The management of complications associated with IgA vasculitis (Henoch Schönlein Purpura) in children and young people

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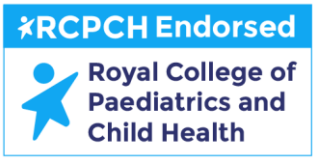
Endorsements

The National Institute for Health and Care Excellence (NICE) has accredited the process used by The UK Kidney Association to produce its Clinical Practice Guidelines. Accreditation is valid until December 2023. More information on accreditation can be viewed at www.nice.org.uk/accreditation



Method used to arrive at a recommendation/Grading the evidence

The guideline was developed under the endorsement of lead organisations (Appendix 1) and followed developmental stages including, forming the multi-speciality IgAV guideline development group (termed the UK IgAV GDG), developing and agreeing the scope, conducting systematic evidence-based literature reviews using pre-defined methodology and working in partnership with relevant stakeholders during a period of formal external consultation (stakeholders listed in Appendix 2). Clinical recommendations were derived from the topic areas and key questions that were identified by the UK IgAV GDG. The UK IgAV GDG defined the population, intervention, comparator and outcome (termed 'PICO') to identify eligible evidence (Appendix 3). Search concepts were used to identify the relevant population and the disease in question (Appendix 4)[1]. The process of screening and identifying relevant articles was performed according to pre-defined eligibility criteria (Appendix 5) and aligned with the Cochrane Handbook for Systematic reviews of interventions, the RCPCH guideline process manual ('Setting Standards for the Development of Clinical Guidelines in Paediatrics and Child Health, 2020')[2], the UK Kidney Association clinical practice guideline development manual, the 'Appraisals of Guidelines for research and evaluation II' instrument[3] and supported by a knowledge and exchange librarian[4,5]. The identified articles were summarised and presented to the UK IgAV GDG during the development process. The papers were critically appraised for their methodological quality using the Critical Appraisal Skills Programme (CASP) checklists[6]. In cases of uncertainty regarding inclusion of studies, discussion occurred between the two members screening the articles. There were no cases of persisting uncertainty or disagreement where a third member of the UK IgAV GDG was required to assist in decision making. Searching of reference lists was included. No searching of grey literature and no hand searching of conference proceedings or journals took place. Three bibliographic databases were used to identify potential studies (appendix 6) and aligned with those recommended in the Cochrane Handbook for Systematic reviews of interventions[4]. All searches were conducted on 11th March 2022 and were used for a parallel document 'Clinical practice guideline: The initial management of IgA vasculitis (Henoch Schönlein Purpura) in children and young people'. The key questions were split into topic areas (Appendix 7) and written to facilitate the systematic review (Appendix 8). The screening process to identify and select the articles relevant for this guideline is illustrated in the PRISMA diagram (Appendix 9). The literature review yielded 82 studies for inclusion. The members of the working group were presented with evidence summaries of the literature relevant to each topic area. The working group used the synthesised evidence to form and grade the recommendations using the modified GRADE terminology to reflect the strength of the recommendation and the quality of the supporting evidence. The strength of the recommendation was split into two tiers, grade 1 is a strong recommendation where the benefits outweigh the risks for most patients, and grade 2 is a weaker

recommendation where the risks and benefits are more balanced or remain uncertain. The strong (grade 1) recommendations use the wording 'we recommend…' whilst the weaker recommendations (grade 2) will use the wording 'we suggest…'. The quality of evidence is graded using alphabetical domains. Grade A evidence refers to high-quality evidence that is derived from consistent results from randomised controlled trials, or overwhelming evidence of other forms. Grade B is moderate quality evidence from clinical trials that may have some flaws or from other study designs with some strength. Grade C evidence is low-quality evidence from observational studies or trials with serious limitations. Grade D evidence is based on case studies alone or expert opinion. The quality of the evidence could be revised by the UK IgAV GDG following discussion after review of the synthesised literature.

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.

Contents

Executive summary

IgA vasculitis (IgAV) in children and young people is a common condition managed by paediatricians across the UK. Despite its frequent presentation and recognised complications, it has been significantly neglected in the research field. Advances in improving outcomes are yet to be seen and each year children continue to experience complications such as developing acute intussusception, some run an unrecognised atypical disease course and/or other children progress to life changing kidney failure. Aligning clinical care for such complications, through the development of nationally agreed best practice recommendations, will aim to improve equity in how children and young people are managed, increase awareness and enhance communication with parents whilst setting a platform for research studies.

We offer evidence-based practice guidelines covering the appropriate management of key complications associated with IgAV in children and young people accompanied by research recommendations and audit measures. We aim to align access to care and standardise the management of children who may experience such complications.

At the time of writing there remains very limited research in this field and the dissemination of these clinical practice recommendations will hopefully act as a catalyst for further studies, including much needed, well conducted clinical trials. The results of which will then strength the literature to inform evidence-based updates of these present recommendations over time.

I am enormously grateful to all of the multi-professional and lay members of the guideline development group for fully supporting this venture, providing encouragement and motivation, and for their dedicated time and effort in developing this guideline to completion.

Dr. Louise Oni

Chair of the UK IgAV Clinical Practice Guideline Working Group

Summary of recommendations

RECOMMENDATIONS FOR USE IN CHILDREN AND YOUNG PEOPLE UNDER THE AGE OF 18 YEARS WITH IGA VASCULITIS (HENOCH SCHONLEIN PURPURA)		
Number	**RECOMMENDATION**	***Grade***
Section 1: CLINICALLY SUSPECTED IGAV NEPHRITIS		
1.1	*We recommend that a kidney biopsy is undertaken to confirm a diagnosis of severe nephritis in children and young people with IgAV, where the definition of severe nephritis includes persisting severe proteinuria (UP: UC >250 mg/mmol for up to 4 weeks), persisting moderate proteinuria (UP: UC 100–250 mg/mmol for 3 months), AKI stage 1 or greater, or nephrotic syndrome (see Section 2.2).*	1C
Section 2: MANAGEMENT OF HISTOLOGICALLY PROVEN IGAV NEPHRITIS		
2.1	*We recommend that the kidney histology should be classified using the ISKDC classification criteria for children and young people with IgAV.*	1C
2.2	*We recommend that a combination of clinical features and the histological ISKDC classification should guide decisions about treatment choices to offer children and young people with IgAV nephritis.* *The following are clinical indications;* • *Persisting severe proteinuria (UP: UC >250 mg/mmol for up to 4 weeks)* • *Persisting moderate proteinuria (UP: UC 100–250 mg/mmol for up to 3 months)* • *AKI stage 1 or greater (serum creatinine >1.5 × previous baseline (if known) or >1.5 × upper limit of normal for age)* • *Nephrotic syndrome (clinical signs of oedema, serum albumin <30 g/L, severe proteinuria UP: UC >250 mg/mmol).* *The following are histological indications;* • *Class II ISKDC classification with persisting clinical indications* • *Class III or above ISKDC classification with clinical indications*	1C
2.3	*We suggest that the management of biopsy proven IgAV nephritis should be directed by, or in conjunction with, a paediatric nephrologist*	2B

