in relapse rates, suggesting either may be a suitable first-choice mild steroid-sparing immunosuppressive agent, in uncomplicated frequently relapsing disease. For children with more complex relapsing or steroid-dependent disease, there is insufficient evidence to suggest a single first-choice agent, however to align practice, we suggest the first choice is restricted to mycophenolate mofetil or tacrolimus.

Management of primary INS resistant to steroids (SRNS)

Number	RECOMMENDATION	Grade
INS 1.18	We suggest that in CYP with nephrotic syndrome that does not respond to standard dose corticosteroid by 6 weeks should undergo screening for genetic causes of nephrotic syndrome.	**2C**
INS 1.19	We recommend that tacrolimus should be commenced as first line immunosuppressive therapy for SRNS.	**1B**
INS 1.20	We recommend tapering prednisolone once a diagnosis of SRNS is established with the aim to discontinue after 6 months if they are not contributing to management (see medication section for tapering guidance).	**2D**
INS 1.21	We recommend stopping immunosuppression in SRNS if a recognised genetic abnormality is detected.	**1D**
INS 1.22	We suggest that if complete response is achieved in SRNS with tacrolimus it should be continued for 2 years.	**2D**
INS 1.23	We suggest if there is a disease relapse following complete response with tacrolimus, the administration of prednisolone 60 mg/m^2 per day should be attempted until response (maximum duration 4 weeks) with subsequent taper whilst ensuring the tacrolimus trough levels are within target range (suggested 4-7 mmol/L).	**2D**
INS 1.24	We suggest that in cases with partial or no response after 3 months of tacrolimus treatment within target range, and no genetic cause has been found, then MMF could be added as an adjunctive treatment.	**2D**
INS 1.25	We suggest in children where there is no response after 6 months of treatment with tacrolimus and consideration of a trial of another immunosuppressive agent, that rituximab, or alternative B cell depleting agent, could be considered.	**2D**
INS 1.26	We suggest consideration of recruitment to clinical trials, off-label treatments available for adults, or the compassionate use of agents under evaluation, in children who have multi-drug resistant disease and high risk of progression to kidney failure.	**2D**

Rationale

The GDG were in general agreement with the 2022 IPNA guidelines that include the early use of RAAS blockage in persisting proteinuria, prompt genetic testing in steroid resistant disease using the NHS genomics service, and the introduction of a calcineurin inhibitor using tacrolimus as first line immunosuppressive therapy. Caution should be noted when using nephrotoxic agents in view of long term impact and when at risk of hypovolaemia due to the nephrotic state.

The group agreed that most clinicians were using tacrolimus as the calcineurin inhibitor of choice due to the preferred side effect profile and no evidence of lower efficacy. There is also ancedotal evidence of reduced dependency and tolerance compared with older agents. The group agreed that MMF would be tried and/or added if there was no response after 3 months and the use of rituximab thereafter. Previous studies evaluating the role of rituximab demonstrated that it was effective in 83.3% of SDNS and 27.2-60% of SRNS [136,137] with a reduction in relapses after treatment by 3.9 episodes per patient per year.

The group identified that there was increasing use of rituximab in clinical practice and guidelines may change in future updates as evidence emerges. The recent identification of anti-nephrin antibodies being present in 44% of patients with INS in a study involving 539 patients (including 182 children) represents a paradigm shift that may see future antibody led monitoring and B cell depleting agents having a more profound purpose in the management of this condition [138], aligned with other antibody mediated forms of GN, however they are not yet available in the clinical setting.

GN subtype 2: IgA related glomerulonephritis

IgA nephropathy (IgAN)

Definitions

To align terminology, we suggest that the following definitions for IgAN are used. Definitions are taken from the IPNA guidelines with minor modifications by the GDG for standard UK practice [9].

Diagnosis	
a	A diagnosis of primary IgA nephropathy is suggested by haematuria (gross and/or microscopic) with or without proteinuria (urinary protein creatinine ratio (UPCR) >20 mg/mmol) in the absence of other aetiologies, and with a normal serum C3 level.
b	Gross haematuria occurring during an upper respiratory infection is suggestive of IgAN.
c	In children with suspected IgAN and nephrotic-range proteinuria (UPCR>200 mg/mmol) and/or reduced eGFR (<90 mls/min/1.73m^2) that is not prompty improving, then a kidney biopsy should be performed.
d	The kidney histology should be classified using the Oxford classification criteria (MEST-C) for children and young people with IgAN.
e	Remission of IgAN is defined as a UPCR < 20mg/mmol on at least 2 urine samples collected at least one month apart, with a normal (>90 mls/min/1.73m^2) or stable eGFR and absence of gross haematuria.
f	A relapse of IgAN is defined as the reappearance of episodic haematuria and a rise in proteinuria (>50 mg/mmol), despite optimal RAAS treatment if appropriate, based on at least 2 first morning urine samples collected 1-2 weeks apart.

Management of IgAN

Number	RECOMMENDATION	Grade
IgAN 2.1	We suggest the use of conservative management in children with IgAN who have isolated microscopic haematuria or infrequent episodic gross haematuria that may be associated with transient proteinuria that completely resolves.	**2C**
IgAN 2.2	We suggest that a combination of clinical features and the histological features should guide shared decision making about the treatment choices. The following are clinical indicators that may suggest active disease that requires treatment; • proteinuria>50 mg/mmol • reduced eGFR considered attributable to active disease • Nephrotic syndrome (clinical signs of oedema, serum albumin <30 g/L, severe proteinuria UP: UC >200 mg/mmol). The following are histological indicators of disease activity; • Mesangial hypercellularity of >50% glomeruli (M1), presence of endocapillary hypercellularity (E1), or cellular crescents in at least one glomerulus (C1 or C2).	**2C**
IgAN 2.3	We suggest the use of the online International IgAN prediction tool at biopsy to inform long term outcome discussions and treatment decisions. (https://qxmd.com/calculate/calculator_713/international-igan-prediction-tool-at-biopsy-pediatrics).	**2D**
IgAN 2.4	We suggest that children with biopsy proven IgAN and features consistent with active disease are treated with immunosuppressive treatment using either or both of the following; • Oral prednisone. • Oral MMF or tacrolimus (preferred CNI).	**2C**

IgAN 2.5	We suggest using both oral prednisolone and an immunosuppressive agent such as tacrolimus or MMF if there is poor response to one agent or as a steroid sparing management strategy.	**2D**
IgAN 2.6	We suggest a review of management options in children where there is no response after 3 months of treatment and concerns about on going active disease.	**2D**
IgAN 2.7	We suggest that in children with rapidly progressive glomerulonephritis secondary to IgAN who present with kidney failure or who are considered at high risk of rapid progression to kidney failure are managed with intravenous methylprednisolone, cyclophosphamide, and/or rituximab.	**2D**
IgAN 2.8	We recommend that tonsillectomy is not routinely performed as a treatment for IgAN in UK children however this may be appropriate in individual cases with recurrent tonsillitis.	**1D**
IgAN 2.9	We suggest using immunosuppressive treatment in children with IgAN for at least 12 months or until complete response has been maintained.	**2D**
IgAN 2.10	We suggest consideration of recruitment to clinical trials, off-label treatments available for adults, or the compassionate use of agents under evaluation, in children who have failed to demonstrate any improvement and continue to have active disease.	**2D**

Rationale

There is not any non-invasive method to diagnose IgAN and therefore the kidney biopsy is an essential part of the treatment pathway because the diagnosis relies on the histological appearances. The criteria for when to conduct a biopsy was agreed to be taken from the IPNA guidelines (9). The MEST-C scoring system is consistent with current clinical practice in the UK sites, supported by international guidelines, and in the absence of anything superior it is suggested for histological categorisation in the diagnosis section (this falls outside of scope of formal treatment recommendations). It is important to acknowledge the limitations of the Oxford scoring system in terms of accurately predicting clinical outcomes in children as highlighted in previous guidance and well described in the systermatic literature review conducted by Howie and Lalayiannis in 2023 [5,9,139].

