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European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis—the SHARE initiative

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Abstract

Objectives. IgA vasculitis (IgAV, formerly known as Henoch–Schönlein purpura) is the most common cause of systemic vasculitis in childhood. To date, there are no internationally agreed, evidence-based guidelines concerning the appropriate diagnosis and treatment of IgAV in children. Accordingly, treatment regimens differ widely. The European initiative SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) aims to optimize care for children with rheumatic diseases. The aim therefore was to provide internationally agreed consensus recommendations for diagnosis and treatment for children with IgAV.

Methods. Recommendations were developed by a consensus process in accordance with the EULAR standard operating procedures. An extensive systematic literature review was performed, and evidence-based recommendations were extrapolated from the included papers. These were evaluated by a panel of 16 international experts via online surveys and subsequent consensus meeting, using nominal group technique. Recommendations were accepted when $\geqslant$80% of experts agreed.

Results. In total, 7 recommendations for diagnosis and 19 for treatment of paediatric IgAV were accepted. Diagnostic recommendations included: appropriate use of skin and renal biopsy, renal work-up and imaging. Treatment recommendations included: the importance of appropriate analgesia and angiotensin-converting enzyme inhibitor use and non-renal indications for CS use, as well as a structured approach to treating IgAV nephritis, including appropriate use of CS and second-line agents in mild, moderate and severe disease along with use of angiotensin-converting enzyme inhibitors and maintenance therapy.

Conclusion. The SHARE initiative provides international, evidence-based recommendations for the diagnosis and treatment of IgAV that will facilitate improvement and uniformity of care.

Key words: childhood/paediatric, IgA vasculitis (Henoch–Schönlein purpura), systemic vasculitis, diagnosis, management, recommendations

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Rheumatology key messages

- IgA vasculitis is the most common cause of systemic vasculitis in childhood.
- These are the first international, evidence-based recommendations concerning the management of childhood IgA vasculitis.
- All IgA vasculitis patients need to be proactively investigated for renal involvement, at diagnosis and throughout follow-up.

Introduction

IgA vasculitis (IgAV; formerly known as Henoch–Schönlein purpura [1]) is the most common systemic vasculitis of childhood with a reported incidence of 3–26.7 cases per 100 000 [2–4]. It is a small vessel vasculitis with IgA-dominant immune deposits that typically involves the skin, gut and glomeruli, and is associated with arthralgia and/or arthritis [5]. Although a common vasculitis in paediatric practice, well-designed controlled studies are lacking. This is partially due to the usual self-limiting nature of the disease [6, 7]. There is a lack of long-term outcome data for patients with various renal features, although renal prognosis is generally good as those with minimal involvement self-resolve. A small minority with persistent renal involvement and crescentic glomerulonephritis on renal biopsy may progress to end-stage renal disease later in life [7, 8]. A key challenge is early, prompt and accurate diagnosis in order to instigate appropriate management and follow-up [9]. There are no internationally agreed, evidence-based recommendations concerning the appropriate diagnosis and treatment of IgAV in children. Lack of robust clinical trials informing management means there is considerable variation in approach between centres and countries [9].

The European SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) initiative was launched in 2012 aiming to improve and optimize care for children and young adults with Paediatric Rheumatic Diseases across Europe and beyond [10]. The objective was to develop international, consensus agreed, evidence-based recommendations for diagnosis and treatment. To date, SHARE recommendations for paediatric APS, juvenile dermatomyositis, FMF, autoinflammatory diseases, childhood-onset lupus and LN have been published [11–16]. The SHARE initiative paid specific attention to the area of systemic vasculitis, in which the rarity in paediatric practice, multi-system nature and complexity of the disorders have made developing evidence-based guidelines challenging.

Here we present SHARE recommendations for IgAV, and IgAV nephritis in particular. In the absence of high-level evidence concerning treatment based on randomized controlled trials, these recommendations aim to provide the general paediatrician or paediatric rheumatologist/nephrologist with less experience with severe IgAV/IgAV nephritis with a practical tool to provide optimal care for children across different European countries. SHARE recommendations for Kawasaki disease (KD) and the rarer childhood systemic vasculitides will be published separately [17, 18].