2.4	*We <u>suggest</u> using the following disease-modifying drugs, or a combination of corticosteroids together with a disease-modifying drug, depending on the clinical and histological features in children and young people with biopsy proven IgAV nephritis.* *Corticosteroids;* • *Prednisolone 1-2mg/kg/day (maximum 60mg/day) for 2-4 weeks then weaned according to clinical response* • *In severe nephritis with adverse clinical and histological features (impaired kidney function, nephrotic syndrome or crescentic features), or where oral absorption is potentially compromised, intravenous methylprednisolone 10–30 mg/kg (maximum of 1 g/day) once daily for three consecutive days may be used followed by the use of oral prednisolone.* *Disease-modifying drug (listed in alphabetical order);* • *Azathioprine* • *Calcineurin inhibitors (ciclosporin or tacrolimus)* • *Cyclophosphamide* • *Mycophenolate mofetil.* *Rapidly progressive glomerulonephritis is managed more aggressively with preference for intravenous treatment.*	2B
2.5	*We <u>suggest</u> that in cases of IgAV nephritis with persisting proteinuria (UP: UC >100 mg/mmol for 3 months or UP: UC >50mg/mmol for 6 months) the use of an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) should be considered as adjunctive or monotherapy under the guidance of a nephrologist, even if they haven't met the threshold for performing a kidney biopsy (section 1.1).*	2C
Section 3: MANAGEMENT OF ACUTE GI BLEEDING		
3.1	*We <u>suggest</u> that corticosteroids (prednisolone 1-2 mg/kg/day for 1-2 weeks) are considered for children and young people with IgAV within 3 days of onset of severe abdominal pain (defined as pain requiring hospital admission) or acute GI bleeding after appropriate clinical review and the exclusion of other causes including intussusception.*	2B
Section 4: MANAGEMENT OF SUSPECTED OR PROVEN INTUSSUSCEPTION		

4.1	*We recommend that specialist surgical and [/or] radiological advice is sought for children and young people with IgAV and abdominal symptoms suggestive of intussusception.*	1C
Section 5: MANAGEMENT OF SUSPECTED OR PROVEN TESTICULAR INVOLVEMENT		
5.1	*We suggest that testicular involvement (orchiditis) should be considered in boys with IgAV who develop painful scrotal oedema that is associated with palpable purpuric lesions.*	2D
5.2	*We suggest that treatment with corticosteroids (prednisolone 1-2 mg/kg/day for 1-2 weeks) should be considered in boys with IgAV who develop orchiditis after appropriate specialist advice such as a surgical opinion has been sought.*	2D
Section 6: MANAGEMENT OF CASES WITH ATYPICAL FEATURES		
6.1	*We suggest that a skin biopsy is undertaken in children and young people with IgAV who have an atypical purpuric/petechial rash or to exclude alternative diagnoses.*	2B
6.2	*We suggest that when a skin biopsy is performed the histological analysis should specifically include evaluation of IgA deposition using immunofluorescence (fresh specimen) or immunohistochemistry (fixed tissue).*	2C
Section 7: DEFINITION OF PERSISTING OR RECURRENT DISEASE		
7.1	*We suggest that children and young people with IgAV and a typical purpuric/petechial rash persisting for more than 1 month should be defined as having persisting disease.*	2B
7.2	*We suggest that children and young people with IgAV who present with a reappearance of the typical purpuric/petechial rash after a symptom-free period of greater than 1 month should be defined as having recurrent disease.*	2B
Section 8: LONG TERM FOLLOW UP IN IGAV		
8.1	*We recommend that children and young people with IgAV have follow up whilst there is evidence of nephritis and for at least 3 years if they have experienced biopsy proven nephritis.*	1C

Quick reference guide

Section 1: CLINICALLY SUSPECTED IGAV NEPHRITIS

- *We recommend that a kidney biopsy is undertaken to confirm severe nephritis.*

Section 2: MANAGEMENT OF HISTOLOGICALLY PROVEN IGAV NEPHRITIS

- *We recommend that the kidney histology is classified using ISKDC classification criteria.*
- *We recommend that a combination of clinical features and the histological ISKDC classification should guide treatment decisions.*
- *We suggest that biopsy proven IgAV nephritis should be managed by, or in conjunction, with a paediatric nephrologist.*
- *We suggest that IgAV nephritis should be managed under the guidance of a nephrologist and if immunosuppression is warranted, we suggest corticosteroids and/or a disease-modifying drugs, depending on the clinical and histological features.*
- *We suggest the use of an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) in persisting proteinuria (UP: UC >100 mg/mmol for 3 months or UP: UC >50mg/mmol for 6 months).*

Section 3: MANAGEMENT OF ACUTE GI BLEEDING

- *We suggest corticosteroids within 3 days of onset of severe abdominal pain or acute GI bleeding after exclusion of other causes including intussusception.*

Section 4: MANAGEMENT OF SUSPECTED OR PROVEN INTUSSUSCEPTION

- *We recommend that specialist surgical and [/or] radiological advice for abdominal symptoms suggestive of intussusception.*

Section 5: MANAGEMENT OF SUSPECTED OR PROVEN TESTICULAR INVOLVEMENT

- *We suggest that testicular involvement (orchiditis) should be considered in boys who develop painful scrotal oedema associated with palpable purpuric lesions.*
- *We suggest that treatment with corticosteroids should be considered in boys orchiditis after appropriate specialist advice such as a surgical opinion has been sought.*

Section 6: MANAGEMENT OF CASES WITH ATYPICAL FEATURES

- *We suggest a skin biopsy in atypical purpuric/petechial rash or to exclude alternative diagnoses.*
- *We suggest that the skin biopsy histological analysis should specifically include evaluation of IgA deposition using immunofluorescence (fresh specimen) or immunohistochemistry (fixed tissue).*

Section 7: DEFINITION OF PERSISTING OR RECURRENT DISEASE

- *We suggest that a typical purpuric/petechial rash persisting for more than 1 month should be defined as persisting disease.*
- *We suggest that a reappearance of the typical purpuric/petechial rash after a symptom-free period of greater than 1 month should be defined as recurrent disease.*

Section 8: LONG TERM FOLLOW UP IN IGAV

- *We recommend long term follow up if they have evidence of nephritis or for 3 years if they have experienced biopsy proven nephritis.*

List of abbreviations

ACEi	Angiotensin converting enzyme inhibitor
ACR	American College of Rheumatology
ARB	Angiotensin receptor blocker
AKI	Acute kidney injury
CASP	Critical Appraisal Skills Programme
CKD	Chronic Kidney Disease
FOB	Faecal Occult Blood
GDG	Guideline Development Group
CNS	Central nervous system
GI	Gastrointestinal tract
HSP	Henoch Schönlein Purpura
ICD	International Classification of Diseases
IgA	Immunoglobulin A
IgAV	Immunoglobulin A vasculitis
ISKDC	International study of Kidney Disease in Children
IVIG	Intravenous Immunoglobulin
LMWH	Low molecular weight heparin
MMF	Mycophenolate mofetil
MSK	Musculoskeletal
MRI	Magnetic Resonance Imaging
PICO	Population, intervention, control and outcome
PLEX	Plasma exchange
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised Controlled Trial
SHARE	Single Hub and Access point for paediatric Rheumatology in Europe
SQS	Semi quantitative score
UC	Urine creatinine
UP	Urine protein.
UP: UC	Urine protein:creatinine ratio