Clinical indicators and histological indicators of when to commence immunosuppressive treatment were taken from guidelines and discussed by the GDG to achieve agreement on thresholds without being too restrictive. The IgAN prediction tool can predict the risk of 30% decline in eGFR or kidney failure in children at the time of biopsy using clinical risk factors and the Oxford MEST histology score [140]. There is updated literature to show that re-evaluation of risk at 1 or 2 years after biopsy is also accurate [141]. Agreement was made that in the absence of any strong evidence that the preferred agent for first line treatment would be corticosteroids and/or the use of MMF. This was partly to align with the management of IgA vasculitis nephritis and C3 glomerulopathy and it was agreed that these agents were most commonly being used, plus the drug lacks nephrotoxicity which was seen as an advantage.
Other agents, such as tacrolimus, remain unevaluated and are therefore included as potential alternative options. For patients at very high risk of disease progression to organ failure the guidelines continue to recommend intravenous agents including the use of intravenous methylprednisolone and cyclophosphamide [5,9] or rituximab despite the negative trial data in adults [142], it was felt that adult trials may not reflect the very acute, inflammatory disease seen in CYP. Tonsillectomy is suggested in international guidelines for Japanese patients however due to the invasive nature of the procedure this should not be performed routinely in the UK and should be reserved for children who have recurrent tonsillitis [5].

IgA vasculitis nephritis (IgAV-N)

Definitions

To align terminology, we suggest that the following definitions for IgAV-N are used. Definitions are taken from the IPNA guidelines with minor modifications by the GDG for standard UK practice [9].

Diagnosis	
a	The diagnosis of IgAV is based on the EULAR/PRINTO/PRES classification criteria (143).
b	The diagnosis of IgAV-N relies on the initial diagnosis and clinical and/or laboratory evidence of nephritis.
c	A definition of relapse of IgAV-N is recurrence of haematuria (gross haematuria or ≥2+ in dipstick or 5 red blood cells/hpf) and/or proteinuria (urine protein/creatinine > 30 mg/mmol on first morning void) in at least 2 urine samples and/or reduced kidney function (eGFR < 90 mL/min/1.73m2 or > 25% reduction from baseline) in a patient who has had a previous diagnosis and achieved complete remission for at least 1 month.
d	All children should be monitored after the initial diagnosis of IgAV for the presence of nephritis and this should be at least monthly for the first six months even if the urinalysis remains normal.

Management of IgAV-N

Number	**RECOMMENDATION**	**Grade**
IgAV 2.11	We recommend that a kidney biopsy should be performed in patients with IgAV and; • Severe – nephrotic range proteinuria UPCR > 200 mg/mmol with or without nephrotic state (oedema, low serum albumin) or eGFR <60 ml/min/m2 • Moderate disease – proteinuria UPCR >100mg/mmol for >2 weeks, without nephrotic state • Mild disease – persisting proteinuria for 4-12 weeks (UPCR <100mg/mmol), absence of the nephrotic syndrome and normal eGFR (>90 ml/min/m2) • Rapidly progressive glomerulonephritis or acute eGFR <30 ml/min/m2	**1C**
IgAV 2.12	We suggest that the kidney histology should be classified using the ISKDC scoring system and the Oxford classification (MEST-C).	**2D**
IgAV 2.13	We recommend not using prophylactic corticosteroids in patients at presentation to prevent the onset of IgAV-N.	**1A**
IgAV 2.14	We recommend conservative management for patients with IgAV-N who have isolated microscopic or macroscopic haematuria with no proteinuria (UPCR 20 mg/mmol).	**1D**
IgAV 2.15	We suggest that children with biopsy proven IgAV-N who have risk factors for disease progression are treated with immunosuppressive treatment using either or both of the following; • oral prednisone. • oral mycophenolate mofetil or tacrolimus (preferred CNI).	**2C**
IgAV 2.16	We suggest treating children with clinical (UPCR ≥ 200 mg/mmol or RPGN) and histological risk for progression (ISKDC ≥ II) with at least a 6-month course of immunosuppression or until complete response has been maintained.	**2C**
IgAV 2.17	We suggest the use of alternative immunosuppressive agents (such as calcineurin inhibitors, or rituximab) in cases of biopsy proven IgAV-N that have either not achieved complete response after the initial treatment for 3 months, if there are deteriorating parameters, or as a steroid sparing intervention.	**2C**
IgAV 2.18	We suggest discontinuing immunosuppression for IgAV-N if there has been complete clinical response and there have been no disease relapses for 12 months.	**2C**

IgAV 2.19	We suggest consideration of recruitment to clinical trials, off-label treatments available for adults, or the compassionate use of agents under evaluation, in children who have failed to demonstrate any improvement and continue to have active disease.	**2D**

Rationale

The criteria to conduct a biopsy are based on recently reported literature [9,144] and were used to construct the parameters outlined in the recommendations. Regarding histological classification for IgAV, the ISKDC criteria continue to be the most commonly used across the national centres however the group recognised limitations in that they are only based on glomerular features and there is growing recognition of the importance of chronic changes such as tubulointerstitial atrophy or fibrosis [145,146]. The group agreed to include both the ISKDC and MEST-C scoring in the recommendations however appreciated that this was often led by pathology colleagues and may require wider input for implementation. This has the additional advantage of alignment with IgAN however an international consensus from expert Pathology colleagues would be the ideal way to inform this topic. The Cochrane collaboration systematically reviewed the evidence related to the early use of corticosteroids in all patients presenting with IgAV to prevent the onset of nephritis and demonstrated no effect [147]. Therefore, there is currently no role for all patients to be routinely treated with steroids for this indication.

In children with microscopic haematuria, the prognosis is good, and treatment wouldn't be indicated therefore they do not justify the associated risks of a kidney biopsy. In a large retrospective real world cohort collating data from 1148 children from across Europe with IgAV and biopsy proven disease, MMF and corticosteroids were the most commonly used treatments in current practice [148]. The group agreed that these would be included and had the advantage of sharing similarity to the management of other forms of IM-GD such as IgAN and C3GN. As IgAV is usually a one-off episode with relapses mostly seen during the first few months after presentation and being rare once management for nephritis has commenced, therefore the duration of treatment for IgAV-N was agreed to be for a period of around 6-12 months with discontinuation once response had been achieved.

GN subtype 3: Membranous nephropathy (MN)

Definitions

To align terminology, we suggest that the following definitions for MN are used. Definitions are taken from the KDIGO guidelines with minor modifications by the GDG for standard UK practice [5].

Diagnosis	
a	The diagnosis of MN is based on the histological description in the absence of any secondary causes (SLE, chronic hepatitis B infection, rarely neoplasia)
b	The diagnosis of MN relies on the finding of positive antibodies (with current panels including phospholipase A2 receptor antibody (PLA2R) and thrombospondin type 1 domain-containing protein 7A (THSD7A)) or characteristic histological features.
c	When a diagnosis of MN is suspected or proven, all patients should have antibody testing performed to reveal markers that may inform disease monitoring and treatment.
d	In antibody positive disease, these markers should be performed every 3-6 months to guide treatment.
e	For children who have not received any treatment prior to the kidney biopsy, we recommend stratifying patients into low- vs medium/high-risk. • Low risk: proteinuria <200mg/mmol over 3 months or nephrotic range proteinuria that has already reduced by 50% and a normal eGFR. • Moderate- to high-risk: Reduced eGFR, nephrotic range proteinuria that has not improved.