Methods

A panel of 16 experts from partners of the SHARE consortium in paediatric rheumatology and paediatric systemic vasculitis, together with paediatric nephrology representation, was established. As SHARE was a European Union-funded project, only experts from across Europe and Turkey were able to be selected, representing a balance of experience and geography, along with a non-European-based independent, non-voting facilitator of the consensus process (B.M.F.). The SHARE methods have previously been described in detail [15, 16] including use of the EULAR standardized operating procedure for developing best practice recommendations [19].

Systematic literature review and study selection

Based on specific research questions identified *a priori* to focus on diagnosis and treatment of IgAV, the PubMed/MEDLINE, EMBASE and Cochrane databases were systematically searched on 20 June 2013. Additional key publications related to IgAV identified between the initial literature search and the final manuscript drafting (30 June 2018) were identified using the same search strategy. While these latter did not directly inform the recommendations, they were included in the manuscript commentary to provide up-to-date face validity and contextualization. All systemic vasculitides synonyms were searched in MeSH/Emtree terms, title and abstract, and articles were assessed using pre-specified inclusion/exclusion criteria pertaining to children and adolescents [20] (supplementary Tables S1 and S2, available at *Rheumatology* online, respectively). The comprehensive literature review was undertaken inclusive of these other forms of systemic vasculitis to ensure that no manuscripts including data on IgAV along with any of these other forms of vasculitis were missed. All articles were screened independently by two reviewers (N.d.G., N.G.) and full text checked when necessary to determine eligibility. Disagreement was resolved by a third reviewer (M.W.B.); agreement was reached in all cases. Additional key articles related to the diagnosis and treatment of IgAV identified between the initial literature search and the final manuscript drafting were identified using the same search strategy.

Validity assessment

All papers were analysed by the expert panel (two reviewers per paper) using standardized data extraction and predefined scoring forms for demographics, diagnostic [21] and therapeutic studies. Discrepancies were

resolved by a third expert (M.W.B.) to reach consensus. Adapted classification tables for diagnostic [22] and therapeutic [23] studies were used to determine the level of evidence and strength of each recommendation (see supplementary Tables S3 and S4, available at *Rheumatology* online).

Establishment of recommendations

Data from the included articles were extrapolated to develop provisional statements regarding diagnosis and treatment of IgAV (N.d.G., N.G., P.B., S.O., S.K. and M.W.B.). These provisional statements were presented to the expert committee ($n = 14/16$) using an online survey (with 100% response rate) [24]. Recommendations were revised according to responses and discussed at a face-to-face consensus meeting (March 2015, $n = 14/16$ experts). An adapted nominal group technique [25] was used to reach consensus as used across all SHARE recommendations (see above), with final recommendations accepted only if $\geqslant 80\%$ agreement was reached among experts.

Results

Literature search and guideline formulation

The overall vasculitis literature search yielded 8077 articles (supplementary Fig. S1, available at Rheumatology online), of which 7766 articles remained after removal of duplications. A total of 5183 articles were then excluded as they did not meet the inclusion criteria (supplementary Fig. S1, available at *Rheumatology* online). A total of 272 articles pertaining to IgAV were identified and together with a parallel detailed evidence synthesis review of the management of IgAV [9] helped inform the development of the draft recommendations. References pertaining to KD ($n = 826$) and to rare paediatric systemic vasculitides ($n = 1485$) informed recommendations described in separate manuscripts (supplementary Fig. S1, available at *Rheumatology* online).

A total of 26 recommendations were accepted at the consensus meeting with 100% agreement throughout: 7 recommendations for the diagnosis and 19 for the treatment of IgAV in children. Of note, 21 out of the 26 accepted consensus recommendations were based on the panel's collective expert opinion alone (i.e. level of evidence 4, strength of evidence D) as there was a lack of more robust published evidence.

Diagnostic recommendations for IgAV

Table 1 summarizes the SHARE recommendations for diagnosing IgAV, including laboratory and wider diagnostic work-up.

Classification criteria for IgAV

There is no single diagnostic test for IgAV and diagnosis relies on clinical criteria and laboratory findings. As a result, many criteria have been developed over the years for defining and classifying the disease, including the ACR classification criteria [27] and the Chapel Hill Consensus Conference definition [1]. The expert panel recognized the strengths of each of these but agreed unanimously that the EULAR/PRINTO/Paediatric Rheumatology European Society-endorsed Ankara 2008 criteria should be used to classify IgAV [26]. This was because they were developed based on a large international registry of patients and were validated specifically for childhood-onset disease. Classification criteria, however, should not be used as diagnostic criteria [28].