Glossary of terms

Term	Definition
Arthritis	Joint swelling and/or functional limitation of movement
Arthralgia	Joint pain
Arthropathy	Arthritis and/or arthralgia
CNS involvement	Cerebral vasculitis presenting as neurological symptoms and/or signs
GI bleeding	Haematochezia, melena, haematemesis and/or occult blood in the stool
GI involvement	GI vasculitis presenting as gastrointestinal symptoms
Haematemesis	Vomiting blood
Haematochezia	The passage of fresh blood often within or alongside stool
Intussusception	Prolapse of one part of intestine into the lumen of the adjoining part causes intestinal obstruction
Melena	Dark black, tarry stools
Nephritis	Kidney inflammation presenting with micro or macroscopic changes in the urine and/or kidney insufficiency
Occult blood	Blood present in the stools that isn't visible to the eye
Orchiditis	Scrotal and/or testicular involvement
Pulmonary haemorrhage	Pulmonary vasculitis presenting with acute bleeding from the respiratory tract
Purpura	A rash of red or purple discoloured spots on the skin that do not blanch on applying pressure
Severe GI involvement	Severe abdominal pain, protein losing enteropathy and/or GI bleeding
Severe GI pain	Bowel angina presenting as abdominal pain that requires hospital admission to assist with symptom management
Severe musculoskeletal involvement	Arthropathy that requires hospital admission to assist with symptom management
Severe skin involvement	Intense subcutaneous oedema, blistering skin and/or necrotic features
Significant nephritis	Heavy proteinuria (equivalent to >2 g/g or urine protein:creatinine ratio of >250mg/mmol), nephrotic syndrome (heavy proteinuria, hypoalbuminaemia <30g/L, oedema), nephritic syndrome (haematuria plus hypertension, impaired kidney function and/or oliguria) and/or kidney insufficiency.

Vasculitis	Inflammation of the blood vessels

Background

This guideline makes recommendations for the management of complications associated with the condition, Immunoglobulin A vasculitis (IgAV, previously known as Henoch Schonlein Purpura, HSP). IgAV is a small vessel vasculitis and it is the most common form of vasculitis in children, with an incidence of ~20 cases per 100,000 children[1-3] and a median age at presentation of 6 years[2]. IgAV usually presents acutely with a purpuric rash that predominates on the lower limbs. It also involves inflammation in the gastrointestinal (GI) tract, musculoskeletal system and/or, importantly, kidney's[4]. GI tract involvement occurs in up to 72% of patients. It usually presents with nausea, vomiting and/or colicky abdominal pain[5]. It can involve GI bleeding manifesting as melaena or haematemesis, that can be severe or life threatening[6]. GI bleeding has been linked to the need for a longer hospital admission[7]. Intussusception due to GI tract inflammation can occur and testicular inflammation is seen with orchiditis occurring in 14% of male patients[6]. During the acute presentation, up to 90% of patients will have musculoskeletal involvement with arthralgia and arthritis that mainly affects the lower limb joints[6]. This can be debilitating, and it can last several weeks. Kidney involvement, termed IgAV nephritis, is seen in around 40-50% of patients and it is usually asymptomatic and requires screening for signs of nephritis. Most patients have a mild nephritis that self resolves with microscopic haematuria or proteinuria being a common finding. IgAV nephritis can present with nephrotic or nephritic syndrome and it is a recognised cause of chronic kidney disease in 1-2% of patients[8]. Rarely, but importantly, IgAV can involve other systems such as the respiratory or neurological, although these are very uncommon in children and young people. There are no current national guidelines to support the best management of this condition and clinical practice varies. The aim of this guideline is to provide best practice recommendations for the management of complications associated with IgAV in children and young people.

Scope

The audience for this guideline will be healthcare professionals working in primary, secondary and tertiary healthcare settings in the UK in which complications associated with IgAV in children and young people are managed. The population that this guideline relates to is children and young people aged 0-18 years presenting with complications associated with IgAV.

Summary and rationale of recommendations

Nephritis recommendations

Number	RECOMMENDATION	Grade
Section 1: CLINICALLY SUSPECTED IGAV NEPHRITIS		
1.1	We recommend that a kidney biopsy is undertaken to confirm a diagnosis of severe nephritis in children and young people with IgAV, where the definition of severe nephritis includes persisting severe proteinuria (UP: UC >250 mg/mmol for up to 4 weeks), persisting moderate proteinuria (UP: UC 100–250 mg/mmol for 3 months), AKI stage 1 or greater, or nephrotic syndrome (see Section 2.2).	1C
Section 2: MANAGEMENT OF HISTOLOGICALLY PROVEN IGAV NEPHRITIS		
2.1	We recommend that the kidney histology should be classified using the ISKDC classification criteria for children and young people with IgAV.	1C
2.2	We recommend that a combination of clinical features and the histological ISKDC classification should guide decisions about treatment choices to offer children and young people with IgAV nephritis. The following are clinical indications; • Persisting severe proteinuria (UP: UC >250 mg/mmol for up to 4 weeks) • Persisting moderate proteinuria (UP: UC 100–250 mg/mmol for up to 3 months) • AKI stage 1 or greater (serum creatinine >1.5 × previous baseline (if known) or >1.5 × upper limit of normal for age) • Nephrotic syndrome (clinical signs of oedema, serum albumin <30 g/L, severe proteinuria UP: UC >250 mg/mmol). The following are histological indications; • Class II ISKDC classification with persisting clinical indications • Class III or above ISKDC classification with clinical indications	1C
2.3	We suggest that the management of biopsy proven IgAV nephritis should be directed by, or in conjunction with, a paediatric nephrologist	
2.4	We suggest using the following disease-modifying drugs, or a combination of corticosteroids together with a disease-modifying drug, depending on the clinical	2B

	and histological features in children and young people with biopsy proven IgAV nephritis. *Corticosteroids;* • *Prednisolone 1-2mg/kg/day (maximum 60mg/day) for 2-4 weeks then weaned according to clinical response* • *In severe nephritis with adverse clinical and histological features (impaired kidney function, nephrotic syndrome or crescentic features), or where oral absorption is potentially compromised, intravenous methylprednisolone 10–30 mg/kg (maximum of 1 g/day) once daily for three consecutive days may be used followed by the use of oral prednisolone.* *Disease-modifying drug (listed in alphabetical order);* • *Azathioprine* • *Calcineurin inhibitors (ciclosporin or tacrolimus)* • *Cyclophosphamide* • *Mycophenolate mofetil.* *Rapidly progressive glomerulonephritis is managed more aggressively with preference for intravenous treatment.*	
2.5	*We <u>suggest</u> that in cases of IgAV nephritis with persisting proteinuria (UP: UC >100 mg/mmol for 3 months or UP: UC >50mg/mmol for 6 months) the use of an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) should be considered as adjunctive or monotherapy under the guidance of a nephrologist, even if they haven't met the threshold for performing a kidney biopsy (section 1.1).*	*2C*

Rationale

A total of 31/33 (94%) of the papers[9-23,1,24-38] mentioned an investigation to confirm nephritis and these all used the kidney biopsy to define the histological disease activity. Of those suggesting histological evaluation, the ISKDC classification criteria was most commonly reported, with inclusion in 21 papers and additional chronicity and/or activity features were reported in 3 studies. The study by Koskela et al (2019) evaluated 53 patients with IgAV nephritis and specifically compared the ISKDC classification criteria with the modified semi-quantitative score (SQS) – a scoring tool that provides additional activity and chronicity data - in terms of predicting active kidney disease or kidney failure and suggested superiority in using the SQS in its ability to predict worse kidney outcomes[39]. The widespread use of the ISKDC classification criteria provided the basis for the second recommendation in this section. Due to the emergence of potential benefit from activity and chronicity data the UK IgAV GDG would suggest these as additional measures to the ISKDC classification.