Management of membranous nephropathy

Number	RECOMMENDATION	Grade
MN 3.1	We suggest the use of RAASi and monitoring clinical response with antibody findings in the first 3 months in patients who have low-risk disease and who have not received any prior treatment.	**2C**
MN 3.2	We suggest a trial of corticosteroids in patients who are at a low risk of disease progression and who are not showing signs of improvement.	**2C**
MN 3.3	We suggest the use of rituximab, or alternative B cell depleting agents, in addition to corticosteroids in patients with MN who are at moderate- to high-risk of disease progression and who have not received any prior treatment.	**2C**
MN 3.4	We suggest the use of alternative immunosuppressive agents (eg: MMF or tacrolimus) in cases that have not achieved complete response after initial treatment for 6-12 months with rituximab or as a steroid sparing intervention.	**2C**
MN 3.5	We suggest discontinuing immunosuppression for MN if there has been complete clinical remission, antibody negativity and no disease flares for 12-24 months.	**2D**

Rationale

There is limited evidence to support the management of MN in childhood onset disease. The recommendations for management are largely derived from adult data [5]. In MN with low levels of proteinuria, normal serum albumin and normal kidney function, the reported outcomes are good and patients in this group also have minimal associated symptom burden. For this group, there appears to be time to consider management using conservative treatment and they may not justify invasive procedures such as the kidney biopsy. In this group immunosuppression may add risks without significant benefit until proven otherwise.

GN subtype 4: Lupus nephritis (LN)

Definitions

To align terminology, we suggest that the following definitions for LN are used. Definitions are taken from the KDIGO guidelines, LN guidelines with minor modifications by the GDG for standard UK practice [6].

Diagnosis	
a	A diagnosis of systemic lupus erythematosus (SLE) can be made when children and young people (CYP) meet the Systemic Lupus Collaborative Clinics (SLICC) criteria, a revised version of the American College Rheumatology SLE classification criteria, that includes symptoms, signs, and investigations suggestive of SLE (149).
b	A percutaneous kidney biopsy should be performed to confirm and grade classification of lupus nephritis (LN) in CYP.
c	We recommend multi-disciplinary team involvement, particularly in partnership with paediatric rheumatologists, for the management of children and young people with SLE and LN.
d	CYP with LN should have the histology graded using the International Society of Nephrology / Renal Pathology Society classification criteria.

Management of lupus nephritis

Number	RECOMMENTATION	Grade
LN 4.1	We recommend that in CYP with suspected or confirmed SLE require percutaneous kidney biopsy to diagnose LN if there is evidence of one or more of the following: - proteinuria and/or albuminuria (UPCR >50 mg/mmol) - nephrotic syndrome - macroscopic haematuria - hypertension - impaired kidney function not related to another cause.	**1C**
LN 4.2	We recommend that patients with LN are treated with hydroxychloroquine (or an equivalent antimalarial) unless contraindicated due to their protective effect on the kidney.	**1C**
LN 4.3	We recommend that patients with Class I or II LN and low-level proteinuria should be managed according to the extra-renal manifestations.	**1B**
LN 4.4	We recommend that patients with Class III or IV LN, with or without a membranous class V component, should be treated with glucocorticoids and mycophenolate mofetil (MMF) to induce disease remission with consideration of adding B cell therapy or tacrolimus (preferred CNI) if there are concerns about risk factors for progression (avoiding the use of CNI if the kidney function is severely impaired).	**1B**
LN 4.5	We recommend that an alternative induction agent to MMF for patients with Class III or IV LN is intravenous cyclophosphamide.	**1B**
LN 4.6	We recommend that patients with active Class V LN, without overlap with other features, are treated with combined immunosuppressive treatment using glucocorticoids, and MMF or tacrolimus (preferred CNI).	**1B**
LN 4.7	We recommend that after completion of induction therapy, patients should be placed on MMF for maintenance treatment.	**1B**
LN 4.8	We suggest the addition of another immunosuppressive agent, such as B cell depletion or tacrolimus (preferred CNI), within the first 3 months for patients with persistent disease activity, concerns about high-risk of disease progression, or inadequate response to initial therapy (avoiding the use of CNI if the kidney function is severely impaired).	**2C**
LN 4.9	We recommend that the total duration of initial immunosuppression plus maintenance immunosuppression for LN should be at least 36 months.	**1B**
LN 4.10	We recommend that if MMF is not suitable for maintenance treatment then azathioprine or tacrolimus (preferred CNI) is considered (avoiding the use of CNI if the kidney function is severely impaired).	**1C**
LN 4.11	We suggest consideration of recruitment to clinical trials, off-label treatments available for adults, or the compassionate use of agents under evaluation, in children who have failed to demonstrate any improvement and continue to have active disease.	**2D**

Rationale

LN runs a chronic relapsing course with 0.14 flares per child per year reported [58] and kidney disease is associated with increased mortality [76], as such they have high demands for long term immunosuppression. There are no clinical indicators to predict the histological findings [59]. Treatment is directed according to the classification of the histological findings and indicated mostly in class 3, 4 or 5 disease, where class 4 disease has the worst prognosis [60,62,69]. Treatment relies on an induction period followed by maintenance over several years. Induction has classically been a choice due to similar outcomes when using MMF or cyclophosphamide together with corticosteroids [59,64,70,73,74,77,82,83]. The recent publication of the KDIGO LN guidelines [6], and recognised suboptimal outcomes [75], advocate for earlier dual immunosuppression in addition to steroids following long standing cohort data supporting the use of adjunctive treatment (mostly B cell depletion using rituximab) [71,80] and recent clinical trial evidence on the beneficial effects of using either belimumab and voclosporin as induction agents in adults. In a study in 2017, 44 children with LN were

treated with MMF or rituximab or cyclophosphamide where more children achieved complete remission with rituximab with lower overall steroid dose observed too [57]. Serious adverse effects were mostly seen in the cyclophosphamide cohort [57].

For belimumab, the evidence of effectiveness in paediatric LN is limited; there was a trend favouring belimumab in one randomized, controlled trial, however the difference failed to achieve statistical significance [150]. Whilst the paediatric trials for voclosporin are underway, it has been translated that children may also benefit from the earlier use of additional therapies, and this has been incorporated as a suggestion. Maintenance treatment has relied on MMF or azathioprine with some suggestions that MMF may be superior [63,85] and the recommended duration being described as 1-4 years in the literature [84]. Agreement on 3 years of treatment was achieved by the GDG. Larger doses of steroids are used in childhood onset disease [66] and adherence to steroid treatment plans is reported to be very poor with personalised approaches preferred and the need to minimise exposure deemed a priority [64]. Hydroxychloroquine has adjunctive benefit in improving proteinuria outcomes, with evidence from a double blind randomised controlled trial involving 60 children [67]. There are reports of worse kidney outcomes according to ethnicity, with African ancestry being worse, however there are no agreed ways to stratify patients at present [72]. There are scattered reports of experimental treatments for refractory disease, including biologics and cell based therapies [68,79], therefore clinical trials are worth considering in patients who are not achieving complete response.

GN subtype 5: ANCA associated vasculitis (AAV)

Definitions

To align terminology, we suggest that the following definitions for AAV are used. Definitions are taken from the KDIGO guidelines with minor modifications by the GDG for standard UK practice [7].

Diagnosis	
a	A diagnosis of AAV is made in the case of a clinical presentation compatible with small-vessel vasculitis in combination with positive myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA serology. Prompt, intenstive treatment is required in this condition therefore waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating.
b	The persistence of ANCA positivity, an increase in ANCA levels, or a change in ANCA from negative to positive may be predictive of future disease relapse and should be considered when making treatment decisions, however the dosing of immunosuppressive therapy should not be based on ANCA titer results alone.