Usefulness of skin biopsy in diagnostic work-up

The typical skin lesions of IgAV are purpura that are palpable and predominantly (but not exclusively) present on the buttocks and lower limbs. The finding of a leucocytoclastic vasculitis associated with IgA deposition in a skin biopsy can help to accurately diagnose IgAV. However, skin biopsy is not required for typical lesions that predominantly involve the lower limbs and buttocks. The expert panel agreed unanimously that a skin biopsy including specific staining for IgA should be performed in case of atypical rash (such as extensive lesions or diffusely distributed lesions) to exclude alternative diagnoses. Where skin biopsies are performed, they should be of the most recent lesions. At the same time, absence of IgA staining on biopsy does not exclude the diagnosis of IgAV [29]. Performing a skin biopsy is also important to exclude other forms of vasculitis such as ANCA-associated vasculitis, particularly in older children who may present initially with features compatible with IgAV.

Diagnostic work-up for IgAV nephritis

Renal involvement of IgAV occurs in 20–80% of children and can present with isolated microscopic (and/or macroscopic) haematuria with or without proteinuria, nephritic and/or nephrotic syndrome. Overall, the prognosis is excellent for those children with mild presentation [30–34]. The key goal for the diagnostic work-up and ongoing disease monitoring of IgAV is early detection of persistent renal involvement, specifically IgAV nephritis. Persistent renal inflammation, if undiagnosed, may progress to permanent renal damage and scarring [35]. However, signs of IgAV nephritis usually are limited to urine abnormalities without clinical symptoms in children who are normotensive with normal renal function and the nephritis may recover without treatment. This makes monitoring and appropriate management difficult without evidence-based guidelines. Indeed, the long-term risk of permanent renal impairment in patients with minor urine abnormalities is low (e.g. 1.6%) [6], but rises considerably in children with nephrotic and/or nephritic syndrome (e.g. up to 19.5%) [6, 36, 37]. Although children with mild renal involvement carry a risk of severe long-term complications, the risk of progression to chronic kidney disease is between 5% and 20% of children with $>50\%$ crescentic glomerulonephritis [8, 38, 39].

All children with suspected IgAV must therefore be proactively investigated for renal involvement, at diagnosis and throughout follow-up. Importantly, the introduction of a standardized pathway for the monitoring of IgAV can facilitate the safe and effective monitoring of children

Table 1 SHARE recommendations for the diagnosis of IgAV

Number	Recommendations: Diagnosis	LoE	SoR
Classification criteria			
1.	The EULAR/PRINTO/PReS-endorsed Ankara 2008 criteria should be used to classify IgAV (formerly known as HSP) [26]	2A	B
Use of biopsy			
2.	A skin biopsy including specific immunofluorescence staining for IgA should be performed in case of atypical rash and/or to exclude alternative diagnoses; skin biopsy is not needed in a patient with the typical purpuric skin rash on lower limbs and buttocks	4	D
3.	Absence of IgA immunofluorescence staining on biopsy does not exclude the diagnosis of IgAV	3	C
Renal work-up			
4.	Renal involvement should be investigated using eGFR and urinalysis (haematuria and UP:UC ratio or UA:UC ratio)	2B	C
5.	A paediatric nephrologist should be consulted if an IgAV patient has moderate proteinuria[a] and/or impaired GFR[b]	4	D
6.	A renal biopsy should be performed if an IgAV patient has severe proteinuria (>250 mg/mmol for at least 4 weeks; although shorter duration of severe proteinuria is also a relative indication for biopsy), persistent moderate (100–250 mg/mmol) proteinuria[c] or impaired GFR[b]	2A	
Imaging			
7.	In severe abdominal pain, an US should be performed by an ultrasonographer with paediatric expertise to exclude intestinal intussusception	4	D