A total of 13/33 (39%) studies described clinical signs, symptoms or investigations that were used as an indication for starting treatment[9,10,13,18-20,23,24,26,28,29,32,34]. These were observational studies and no studies

compared the effect of using differing indications on when to commence treatment, such as clinical features versus histological findings. The ISKDC histological classification criteria alone was used in 9 of these studies (9/13; 69%). A further 2 studies (2/13; 15%) used a combination of histological features and clinical features. The SHARE recommended using a combination of clinical and histological features in order to direct treatment[26] and the UK IgAV GDG felt that this best reflected current clinical practice. In 2021, an international working group of paediatric nephrologists refined this aspect of the SHARE recommendations to produce the following absolute indications that were incorporated into the recommendation [40].

Absolute indications:

- Persisting severe proteinuria (UP: UC >250 mg/mmol for 4 weeks)
- Persisting moderate proteinuria (UP: UC 100–250 mg/mmol for 3 months)
- Acute kidney injury stage 1 or greater (serum creatinine >1.5 × previous baseline (if known) or >1.5 × upper limit of normal for age)
- Nephrotic syndrome (clinical oedema, serum albumin below lower limit of normal for age, moderate/severe proteinuria)

Relative indications:

- Reproducible severe proteinuria (UP: UC >250 mg/mmol) at any time point
- Serum creatinine above upper limit of normal

There were 26/33 (79%) nephritis studies that were included in the evidence regarding treatment options[9,10,12-14,18,19,41,20-23,1,24,26-28,30-38]. Due to the heterogeneity of the studies that were generally of poor quality, no studies provided conclusive evidence of a preferred treatment option or regimen. Treatments suggested to demonstrate benefit included; corticosteroids (prednisolone, dexamethasone, intravenous methylprednisolone) in 22 studies[10,9,12-14,18,19,41,20-23,1,24,26,30,31,34-38], cyclophosphamide (intravenous or oral) in 13 studies[10,9,13,14,19,21,22,1,26,31,32,36,38], azathioprine in 8 studies[9,13,14,19,26,30,36,38], cyclosporin A in 5 studies[10,19,20,24,27], MMF in 4 studies[10,19,26,38], tacrolimus in 2 studies[10,35], IVIG in 2 studies[12,37], urokinase in 3 studies[22,23,1], triptolide in 1 study[34], LMWH in 1 study[33], PEX in 2 studies[1,28], warfarin in 2 studies[23,1], and dipyridamole in 3 studies[23,1,31]. The 22 studies that included corticosteroids consisted of 1 open label multicentre randomised controlled trial (13 participants), 2 single centre open label trials (totalling 85 patients), 8 single centre retrospective studies, 5 single centre prospective studies, 3 multicentre retrospective studies, 1 systematic literature review and meta-analysis and the SHARE recommendations. Trial data were limited and multiple other treatments were often used. Of the 13 studies that mentioned cyclophosphamide 1 was a multicentre randomised controlled trial (56 participants) which found no benefit on kidney outcomes. The 8 studies that involved azathioprine were cohort studies and there were no clinical trials. There were no clinical trials involving MMF, the studies included that used MMF for IgAV nephritis were 2 single centre retrospective studies, 1 systematic literature review and meta-analysis and the SHARE recommendations. The cyclosporin A studies included 2 clinical trials, 1 single centre open label study (n=7 participants) and 1 multicentre open label randomised controlled trial (n=13 participants) and these reported an apparent benefit. Other included studies that involved cyclosporin A were 1 single centre retrospective study, 1 multicentre prospective study and 1 systematic literature review and meta-analysis. The two tacrolimus studies consisted of 1 single centre, open labelled pilot trial (n=25 participants) and 1 single centre retrospective cohort study both of which reported benefit. The UK IgAV GDG believed that it was important to include some guidance in

this topic, however the evidence didn't support any preferred treatment(s) for IgAV nephritis. The recommendation (nephritis 4) was therefore developed to include several options.

The use of ACEi/ARB were mentioned in 6 studies[9,13,14,18,19,26]. These were generally poor quality and none of the studies were randomised controlled trials evaluating the benefit of ACEi/ARB use specifically. As the use of ACEi/ARB is so well established, and data is supportive in IgA nephropathy [42], in patients with proteinuria the expert opinion of the UK IgAV GDG was to include this recommendation for patients with IgAV nephritis as this best reflected current practice.

Audit measures

i. The proportion of children and young people with suspected IgAV nephritis who had a kidney biopsy investigation performed to confirm a diagnosis of severe nephritis.
ii. The proportion of children and young people with proven IgAV nephritis who had a kidney biopsy that was scored using the ISKDC classification criteria.
iii. The proportion of children and young people with severe IgAV nephritis who had treatment decisions based on the absolute clinical indications and histological ISKDC classification

Research recommendations

i. In children and young people with IgA vasculitis, what is the benefit of additional kidney histology descriptors to accurately predict long term kidney outcomes?
ii. In children and young people with IgA vasculitis, what are the best indications for when to perform a kidney biopsy to capture disease that requires treatment?
iii. In children and young people with IgA vasculitis, what is the best treatment for IgAV nephritis to prevent progression to CKD?
iv. In children and young people with IgA vasculitis, is there a benefit to using early ACEi/ARB treatment for proteinuria?