Management of ANCA associated vasculitis

Number	**RECOMMENTATION**	**Grade**
ANCA 5.1	We recommend that corticosteroids in combination with rituximab or cyclophosphamide are used as induction treatment of new-onset AAV.	**1B**
ANCA 5.2	We suggest not routinely using plasma exchange in patients with new-onset AAV with active glomerulonephritis however it could be considered in rapidly progressive organ or life threatening AAV.	**1B**
ANCA 5.3	We suggest considering the use of avacopan in children who are post pubertal with AAV to support induction treatment alongside rituximab or cyclophosphamide as a method to minimise steroid use in accordance with nationally approved requirements.	**2D**

ANCA 5.4	We recommend the use of 6-monthly rituximab treatment as maintenance in CYP whose disease has entered remission.	**1B**
ANCA 5.5	We suggest the use of MMF as an alternative maintenance treatment if rituximab is not suitable.	**2B**
ANCA 5.8	We recommend that relapses in AAV are treated with rituximab if they are not already receiving this treatment	**1C**
ANCA 5.11	We suggest considering discontinuation of immunosuppressive therapy if there has been no response in 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease that require treatment.	**2C**
ANCA 5.12	We suggest using plasma exchange for patients who present with an overlap syndrome of ANCA-associated vasculitis and anti- glomerular basement membrane (GBM).	**2D**
ANCA 5.13	We recommend the optimal duration of treatment is between 18 months and 4 years after induction of remission.	**2C**
ANCA 5.15	We suggest consideration of recruitment to clinical trials, off-label treatments available for adults, or the compassionate use of agents under evaluation, in children who have failed to demonstrate any improvement and continue to have active disease.	**2D**

Rationale

AAV can deteriorate quickly with rapid progression of sclerotic histological changes over days [87,88,91,98], and it therefore needs prompt, intensive treatment at the time of diagnosis [93]. Previously there was variability in the immunosuppressive treatments used [94], however recent induction treatment with either rituximab or cyclophosphamide together with corticosteroids has been advocated in guidelines, and reflected in cohort data, due to evidence showing equivocal outcomes [8,86,95,97]. Rituximab may have a preferred side effect profile. Plasma exchange is still in widespread use [88,91,92,96], despite the evidence supporting benefit being very limited and trials in adult patients demonstrating uncertain effects [151]. Meta-analysis has suggested that adults with AAV are managed with plasma exchange if the creatinine is >300 mmol/L. Steroid toxicity remains a concern in this condition [89,92] and avacopan has been shown to act as a steroid sparing agent. Access to avacopan is available in the NHS for post pubertal children who have a diagnosis of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) and meet specific criteria that includes discussion in an MDT that must include 2 consultants including a paediatric expert in the field and a paediatric pharmacist and according to trust policy regarding the use of unlicensed medicines.

Longer term, the disease demonstrates frequent relapses with high cumulative morbidity secondary to infection and disease, therefore regular review of maintenance treatment is important and timed dosing of B cell depletion alone is advocated within guidelines in patients who have achieved adequate response [7]. For the subtype eosinophilic granulomatosis with polyangiitis, kidney involvement is extremely rare and therefore considered outside the scope of this guideline [152].

GN subtype 6: Anti-GBM disease

Definitions

To align terminology, we suggest that the following definitions for anti-GBM are used. Definitions are taken from the KDIGO guidelines with minor modifications by the GDG for standard UK practice [5].

Diagnosis	
a	A diagnosis of anti-GBM disease is made according to clinical features, histology and positive anti-GBM antibody findings.
b	Anti-GBM disease can progress very rapidly, within hours to days, therefore if there is a high degree of suspicion for the diagnosis, treatment should not be delayed.
c	In anti-GBM the biopsy can be performed to support the management after the initial treatment has been initiated.

Management of anti-GBM disease

Number	RECOMMENTATION	Grade
GBM 6.1	We recommend the use of intravenous glucocorticoids, cyclophosphamide, and plasmapheresis for CYP presenting with anti-GBM disease.	**1C**
GBM 6.2	We suggest reviewing the intensity and duration of the immunosuppressive treatment if a CYP requires dialysis at presentation, in the absence of pulmonary haemorrhage, if they are considered to have a low chance of reversible disease for example when the kidney biopsy shows 100% crescents or more than 50% global glomerulosclerosis.	**2C**
GBM 6.3	We suggest that children are given a trial of immunosuppressive treatment even when the kidney biopsy shows 100% crescents or more than 50% global glomerulosclerosis to test for any acute reversibility.	**2C**
GBM 6.4	We suggest for patients who do respond to therapy that maintenance therapy with a long-term immunosuppressive agent is not required as anti-GBM disease rarely relapses.	**1C**
GBM 6.5	We suggest that if a patient is positive for both anti-GBM antibodies and ANCA (seen in up to 30% of patients), they should be given maintenance immunosuppression, aligned with the management of AAV.	**2C**
GBM 6.6	We suggest the use of an additional immunosuppressive agent, such as rituximab or MMF, within the first 3 months for patients with persistent disease activity, concerns about high-risk of disease progression, or inadequate response to initial therapy.	**2D**
GBM 6.7	We suggest consideration of recruitment to clinical trials, off-label treatments available for adults, or the compassionate use of agents under evaluation, in children who have failed to demonstrate any improvement and continue to have active disease.	**2D**

Rationale

Anti-GBM produces an acute, severe disease with rapid destruction to the kidney within hours to days. It therefore requires urgent management and intensive induction treatment. Due to very limited paediatric specific data, management is largely aligned with adult practice and derived from data based on adult disease. In adult practice, patients with high risk of a poor outcome due to severe irreversible biopsy changes and dialysis dependency may not receive immunosuppression as the risk is believed to outweigh the benefits. The GDG felt that in children the norm was to offer a period of immunosuppression to determine whether there is any reversibility because even delaying dialysis by a few months in a child could have an impact on education and social wellbeing. This is consistent with a report published in 2018 which demonstrated in 24 patients the biopsy findings did not determine the therapeutic

choice and all children received intensive induction therapy (99). As the disease is usually a single presentation it does not require long term immunosuppression unless relapses are clinically evident [5].

GN subtype 7: C3 glomerulopathy (C3G) and immune complex MPGN (IC-MPGN)

Definitions

To align terminology, we suggest that the terms C3G and IC-MPGN are used. Definitions are taken from the KDIGO guidelines with minor modifications by the GDG for standard UK practice [5].

Diagnosis	
a	The diagnoses of C3G and IC-MPGN are made using histological analysis and the exclusion of underlying disease (such as chronic infection, endocarditits, post infectious causes).
b	C3G and IC-MPGN can be categorised into mild, moderate, and severe disease. These categories are dependent on the amount of proteinuria and impairment in kidney function. • Mild – UPCR <100mg/mmol, absence of the nephrotic syndrome, and normal eGFR (>90 ml/min/m^2) • Moderate – UPCR >100mg/mmol, without nephrotic state or eGFR 60-90 ml/min/m^2 • Severe – nephrotic state (proteinuria, oedema, low serum albumin) or eGFR <30-60 ml/min/$m^{2,}$ • Rapidly progressive glomerulonephritis with deteriorating kidney function or eGFR <30 ml/min/m^2

Management of C3G and IC-MPGN

Number	**RECOMMENTATION**	**Grade**
ICGN 7.1	We suggest categorising patients into mild, moderate, and severe disease according to clinical features to guide treatment decisions.	**2C**
ICGN 7.2	We recommend that mild disease is managed with RAAS only and clinical response is monitored.	**1C**
ICGN 7.3	We recommend that CYP with C3G or IC-MPGN that is categorised as moderate or severe are treated with immunosuppressive treatment using the following as first line treatment; • oral prednisone • oral mycophenolate mofetil.	**1C**
ICGN 7.4	We suggest considering the use of an additional immunosuppressive agent, such as rituximab if any of the following apply; an auto-antibody is suspected to be contributing to disease activity for patients with persistent disease activity, concerns about high-risk of disease progression, or inadequate response to initial therapy after 3-6 months.	**2C**
ICGN 7.5	We suggest consideration of emerging complement inhibitors, recruitment to clinical trials, off-label treatments available for adults, or the compassionate use of agents under evaluation, in children who have failed to achieve adequate response.	**2D**

Rationale

The management of these conditions in children and young people are similar to adults, and relatively consistent in the literature [5]. Mild patients are managed for proteinuria only with progression to immunosuppression if more significant clinical features [110]. Observational data and international guidance report that MMF together with corticosteroids decrease progression to kidney failure compared to other immunosuppressives [5,100–102,106,108,109,112]. Beyond MMF, treatment options are not clear therefore use of immunosuppressive agents used for other subtypes of IM-GD are reflected in real world evidence [100]. There remain unmet needs for this condition with clinical remission achieved in around 60% [104] and patients can progress to CKD despite broad spectrum immunosuppression [103]. There is some evidence to support complement pathway inhibition [104] and high quality clinical trials evaluating more specific treatments using complement pathway inhibition are underway [153]. These should provide evidence to support future updates. When considering emerging therapies or for the management of atypical cases, we suggest discussion with the National Renal Complement Therapies Centre (https://www.atypicalhus.co.uk).

GN subtype 8: Post infectious glomerulonephritis (PIGN)

Definitions

To align terminology, we suggest that the following definitions for PIGN are used. Definitions are taken from the KDIGO guidelines with minor modifications by the GDG for standard UK practice [5]. For the purposes of UK practice the recommendations are focused on post streptococcal as the infectious cause of glomerulonephritis however the GDG acknowledge the many other infections that may act as triggers and are especially relevant in other global settings.

Diagnosis	
a	A diagnosis of post infectious GN (PIGN) can be made when there is evidence of nephritis that is assumed to be secondary to immune mediated glomerular injury due to the host response to streptococcal infection and after the exclusion of other causes.
b	Post infectious GN should be suspected in the setting of acute nephritis with a recent pharyngitis or cellulitis that has occurred within the past 2 weeks.
c	If there is no history of pharyngitis or cellulitis, and post infectious nephritis is the likely diagnosis, an alternative source of infection should be considered (other bacterial, viral, fungal, protozoal, and helminthic infections).
d	A kidney biopsy is not recommended to diagnose PIGN however it should be considered under the following circumstances: 1. Progressive or rapid decline in kidney function • Severe (nephrotic state (proteinuria, oedema, low serum albumin) or eGFR 30-60 ml/min/m^2) or moderate features (persisting proteinuria UPCR >100mg/mmol, without nephrotic state or eGFR 60-90 ml/min/m^2) that demonstrates worsening or fails to improve during the acute phase (<3 months from diagnosis). 2. Normal serum complement C3 levels throughout the disease course or a failure of the complement C3 levels to recover at 3 months after the initial diagnosis. 3. Positive autoantibodies, ANA, dsDNA, anti-GBM or ANCA. 4. Concerns regarding other diagnoses, for example: • Extra-renal manifestations of systemic disease
e	Persistent microscopic haematuria is common in PIGN and this may persist for up to 2 years. If this is an isolated finding it is generally not considered an indication to perform a kidney biopsy.

Management of post infectious GN

Number	RECOMMENDATION	Grade
PIGN 8.1	We recommend conservative treatment in most cases of acute PIGN which includes the management of fluid overload, hypertension, low salt diet, and electrolyte imbalances.	**1C**
PIGN 8.2	We do not recommend routine use of immunosuppression in all CYP with PIGN.	**1C**
PIGN 8.3	We suggest that children with persisting or worsening nephritis together with histological features of disease activity may warrant the use of immunosuppression.	**2C**
PIGN 8.4	We suggest the use of corticosteroids, either intravenous or oral depending on the clinical situation, as a first line treatment in children who are deemed appropriate for immunosuppression.	**2C**
PIGN 8.5	We recommend that children with a rapidly deteriorating kidney function should be treated as RPGN.	**1C**

Rationale

The GDG decided to include the management of post infectious IM-GD to be focused on post streptococcal disease as the most common cause in this country. Conservative management was universally consistent in the GDG, literature, and guidelines [5,113]. Rapidly worsening cases justify treatment with corticosteroids as first line treatment [5]. The majority of patients will have a good outcome (>70%) [115]. The diagnosis and management of shunt nephritis, endocarditis related, IgA dominant infection related and viral infection related (including HepB, Hep C, HIV, Schistosomiasis, filariasis, and malaria) were felt to be beyond the scope of this guideline.

Research and audit

Summary of clinical research recommendations

The following 12 items were highlighted as research priority areas during the harmonisation process and it is likely that further priorities will evolve following implementation.

1. The incidence and impact of adrenal insufficiency in children and young people managed with high dose corticosteroids.
2. The use of alternate day compared to single day dosing of corticosteroids in IM-GD.
3. The use of B cell depletion or two immunosuppressive agents during the induction phase or first year of treatment for patients with idiopathic nephrotic syndrome at risk of prolonged or complex disease.
4. Detailed and routine data collection of the side effects of drugs used to manage IM-GD.
5. The longer-term health impact of B-cell depletion on CYP with IM-GD.
6. Role of anti-nephrin antibodies in idiopathic nephrotic syndrome and their role in personalised treatment approaches.
7. The role of broad spectrum and specific immunosuppressive therapies in each of the subtypes of IM-GD.
8. The safe and effective use of SGLT2i in IM-GD in children.
9. The optimal blood pressure targets and long term cardiovascular risk for CYP with IM-GD.
10. Improving adherence through the use of longer acting immunosuppressive treatments for IM-GD.
11. The role of therapeutic drug monitoring targets and clinical response in CYP with IM-GD.
12. The risk-stratification of patients with IM-GD based on individual patient baseline characteristics (including ethnicity, genotype risk), features of early nephritis, response to immunosuppressive treatment and novel biomarker discovery.

Scientific priorities for translational research in childhood IM-GD

This guideline also presents an opportunity to highlight areas where further scientific research is critically needed. Understanding the immunopathology of IM-GD and developing predictive tools for treatment response will improve outcomes and enable precision therapy. These efforts will require collaboration across disciplines including nephrology, immunology, multi-omics and data science. We identify the following scientific priorities and cite recent advances aligned with these goals:

Genetic susceptibility: HLA and non-HLA variants contribute to disease risk in IM-GD [154–156]. Further UK-based genomic studies are needed to identify risk alleles, inform screening, develop polygenic risk tools for early stratification and prioritise drug targets. These efforts must include ethnically diverse cohorts to ensure findings are representative of the UK paediatric population and to address disparities in disease outcomes.

Immune signatures and biomarkers: Immune phenotyping, T and B cell clonotype profiling and analysis of proteins from blood and urine may help predict treatment response and disease course [157,158]. Longitudinal sampling enables tracking of immune dynamics over time, with microsampled or dried urine offering a non-invasive scalable option [159,160]. Unbiased approaches such as single-cell transcriptomics and proteomics can uncover disease mechanisms and novel biomarkers linked to disease activity and relapse [161,162]. The oral and gut microbiome may also modulate immune activity and offers potential as a biomarker or therapeutic target [163]. Embedding these tools into trials will support a move towards more personalised approaches to immunosuppression.