IgAV associated gastrointestinal and urological involvement recommendations

Number	RECOMMENDATION	Grade
Section 3: MANAGEMENT OF ACUTE ABDOMINAL PAIN AND/OR GI BLEEDING		
3.1	*We suggest that corticosteroids (prednisolone 1-2 mg/kg/day for 1-2 weeks) are considered for children and young people with IgAV within 3 days of onset of severe abdominal pain (defined as pain requiring hospital admission) or acute GI bleeding after appropriate clinical review and the exclusion of other causes including intussusception.*	*2B*
Section 4: MANAGEMENT OF SUSPECTED OR PROVEN INTUSSUSCEPTION		
4.1	*We recommend that specialist surgical and [/or] radiological advice is sought for children and young people with IgAV and abdominal symptoms suggestive of intussusception.*	*1C*
Section 5: MANAGEMENT OF SUSPECTED OR PROVEN TESTICULAR INVOLVEMENT		
5.1	*We suggest that testicular involvement (orchiditis) should be considered in boys with IgAV who develop painful scrotal oedema that is associated with palpable purpuric lesions.*	*2D*
5.2	*We suggest that treatment with corticosteroids (prednisolone 1-2 mg/kg/day for 1-2 weeks) should be considered in boys with IgAV who develop orchiditis after appropriate specialist advice such as a surgical opinion has been sought.*	*2D*

Rationale

There were 23 papers identified (23/82; 28%) relevant to gastroenterology and urological involvement. Of these, 18 studies (18/23; 78%) included management for GI bleeding[43,16,17,44,21,45,26,46-56] and 16 of these studies (16/18; 89%) reported the positive use of, or recommended, corticosteroids for the treatment of GI bleeding[56,55,54,53,52,51,50,48,47,46,43,16,17,21,45,26]. . The studies included a systematic literature review with meta-analysis by Weiss et al (2007) included three RCTs and 12 retrospective studies evaluating the use of early steroids in reducing the duration and/or severity of GI symptoms. They reported a statistically significant reduction in the time to abdominal pain resolving within 24 hours following the use of corticosteroids[57]. The SHARE consensus-based recommendations suggested that in severe abdominal pain and/or GI bleeding, once intussusception has been excluded, corticosteroids could be considered (eg: oral prednisolone 1-2 mg/kg/day for 1-2 weeks) [26]. The UK IgAV GDG discussed the timing of when to commence corticosteroids, Weiss et al (2010) and Zhao et al (2021) used large cohort data to demonstrated that corticosteroids significantly decreased the need for abdominal surgery, endoscopy and abdominal imaging if they were administered within 72 hours of symptom onset [58,59]. The UK IgAV GDG acknowledged the variable quality of the studies but they were satisfied that there was sufficient evidence to recommend that early treatment (defined as that administered within 3 days of pain onset) with corticosteroids is likely to confer a benefit to those children and young people requiring hospitalisation. Due to the paucity of evidence the group derived several research

recommendations in this area including whether early treatment prevents GI complications, the best investigations for GI involvement, the most important outcomes and the ideal timing and duration of corticosteroids.

Ten studies informed the intussusception recommendation (10/23; 43%)[16,60,61,21,62,63,58,52,53,55]. Most reported the use of surgical intervention in cases of intussusception. A systematic review by Weiss et al (2007) described a protective effect of early corticosteroid exposure on reducing the risk of intussusception with a significantly reduced hazard ratio (0.39 [95% confidence interval (CI): 0.17–0.91]) among patients exposed to corticosteroids. Zhao et al (2021) reported that the use of corticosteroids given within 72 hours reduced the risk of intussusception. The recommendation was written to highlight the importance of specialist advice in the management of intussusception to reflect clinical practice. The use of corticosteroid treatment appeared to have a potential preventative role in the evidence.

Two studies (2/23; 9%) defined testicular involvement in IgAV[17,52]. One of these studies provided a clear definition of orchiditis as painful, acute scrotal oedema associated with palpable purpuric lesions[52]. GDG members agreed that this definition most appropriately described orchitis. 5 studies (5/23; 22%) evaluated treatment for testicular involvement[52,17,26,56,50,64]. Of these, 3 studies (3/5; 60%) used corticosteroids (these cohort studies totalled only 15 patients)[17,50,52]. The SHARE recommendations suggested using corticosteroids in orchiditis[26]. There were therefore limited data, however, members agreed that a short course of corticosteroids (1-2mg/kg/day over 1-2 weeks) is likely to improve testicular inflammation and pain.

Audit measures

i. The proportion of children and young people with IgAV and abdominal symptoms suggestive of intussusception who received a surgical and radiological opinion.

Research recommendations

i. In children and young people with IgA vasculitis, does early treatment prevent GI complications?
ii. In children and young people with IgA vasculitis, what are the best tests to indicate GI involvement that requires treatment?
iii. In children and young people with IgA vasculitis, what are the most important GI outcomes?
iv. In children and young people with IgA vasculitis, what is the optimal timing and duration of corticosteroids for severe GI involvement?

IgAV associated skin involvement recommendations

Number	RECOMMENDATION	*Grade*
Section 6: MANAGEMENT OF CASES WITH ATYPICAL FEATURES		
6.1	*We suggest that a skin biopsy is undertaken in children and young people with IgAV who have an atypical purpuric/petechial rash or to exclude alternative diagnoses.*	*2B*
6.2	*We suggest that when a skin biopsy is performed the histological analysis should specifically include evaluation of IgA deposition using immunofluorescence (fresh specimen) or immunohistochemistry (fixed tissue).*	*2C*

Rationale

Three studies (3/83; 4%) included specific indications in children with IgAV. These studies suggested the use of a skin biopsy in atypical cases or in cases of diagnostic uncertainty. The SHARE recommendations included a similar indication and mentioned the need for specific IgA staining to be performed. The limited evidence made this a weak recommendation and the UK IgAV GDG agreed that it would be important to include specific mention of histological analysis for IgA deposition as it forms the basis of the EULAR/PRINTO/PRES classification criteria and it would therefore assist in cases of diagnostic uncertainty.

IgAV persisting, prolonged, recurrent disease recommendations

Number	RECOMMENDATION	*Grade*
Section 7: DEFINITION OF PERSISTING OR RECURRENT DISEASE		
7.1	*We <u>suggest</u> that children and young people with IgAV and a typical purpuric/petechial rash persisting for more than 1 month should be defined as having persisting disease.*	*2B*
7.2	*We <u>suggest</u> that children and young people with IgAV who present with a reappearance of the typical purpuric/petechial rash after a symptom-free period of greater than 1 month should be defined as having recurrent disease.*	*2B*

Rationale

Eight studies (8/82; 10%) included a definition for persisting disease. All studies agreed on the timing and definition of persisting disease as the presence of persisting skin lesions for >1 month. The definition for recurrent disease was less clear with 34 (34/82; 42%) studies providing a definition and within these most studies considered a prior diagnosis of IgAV followed by an asymptomatic period then return of classical symptoms/signs as a recurrence or a relapse. There was a range in the reported symptom-free period used in the literature that spanned from 2 weeks to 6 months, however the majority of studies (n=19/34; 56%) required an asymptomatic period of 1 month between episodes. The UK IgAV GDG agreed that a time interval of 1 month of being symptom free should be used as a suggested parameter to define recurrent disease and this aligned with the time interval used to define persisting disease which may assist with implementation into clinical practice. No studies were identified to guide appropriate management strategies for IgAV that is persisting or recurrent and in the absence of evidence or consensus the GDG agreed to make this a research recommendation.

Research recommendations

i. In children and young people with IgA vasculitis, what is the best management for persisting or recurrent disease?
ii. In children and young people with IgA vasculitis, what is the threshold for further investigations in persisting and/or recurrent disease?

Long term follow up recommendations

Number	RECOMMENDATION	*Grade*
Section 8: LONG TERM FOLLOW UP IN IGAV		
8.1	*We recommend that children and young people with IgAV have follow up whilst there is evidence of nephritis and for at least 3 years if they have experienced biopsy proven nephritis.*	*1C*

Rationale

There were 22 studies (22/82; 27%) that suggested indications for long term follow up (follow up performed over years rather than the usual 6 months) in patients with IgAV but none of these studies directly compared the outcome of following up patients with differing indications[65,10,14,13,16,17,41,23,45,46,66,29,32,48,24,67,68,34,69,36,38,56]. 17 studies (17/22; 77%) suggested that the only long term concern was persisting kidney disease[56,38,36,69,34,67,24,32,29,45,23,17,16,13,14,10,65]. There were very few high-quality long-term studies to support this recommendation and the UK IgAV GDG recognised that there will be individual cases that warrant specific long-term monitoring. However, it was agreed that the most reported long-term consequence of this condition is CKD and therefore the recommendation focused on follow up according to a history of severe nephritis that required treatment or persisting abnormalities in the kidney function or urinalysis.

Audit measures

i. The proportion of children and young people with IgAV and severe or persisting nephritis who received long term follow up.

Summary of audit measures

The audit measures align with the strong recommendations (strength grade 1) suggested in this clinical practice guideline. A summary of the audit measures are as follows;

i. The proportion of children and young people with suspected IgAV nephritis who had a kidney biopsy investigation performed to confirm a diagnosis of severe nephritis.
ii. The proportion of children and young people with proven IgAV nephritis who had a kidney biopsy that was scored using the ISKDC classification criteria.
iii. The proportion of children and young people with proven IgAV nephritis who had treatment decisions based on a combination of clinical features and histological finding
iv. The proportion of children and young people with IgAV and suspected/proven intussusception who had a surgical and radiological opinion and consideration of using corticosteroids.
v. The proportion of children and young people with IgAV and severe or persisting nephritis who received long term follow up.

Summary of Research Recommendations

The research recommendations suggested throughout the guideline are as follows;

i. In children and young people with IgA vasculitis, what is the benefit of additional kidney histology descriptors to accurately predict long term kidney outcomes?
ii. In children and young people with IgA vasculitis, what are the best indications for when to perform a kidney biopsy to capture disease that requires treatment?
iii. In children and young people with IgA vasculitis, what is the best treatment for IgAV nephritis to prevent progression to CKD?
iv. In children and young people with IgA vasculitis, is there a benefit to using early ACEi/ARB treatment for proteinuria?
v. In children and young people with IgA vasculitis, does early treatment prevent GI complications?
vi. In children and young people with IgA vasculitis, what are the best tests to indicate GI involvement that requires treatment?
vii. In children and young people with IgA vasculitis, what are the most important GI outcomes?
viii. In children and young people with IgA vasculitis, what is the optimal timing and duration of corticosteroids for severe GI involvement?
ix. In children and young people with IgA vasculitis, what is the best management for persisting or recurrent disease?
x. In children and young people with IgA vasculitis, what is the threshold for further investigations in persisting and/or recurrent disease?

Lay Summary

The condition called immunoglobulin A vasculitis (known as IgAV) was previously called Henoch Schönlein Purpura. It is a condition where the immune system becomes overactive after a normal childhood illness. It causes a red/purple rash that is usually on the legs. It can also cause tummy aches, sore joints and kidney problems. Testing the urine for kidney problems at an early stage is important to find out about kidney problems. About half of the children with IgAV will have inflamed kidneys when the urine is tested. The kidneys can get inflamed even after the rash has gone. The condition is more common in primary school aged children, but it can come on at any age. In most children it lasts a few weeks and then it goes away forever. A few children will get long term problems that are usually due to the kidney problems. The aim of this work was to make a guide for how to look after children who may get complications from IgAV.

This guideline has been developed by a group of specialists in the UK and it includes parents of children with IgAV. Other associations also helped. They made a working group called the UK IgAV guideline development group (GDG). The group started by deciding on the most important questions for how to manage children with IgAV. They checked the medical studies reported over the past 20 years. Using the medical studies and group discussion, the group made recommendations. These are written below. A poster is shown in Appendix 10 that shows how they did the work and a poster in Appendix 11 shows the recommendations.

Lay version of recommendations

The lay version of the best practice recommendations are;

1. In children and young people with IgAV and inflamed kidneys, the best test is the kidney biopsy.
2. In children and young people with IgAV the kidney biopsy test should be scored using set criteria (called the ISKDC classification criteria) to give extra detail on how the kidney looks.
3. In children and young people with IgAV the decision to treat the inflamed kidneys should be made based on the ISKDC class and on kidney tests (urine, blood tests) for the patient.
4. In children and young people with IgAV who have had a kidney biopsy, the treatment should be managed by a children's kidney doctor.
5. In children and young people with IgAV who need immune damping medicines for the kidneys, the first medicine used is usually corticosteroids, with one of the following medicines; azathioprine, calcineurin inhibitors, cyclophosphamide or mycophenolate mofetil.
6. In children and young people with IgAV and kidney problems with protein in the urine then a medicine called an ACEi or an ARB might be helpful
7. In children and young people with IgAV and severe bleeding from the gut, treatment with steroid medicine may be helpful and should be given within the first 3 days.
8. In children and young people with IgAV who develop a problem where the gut telescopes in on itself (called 'intussusception') a surgeon and radiology specialist should be involved.
9. Boys with IgAV who have the rash on the testicles and the testicles are swollen or sore may have inflamed testicles (called 'orchiditis').
10. In boys with IgAV who get inflamed testicles may need a surgeon to review them and steroid medicine might help.

11. In children and young people with IgAV, a skin biopsy test should be done if there is something unusual about the rash or if anyone is unsure about the diagnosis.
12. When a skin biopsy test is done the laboratory should do a staining test to look for IgA.
13. Children and young people with IgAV and a typical rash that lasts more than a month have persisting disease.
14. Children and young people with IgAV and a typical rash that comes back a month after it had gone away have recurrent disease.
15. Long term checks are needed for children and young people with IgAV who had bad kidney inflammation or if they still have problems with their kidneys.

Lay research recommendations

i. In children and young people with IgA vasculitis, what is the best way to score the kidney biopsy pictures that tells how the kidneys will be in the future?
ii. In children and young people with IgA vasculitis, what are the best ways to indicate when to do the kidney biopsy test?
iii. In children and young people with IgA vasculitis, what is the best medicine to calm the kidneys and stop any damage?
iv. In children and young people with IgA vasculitis, can the early use of ACEi/ARB medicines help the kidney inflammation?
v. In children and young people with IgA vasculitis, what is the best treatment to stop gut problems from coming on?
vi. In children and young people with IgA vasculitis, which tests are the best ones to tell us about gut problems and tell us when treatment is needed?
vii. In children and young people with IgA vasculitis, what are the most important gut problems to measure?
viii. In children and young people with IgA vasculitis, when is the best time to start steroids for gut problems and how many days should they be used for?
ix. In children and young people with IgA vasculitis, what is the best treatment for when the condition keeps coming back or doesn't go away?
x. In children and young people with IgA vasculitis, what is the threshold for further investigations in persisting and/or recurrent disease?