Tissue molecular profiling: Techniques such as spatial transcriptomics, spatial proteomics and multiplex imaging enable molecular analysis of kidney biopsies in IM-GD at subcellular resolution [164,165]. These approaches can uncover pathways driving inflammation, track changes in cell states [166], and infer cell-cell signalling networks within diseased glomerular and interstitial compartments [167]. Advances in data integration and intuitive visualisation tools have made

this technology increasingly accessible [168,169]. Protein-based platforms enable deep and iterative immunophenotyping from a single biopsy [170]. Profiling can be performed on archived tissue or in parallel using biobanking within clinical trials.

Improved animal models to test novel therapeutics: Traditional chemically induced mouse models of IM-GD do not reflect the complexity, chronicity, relapsing or heterogeneity of paediatric inflammatory disease. Genetically engineered and humanised mouse models now offer improved biological relevance, enabling the study of disease mechanisms, immune regulation and therapeutic response. Alternative models such as zebrafish are also being explored for their ease of genetic manipulation and scalability for in vivo drug screening [171]. Such models can also be compared directly with human tissue datasets to assess translational validity [172–174]. These systems provide a platform for preclinical testing of targeted therapies, including gene- and cell-based approaches, before advancing to trials in children [175,176].

Patient-derived *in vitro* models: Emerging organoid technologies, complex cell co-culture models [177–180] and glomerulus-on-a-chip platforms [181] replicate key features of the glomerular filtration barrier and offer improved systems to study IM-GD. Urine-derived cells provide a non-invasive source of cells from children [182,183], and can be used to generate kidney organoids for disease modelling and drug testing [184]. These platforms are particularly valuable in rare, refractory, or biopsy-limited cases, and support the development of precision therapies tailored to individual patients.

AI-Driven Data Integration and Target Discovery: Artificial intelligence tools enable the integration of complex molecular and spatial data to identify disease pathways and predict cellular responses to specific therapies [185,186]. These virtual experiments help prioritise potential drug targets before moving to laboratory or clinical testing [187]. With the support of high-quality reference datasets [188], these approaches offer a powerful route to accelerate target discovery and personalised treatment for IM-GD in children.

Summary of audit recommendations

- The recommended consensus statements within this document can be used to form the standard criteria for conducting audit to ensure compliance and guide improvements.

Lay summary

The glomerular disease guideline is a document to support decisions about treatments in children and young people. They are divided into the different types of glomerular disease. It focuses on medicines that calm the immune system and only on the first year after getting a diagnosis. The guidelines say which medicines could be considered if they start with 'we suggest' and say which medicines most doctors would consider using if they start with 'we recommend'. The guidelines should help children and young people get similar treatments where ever they live and they will be updated to incorporate new treatments as they become available.

Dissemination

The group discussed the importance of implementation and how to disseminate and publicise the findings. Ideas for implementation included through specialist networks including;

- Regional study days, network meetings.
- Sharing the document with the special interest in paediatric nephrology (SPIN) community using established connections and regional meetings.
- Sharing the lay summary with relevant patient support groups.
- Submitting the work to the Royal College of Paediatrics and Child Health (RCPCH) and/or UK Kidney Week (UKKW) conference.
- Adding hyperlinks to the Infokid portal.

Sources of further patient information

1. https://www.infokid.org.uk/
2. http://www.alportuk.org/
3. https://nstrust.co.uk/
4. https://www.medicinesforchildren.org.uk/

Appendix 1: A brief overview of key immunosuppressive medications for IM-GD in children

Corticosteroids

Intravenous steroid

Maximum routine dose of IV methylprednisolone 500mg for 3 days (aligned with adult practice). Deviation may be necessary for atypical or severe cases.

Oral steroid suggested tapering after induction treatment

Maximum routine single oral dose 60mg once a day in the morning. Suggested taper period over 3 or 6 months using the example regimens as below.

Taper period: 3 months	Select starting dose of oral prednisolone (mg/day)				
Weeks	**40**	**35**	**30**	**25**	**20**
1-4	40	35	25	25	20
5-6	30	25	20	20	15
7-8	20	15	15	15	10
9-12	10	10	10	10	5
11-12	5	5	5	5	2.5

Taper period: 6 months	Select starting dose of oral prednisolone (mg/day)				
Weeks	**40**	**35**	**30**	**25**	**20**
1-4	40	35	30	25	20
5-8	30	25	25	20	15
9-12	20	20	20	15	10
13-16	15	15	15	10	7.5
17-20	10	10	10	5	5
21-24	5	5	5	2.5	2.5

B cell depletion

Rituximab

NHS England guidance for the use of rituximab in idiopathic childhood nephrotic syndrome suggests the use of two high doses of rituximab (750mg/m² (max 1g) per dose) however it was acknowledged that several local protocols have begun to incorporate a single half dose of rituximab and this is standard clinical practice in some centres supported by case series to support efficacy [189]. It was therefore agreed by the GDG that it may be appropriate to use either a lower single dose, or standard regimen, in uncomplicated cases of IM-GD. The standard dose is recommended for complex or non responding idiopathic NS and other forms of more severe glomerulonephritis. Detailed administration, monitoring guidance and long term safety profile considerations of rituximab are beyond the scope of this document and local or national protocols should be used.

- **Standard dosing (NHS England),**

750mg/m² (max 1g to nearest 50mg) D1 & D15 (minimum of 6 months time period between subsequent courses)

- **Single dosing (deemed more suitable for less complex iNS eg: SSNS, SDNS)**

Single dose of 375mg/m² (max 500mg to nearest 50mg) usual minimum interval 6 months time period between subsequent doses (repeat dose at D15 or if there has been inadequate clinical and/or B cell response)

Cyclophosphamide (CYC)

This agent is being less commonly used since the emergence of alternative agents that may have a more favourable long term side effect profile. The risks of irreversible adverse side effects, such as later infertility, are seen with increasing cumulative dose and therefore minimising the dose exposure should be an active consideration.

Oral - preferred route as a disease modifying agent in idiopathic nephrotic syndrome; please refer to local protocols for more detailed administration instructions

Oral cyclophosphamide is taken at a dose of 2-3mg/kg once daily for an 8 week course. Weekly full blood count monitoring is required with dose adjustment or stopping if abnormalities occur. Patients should be educated on the long term side effects which include a risk of infertility seen with high cumulative doses.

Intravenous – preferred route for rapidly progressive glomerulonephritis; please refer to local protocols for more detailed administration instructions

- CYCLOPS study [190]

500mg/m² (max 1.2g) week 0 then 750mg/m² (max 1.2g) week 2 and 4 then 3 weekly thereafter for the next 3-6 doses (max 6-10 doses); provides up to 9 doses at max 10.8g cumulative total dose.

- NIH-IV CYC [191]

500mg/m² (max 1g) week 0 then 750mg/m² (max 1g) week 2 then monthly 1g/m² monthly (max 1g) for 5 further doses; provides 7 doses at max 7g cumulative total dose.

- EURO-LUPUS 2010 study [192]

500mg/m² (max 500mg) every 2 weeks for 3 months (max dose 1g/monthly); provides 6 doses at max 3g cumulative total dose.

Patients with Renal Impairment

CYC is excreted primarily by the kidneys. Patients with renal impairment may be exposed to higher plasma levels of CYC and its metabolites resulting in toxicity due to reduced renal excretion and therefore it's administration should be discussed with a specialist pharmacist.