Acknowledgements

This document has been externally reviewed by key stake holders and during an open consultation process according to the instructions described in the UKKA Clinical Practice Guidelines Development Policy Manual. We would like to thank everyone who has contributed to this process.

Appendix

Appendix 1: Lead organisations

Name
British Association of Paediatric Nephrology (BAPN)
UK Kidney Association (UKKA)
Royal College of Paediatrics and Child Health (RCPCH)

Appendix 2: Stakeholders

Name
British society of Paediatric gastroenterology, hepatology and nutrition (BSPGHAN)
British Society of Rheumatology (BSR)
Association of Paediatric Emergency Medicine APEM
Royal College of Emergency Medicine RCEM
Paediatric Emergency Medicine research collaborative for the UK and Ireland (PERUKI)
British Society of Paediatric radiology BSPR
Vasculitis UK

Appendix 3: PICO domains

Population	Intervention	Comparison	Outcome
Children and young people (aged <18 years) with a confirmed diagnosis of IgAV	Classification tool Clinical signs and symptoms Kidney tests Therapeutics	Any intervention compared with any other or no intervention	Diagnosis Complications Duration of symptoms Severity of symptoms

Appendix 4: Search concepts

Search number	Search terms

1	pediatric
2	paediatric
3	child*
4	Adolescen*
5	**1 OR 2 OR 3 OR 4**
6	immunoglobulin A vasculitis
7	IgA vasculitis
8	IgAV
9	Henoch schonlein purpura
10	HSP

Appendix 5: Study eligibility

Criteria	Inclusion	Exclusion
Publication date	Papers published between 2002 to 2022	Papers published prior to 2002
Research type	Primary research	Secondary research
Study type	Randomised controlled trials (RCT) If no RCT available to consider; Cohort studies Case series >5 patients Case control studies Meta-analysis Systematic reviews	Case reports Editorials Comments Annotations Letters Commentaries Books and book chapters Updated systematic reviews by same methodology eg Cochrane (most recent version will be included) Non-traditional therapies (eg: Chinese medicines) and surgical intervention

Publication and study status	Published Completed	Unpublished Ongoing
Language	English	Non-English
Text availability	Full text available	Full text unavailable

Appendix 6: Bibliographic databases

Bibliographic databases	Access uniform resource locator (URL)
MEDLINE	https://www.nlm.nih.gov/medline
EMBASE	https://www.embase.com
Cochrane central register of controlled trials (CENTRAL)	https://www.cochranelibrary.com/central

Appendix 7: Topic areas and key questions

Topic area	Key questions
IgAV associated nephritis	In children and young people with IgAV how to confirm the diagnosis of IgAV nephritis? In children and young people with IgAV how to classify / grade IgAV nephritis? How to define nephritis that requires treatment in children and young people with IgAV? What are acceptable treatments for children and young people with IgAV nephritis?

IgAV associated gastrointestinal, urological involvement	What are acceptable treatments for children and young people with IgAV associated GI bleeding? What interventions should be considered for the management of intussusception in children and young people with IgAV? How to diagnose testicular involvement in children and young people with IgAV? What are acceptable treatments for the management of testicular involvement in children and young people with IgAV?
IgAV associated skin involvement	What are the indications for performing a skin biopsy in children and young people with IgAV?
IgAV persisting, prolonged, recurrent disease	In children and young people with IgAV how do we define persisting disease? In children and young people with IgAV how do we define recurrent disease?
Long term follow up	In children and young people with IgAV, which patients may need long term follow up?

Appendix 8: Key questions formatted for systematic review

IgAV associated nephritis

1) In children and young people under the age of 18 years with IgAV, what are the best investigations to confirm a clinical diagnosis of nephritis?
2) In children and young people under the age of 18 years with IgAV, what are the best classification tools to grade a histological diagnosis of IgAV nephritis
3) In children and young people under the age of 18 years with IgAV, what clinical signs, symptoms or investigations define nephritis that requires treatment to reduce the risk of chronic kidney disease?

4) In children and young people under the age of 18 years with IgAV, what are acceptable treatments for nephritis to reduce the risk of chronic kidney disease?

IgAV associated gastrointestinal, urological involvement

1) In children and young people under the age of 18 years with IgAV, what are acceptable treatments for gastrointestinal bleeding that would reduce the duration and/or severity of symptoms?
2) In children and young people under the age of 18 years with IgAV, what are acceptable treatments or interventions for the management of intussusception that would reduce the duration and/or severity of symptoms?
3) In children and young people under the age of 18 years with IgAV, what clinical signs, symptoms or investigations would support a diagnosis of testicular involvement that requires treatment?
4) In children and young people under the age of 18 years with IgAV, what are acceptable treatments or interventions for the management of testicular involvement that would reduce the duration and/or severity of symptoms?

IgAV associated skin involvement

1) In children and young people under the age of 18 years with IgAV, what clinical signs or symptoms would support for the need to perform a skin biopsy to support a diagnosis?

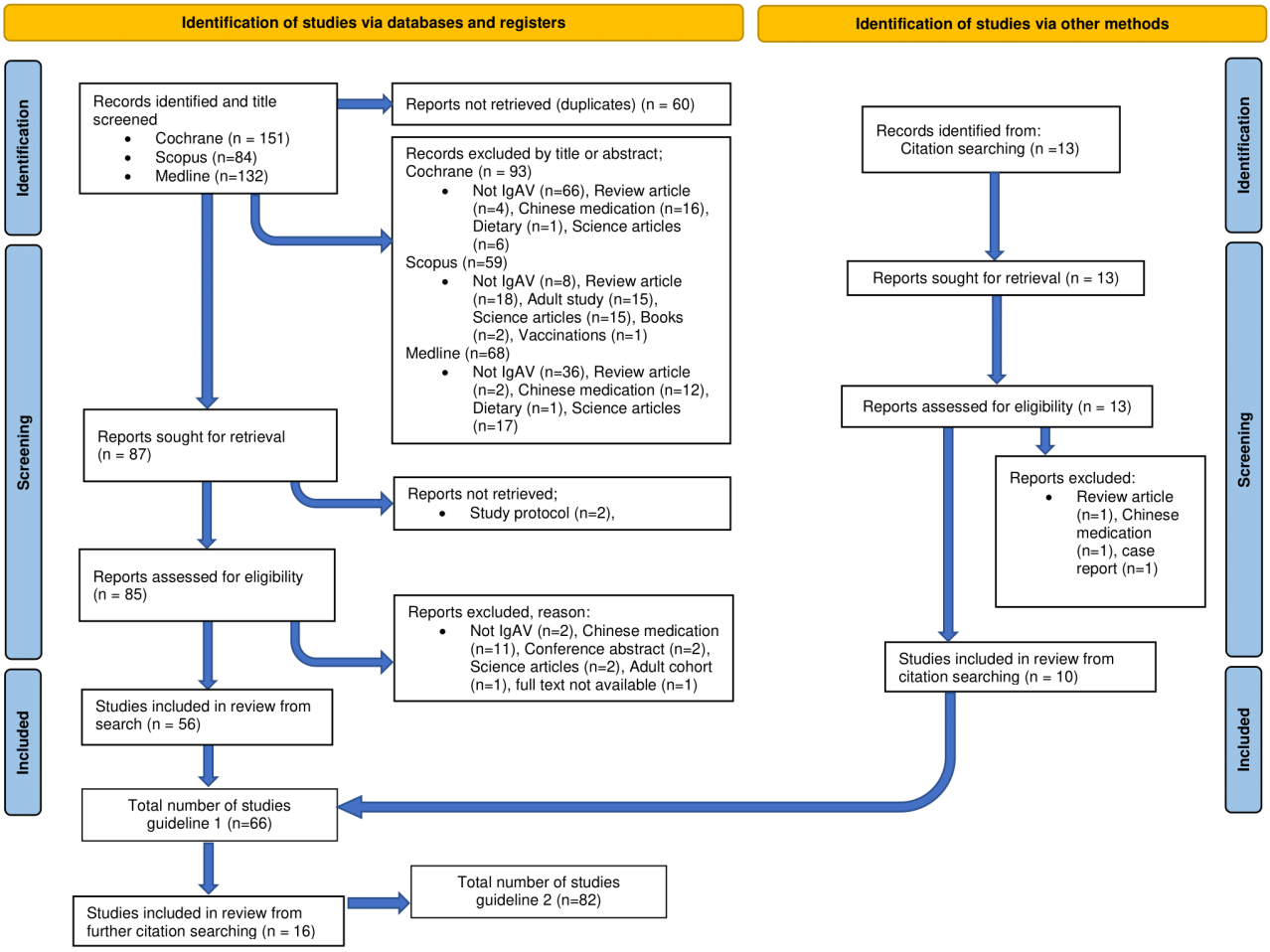
IgAV persisting, prolonged, recurrent disease