Recommended dosage adjustments for cyclophosphamide in patients with renal impairment GFR (mL/min)	
20-50	Dose as in normal renal function
10-20	75 – 100% of normal dose depending on clinical indication
<10	50-100% of normal dose depending on clinical indication

Recommended dosage adjustments for cyclophosphamide in patients undergoing renal replacement therapies	
Type of renal replacement therapy	**Dose**
Continuous (CAPD)	Dialysed. Dose as in GFR <10mL/min. Following dose, do not perform CAPD exchange for 12 hours
HD	Dialysed. Dose as in GFR <10mL/min. Dose at minimum of 12 hours before HD session
HDF/High flux	Dialysed. Dose as in GFR <10mL/min. Dose at minimum of 12 hours before HDF session
CAV/VVHD	Dialysed. Dose as in GFR = 10-20mL/min

Calcineurin inhibitors

- **Tacrolimus**

This is dosed according to the British National Formulary for children (BNFc) with a starting dose of 100 – 150 micrograms/kg/day (max 5mg) in 2 divided doses taken 12 hours apart. Once daily formulations are also available. It is suggested to start at a lower dose then increase guided by clinical response and therapeutic levels. Due to the different formulations available it is advised to prescribe tacrolimus by the brand name, e.g., Modigraf granules/ Adoport capsules. The treatment relies on therapeutic drug monitoring using a 12 hour trough level (target range for most IM-GD is around 4-7 µg/L) weekly until in range then monthly to quarterly. It requires monitoring of blood pressure, full blood count, renal function, magnesium, liver function tests, and fasting blood glucose, and ideally lipids approximately every 3 months.

- **Ciclosporin**

Due to alternative agents being available, ciclosporin is now less commonly used and the GDG felt that colleagues should be encouraged to prescribe the newer agents because they have a more favourable side effect profile. Please refer to local guidance or the BNFc to guide the use of this treatment.

Mycophenolate mofetil (MMF)

Oral mycophenolate mofetil is taken twice a day with a daily starting dose of 300mg/m^2 that is usually taken for 1-2 weeks then the dose is increased to 600mg/m^2 per day from day 8 if the treatment is tolerated. If the gastrointerestinal side effects make the treatment intolerant, consider the use of Mycophenolic acid (360mg of mycophenolic acid is equivalent to 500mg of MMF). The treatment needs monitoring of full blood count and liver function tests that should be 1-2 weekly after starting then a month later and eventually every 3-4 months whilst on treatment. Awareness should be made that this is a teratogenic agent and therefore the importance of avoiding pregnancy during treatment for patients of child-bearing potential.

Levamisole

The dose of levamisole is 2–2.5 mg/kg given on alternate days (with maximum dose of 150 mg). Due to the potential risk of new ANCA antibodies associated with long term use, consider measuring ANCA titres every 6–12 months. Patients need to be seen every 3-4 months for monitoring clinically and measuring full blood count and hepatic transaminases. The drug may increase the serum creatinine through it's effect on tubular secretion.

Appendix 2: Proteinuria measurements conversion table

(adapted from KDIGO (5))

	Conventional unit	Conversion factor	SI unit
Protein-creatinine ratio	mg/g	0.113	mg/mmol

Conventional unit x conversion factor = SI unit.

Measure	Normal to mildly increased	Moderately increased	Severely increased
ACR mg/mmol mg/g	 <3 <30	 3-30 30-300	 >30 >300
PCR (mg/mmol) (mg/g)	 <15 <150	 15-50 150-500	 >50 >500

For pragmatic reasons the relationships among measurement methods within a category are not exact. Creatinine excretion varies with age, sex, race and diet and the reagent strips may depend on urine concentration. ACR, albumin-to-creatinine ratio; PCR, protein-creatinine ratio.

Appendix 3: Definitions used for grading evidence

The outline for the methodology is available in the UKKA Clinical Practice Guideline Development manual, January 2022.

Grade	Implication
Level 1 'We recommend'	Most patients should receive the recommended course of action
Level 2 'We suggest'	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with their values and preferences.

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect.

Appendix 4: Universal kidney care for children and young people with kidney disease

Proteinuria management

Definition:

Proteinuria should be quantified using the urine protein to creatinine ratio (UPCR) or urine albumin to creatinine ratio (UACR) collected from a first morning sample and measured on 3 different occasions for the initial confirmation to avoid confounding factors such as infection or menstruation.

Indications for treatment:

In IM-GD, renin angiotensin aldosterone inhibitor (RAASi) treatment (either Angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)) should be started in patients with persistent proteinuria who have not demonstrated complete response after at least 4 weeks of immunosuppressive treatment. Persisting proteinuria should be defined according to KDIGO thresholds [5].

Caution should be made when starting treatment in children and young people who are (i) in a nephrotic state where there may be concerns about hypovolaemia and/or (ii) have a rapidly changing or unstable kidney function. Disease specific indications may warrant earlier indications for example beyond IM-GD in children with Alport syndrome (AS) where boys with X-linked AS (XLAS) or children of either sex with autosomal recessive AS benefit from consideration of starting RAASi treatment anytime after the age of 2 years as a disease modifying treatment [193]. This is independent of the threshold for proteinuria and preliminary evidence suggests it may extend the kidney lifespan by >10 years. This should be reviewed on an individual basis after an informed discussion with the patient and family. For girls with XLAS or any children with heterozygous vairiants in *COL4A3* or *COL4A4* the treatment of RAASi should be commenced when there is evidence of persistent proteinuria.

Treatment:

ACEi or ARB should be started using an age-appropriate dose according to the BNFc up to the maximum dose tolerated. The goal is to achieve optimal RAASi treatment as tolerated to minimise proteinuria. In patients with clinical signs of oedema the mangement of proteinuria should include fluid and salt restriction as appropriate. Some children and young people may require diuretics and intravenous albumin infusions. The detailed use of these agents is beyond the scope of this document.

Monitoring:

In children and young people starting RAASi the kidney function should be checked within 14 days of commencing treatment. Combined use of ACEi and ARB is not recommneded due to safety concerns related to hyperkalaemia and uncertain additional benefit. A rise in serum creatinine by up to 15-20% may be seen following commencement of RAASi. The ACEi/ARB should be stopped if the kidney function continues to worsen and/or there is refractory hyperkalaemia (potassium concentration >5.5 mmol/L). Patients should be informed about the adverse event profile of these agents and counselled to withhold the use of ACEi or ARB treatment when there may be a risk of volume depletion (for example intercurrent diarrhoea and vomiting). They should also be aware of the risks of teratogenicity in pubertal females who may be sexually active.

Hypertension management

For the management of hypertension in children please refer to either the European Society of Hypertension Pediatric Hypertension Guidelines or the American Academy of Pediatrics' clinical practice guideline for screening and management of high blood pressure in children and adolescents [194,195]. These guidelines suggest that the first line treatment for hypertension in IM-GD should be either an ACEi or ARB if not contraindicated and the target systolic blood pressure should be <50th centile for age, sex and height [196]. Confirmation of hypertension or a satisfactory BP

target should ideally be obtained using a 24-hour ambulatory BP monitor if appropriate and the target systolic BP should be no more than 120 mmHg as this is the recommended maximum adult target.

Hyperlipidaemia management

Definition:

A random blood lipid profile should be measured in children and young people with IM-GD especially in patients with nephrotic-range proteinuria >3 months duration.

Indications for treatment:

Treatment should be considered in cases of persistent hyperlipidaemia defined as a LDL cholesterol concentration of >3.4 mmol/L [(5)].

Treatment:

Lifestyle modifications should be considered as the first line intervention followed by consideration of the use of a statin as clinically appropriate. These decisions should be made using informed shared decision-making, as specific data relating to the benefits of reducing hyperlipidaemia in CYP are lacking.