1) In children and young people under the age of 18 years with IgAV, what clinical signs or symptoms would support a diagnosis of persisting disease?
2) In children and young people under the age of 18 years with IgAV, what clinical signs or symptoms would support a diagnosis of recurrent disease?

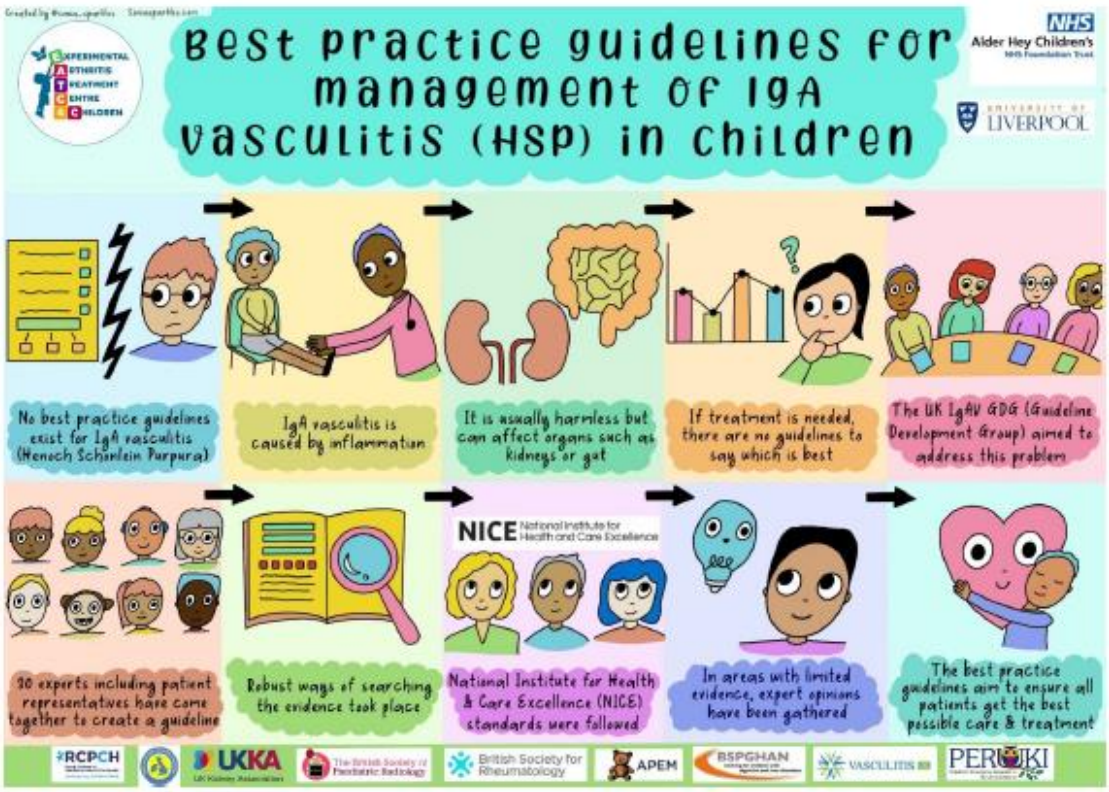
Long term follow up

1) In children and young people under the age of 18 years with IgAV, what clinical signs or symptoms would indicate the need for follow up after initial screening to detect long term complications?

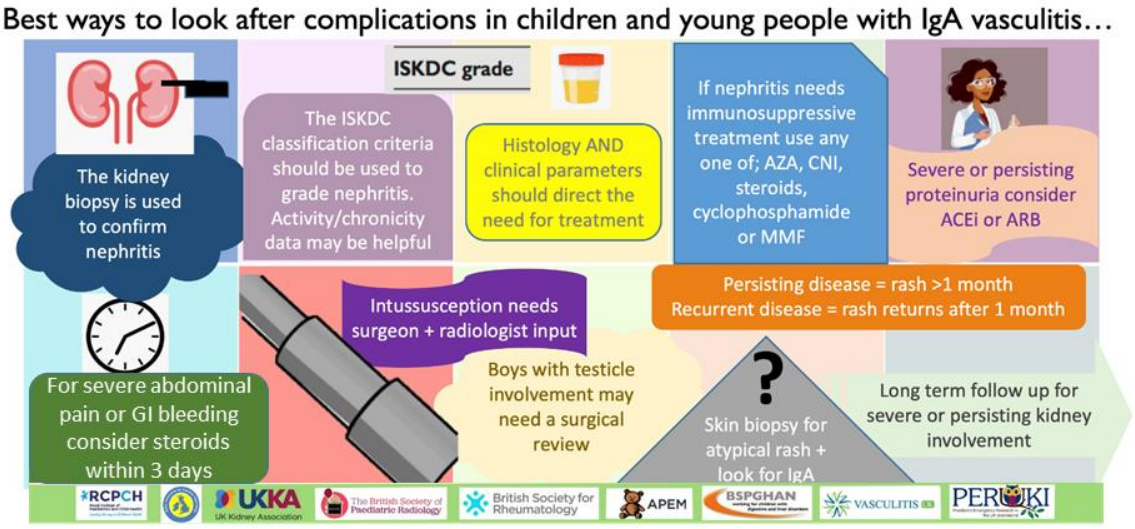
Appendix 9: PRISMA diagram of selected studies



Appendix 10: Summary information poster: outline of methodology



Appendix 11: Summary information poster: recommendations



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