Monitoring:

The effects of LDL-C lowering medication should be assessed by measurement of the lipid profile and appropriate safety indicators measured approximately 4-12 weeks after statin initiation and/or dose adjustment and subsequently every 3-12 months thereafter depending on the clinical situation. The goal of treatment is aligned with that in adult patients to improve or stabilise the LDL-C levels to reduce the long term adverse cardiovascular risks.

Thromboembolic management

Definition:

A thromboembolic (TE) event (eg: venous thrombosis, arterial thrombosis, pulmonary embolism) is one occurring in a CYP with kidney disease particularly in the context of a nephrotic state.

Indications for treatment:

Full anticoagulation is indicated if there is a confirmed TE event after evaluation of the individual's bleeding risk. Prophylactic anticoagulation is indicated if the patient is in a nephrotic state and the risk of a TE exceeds the risks of using anticoagulation. Consideration should be given to evaluation of anti-phospholipid antibodies and potential anti-phospholipid syndrome especially in certain IM-GD subgroups such as SLE.

Factors associated with increased TE risk include [(5)];

- Serum albumin <20-25g/L

AND

- Proteinuria >10g/day (UPCR >1000 mg/mmol)
- BMI >35 kg/m^2
- Genetic risk for thromboembolic events
- Recent major high-risk surgery (orthopaedic or abdominal)
- Prolonged immobilisation
- Central venous access

Contraindications to consider prior to commencing anticoagulation include;

- Patient preference
- Medication adherence
- Bleeding diathesis
- Central nervous system lesions prone to haemorrhage

- Genetic mutations influencing warfarin metabolism
- Prior gastrointestinal bleeds
- Risk of falls.

Treatment:
Treatment should be according to local recommended practices for full or prophylactic anticoagulation. This may include low molecular weight heparin, warfarin or direct oral anticoagulants.

Prophylaxis of infection

Definition:
Preventative measures used to avoid infections in CYP with IM-GD.

Indications for treatment:
Prophylactic treatment may be considered in CYP who are on immunosuppression and/or patients who are clinically nephrotic and/or who have CKD.

Treatment:
Patients should be vaccinated according to the Public Health England Green Book recommendations [197] with caution being made in acknowledging that live vaccines are contraindicated in patients receiving (or having recently received) immunosuppression and patients may need additional doses to achieve full protection. In clinically appropriate patients there should be screening for tuberculosis (TB), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and syphilis. Contact with chicken pox or measles whilst on immunosuppression will require specific evaluation of protective antibodies according to local protocols.

Prophylactic use of anti-infective treatment such as antibiotics, antiviral or antifungal agents are not recommended routinely. This includes the use of prophylactic penicillin for relapses of nephrotic syndrome. Antibiotics such as trimethoprim-sulfamethoxazole (TMP-SMX; Co-trimoxazole), or an alternative agent according to local protocols, anti-viral or anti-fungal agents should be considered in patients who are receiving regular high dose intravenous treatments, plasma exchange or multiple (≥ 3) immunosuppressive agents when the clinical risk of infection is deemed to be high. This is of relevance to patients with ANCA, anti-GBM and LN where induction therapy typically requires multiple immunosuppressive agents. Patients with evidence of active infection should be treated and managed in partnership with other specialists as needed. Episodes of previous active infections may be an indication to support the use of future prophylactic agents.

Vitamin D

Vitamin D levels should be routinely measured, and any deficiency or insufficiency should be managed according to local and national recommendations in patients unless contraindicated.

Appendix 5: Clinical guideline group

Name	Centre	Title	Project Role
Louise Oni	University College London, University of Liverpool	Clinical Associate Professor Paediatric Nephrologist	Project lead
Daniyal Jafree	Addenbrookes Hospital, Cambridge	Post-doctoral researcher and junior doctor	Expert trainee specialist
Wen Ding	Bristol Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Sally Johnson	Newcastle Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Amanda Newnham	Leeds Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Rona Smith	University of Cambridge	Consultant Nephrologist	Expert adult vasculitis specialist
Evgenia Preka	Paris Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Matko Marlais	Great Ormond Street Children's Hospital	Consultant Paediatric Nephrologist	Guideline methodology specialist & expert specialist
Mohan Shenoy	Royal Manchester Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Ben Reynolds	Glasgow Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Matthew Harmer	Southampton Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Samantha Williamson	Leeds Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Ramnath Iyer	Birmingham Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Felicity Beal	Birmingham Children's Hospital	Paediatric Nephrology Trainee	Expert specialist
Martin Christian	Nottingham Children's Hospital	Consultant Paediatric Nephrologist	Guideline methodology specialist & expert specialist
Angela Lamb	Glasgow Children's Hospital	Paediatric Renal Pharmacist	Expert pharmacy specialist
Pallavi Prasad	Alder Hey Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Stephen Marks	Great Ormond Street Children's Hospital	Professor of Paediatric Nephrology	Expert specialist
Mordi Muorah	Birmingham Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Emma O'Hagan	Belfast Children's Hospital	Consultant Paediatric Nephrologist	Expert specialist
Hazel Webb	Great Ormond Street Children's Hospital	Advanced Paediatric Nurse Practitioner	Expert nursing specialist
Ania Koziell	Kings University, London	Senior Lecturer in Paediatric Nephrology	Expert specialist
Elin Davies	University of Liverpool	Nephrology clinical fellow	Expert trainee specialist
Roger Deering	Leeds Children's Hospital, Leeds	Consultant Paediatric Nephrologist	Expert specialist
Caroline Platt	Bristol Children's Hospital, Bristol	Consultant Paediatric Nephrologist	Expert specialist
Emma Rigby	Evelina Children's Hospital, London	Specialist paediatric nurse	Expert nursing specialist

Hannah Cottis	Royal Devon Hospital, Devon	Consultant Paediatrician with an interest in Paediatric Nephrology	Expert specialist
Alan Salama	University college London, London	Professor of Nephrology	Expert adult vasculitis specialist
Paul Brogan	University college London, London	Professor of vasculitis	Expert vasculitis specialist
Francesca De Zan	Cardiff Children's Hospital, Wales	Consultant Paediatric Nephrologist	Expert specialist
Eve Smith	University of Glasgow, Glasgow	Consultant Paediatric Rheumatologist	Expert rheumatology specialist
Sarah Roy	Evelina Children's Hospital, London	Consultant Paediatric Nephrologist	Expert specialist
Colin Higgins	Evelina Children's Hospital, London	Consultant Paediatric Nephrologist	Expert specialist
Moin Saleem	University of Bristol	Consultant Paediatric Nephrologist	Expert specialist
William Simmons	Alder Hey Children's Hospital, Liverpool	Consultant Paediatric Pathologist	Expert pathology specialist
Aisling McMahon	n/a	Kidney Research UK	Charity partner
Wendy Cook	n/a	Nephrotic syndrome Trust	Charity partner
Kathryn Croker	n/a	Patient	Patient with lived experience
Kelly Vernon	University of Liverpool	UK Kidney Ecosystem	Administrator

Appendix 6: List of stakeholders

LifeArc-Kidney Research UK Centre for Rare Kidney Diseases
Kidney Care UK, including kidney Patient Involvement Network KPIN
Kidney Research UK
GenR - YPAG groups
Nephrotic Syndrome Trust
Kidney kids
UKIVAS
MPGN/DDD support group
British association of paediatric nephrology (BAPN)
Lupus UK
NHSBT/plasmapheresis
British society rheumatology (BSR)
RCPCH
Vasculitis UK
Royal college pathologists (RCPath)
Paediatric Nephrology Nurses Group (PNNG)
Neonatal and Paediatric Pharmacy Group (NPPG)
PMNG dieticians
Psychology
Child physio society
Royal College of Physicians (RCP)
Royal College of General Practitioners (RCPGP)

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