[a]Moderate proteinuria: UP:UC ratio 100–250 mg/mmol in an early morning urine sample. [b]Impaired GFR: <80 ml/min/1.73 m^2. [c]Persistent proteinuria, defined as per severity—see Table 2 for full definitions; note, for severe proteinuria >250 mg/mmol, renal biopsy may also be considered before 4 weeks (relative indication for biopsy), and persistence >4 weeks at this level is regarded as an absolute indication for renal biopsy. SHARE: Single Hub and Access point for paediatric Rheumatology in Europe; LoE: level of evidence; 1A: meta-analysis of cohort studies; 1B: meta-analysis of case–control studies; 2A: cohort studies; 2B: case–control studies; 3: non-comparative descriptive studies; 4: expert opinion [22]; SoR: strength of recommendation: A: based on level 1 evidence; B: based on level 2 or extrapolated from level 1; C: based on level 3 or extrapolated from level 1 or 2; D: based on level 4 or extrapolated from level 3 or 4 expert opinion [19]; HSP: Henoch-Schönlein purpura; IgAV: IgA vasculitis; PReS: Paediatric Rheumatology European Society; UP:UC: urine protein:urine creatinine ratio; UA:UC: urine albumin:urine creatinine ratio; eGFR, estimated glomerular filtration rate.

[40]. Specifically, the panel agreed that renal involvement should be investigated with blood pressure measurement, early morning urinalysis and assessment of renal function with estimated glomerular filtration rate (eGFR). eGFR is calculated from plasma creatinine and height using the Schwartz formula, and may provide a more accurate estimate of renal function corrected for body surface area, than plasma creatinine alone [41, 42]. Urinalysis should include determination of the presence of haematuria and quantification of albuminuria and/or proteinuria [with early morning (first sample of day) urine albumin:urine creatinine or urine protein:urine creatinine ratio] [43]. Furthermore, blood pressure measurement and urinalysis need to be monitored for at least 6–12 months even if the initial blood pressure measurements and urinalysis are normal.

Although routine monitoring of a child's renal status using this approach is appropriate, and the natural disease course of IgAV means that the majority of patients with renal involvement initially will recover, there needs to be a safe and appropriate threshold for referral for expert paediatric nephrology opinion [40]. Table 2 provides definitions regarding the severity of IgAV nephritis and proteinuria, as agreed by the expert panel. Mild IgAV nephritis indicates normal eGFR and mild–moderate proteinuria. It corresponds generally to either no clear indication for renal biopsy, or (if biopsied) to histological evidence of Class I (minimal changes) or Class II (mesangial changes only) according to the International Study of Kidney Disease in Children histological classification of IgAV nephritis [44]. However, for moderate proteinuria (urine protein:creatinine ratio 100–250 mg/mmol, in an early morning urine sample) and/or impaired eGFR (<90 ml/min/1.73 m^2), the panel all agreed that a paediatric nephrologist should be consulted.

The panel considered indications for renal biopsy in patients with suspected IgAV nephritis. It was recommended that renal biopsy should be performed in case of impaired eGFR, or if there is severe or persistent proteinuria (with definitions of persistence dependent upon the severity of the proteinuria; Tables 1 and 2). Additional indications for which renal biopsy should be considered include: acute kidney injury with worsening renal function as part of rapidly progressive glomerulonephritis; patients who are nephrotic (e.g. heavy proteinuria, hypoalbuminaemia and oedema) or nephritic (e.g. impaired eGFR, hypertension, haematuria/proteinuria) at any time point. Moderate IgAV nephritis (Table 2) usually equates to Class III histology; severe IgAV nephritis usually corresponds to Class IV or V in the International Study of Kidney Disease in Children histological classification, with >50% crescent formation [44].

Table 2 Definitions of severity of IgAV nephritis

Severity of IgAV nephritis	Definition
Mild	Normal GFR[a] and mild[b] or moderate[c] proteinuria
Moderate	<50% crescents on renal biopsy and impaired GFR[d] or severe persistent proteinuria[e] [44]
Severe	>50% crescents on renal biopsy and impaired GFR[c] or severe persistent proteinuria[e] [44]
Persistent proteinuria [43]	• UP:UC ratio >250 mg/mmol for 4 weeks[e] [44] • UP:UC ratio >100 mg/mmol for 3 months • UP:UC ratio >50 mg/mmol for 6 months

[a]Normal GFR: >80 ml/min/1.73 m^2. [b]Mild proteinuria: UP:UC ratio <100 mg/mmol (in an early morning urine sample). [c]Moderate proteinuria: UP:UC ratio 100–250 mg/mmol (in an early morning urine sample). [d]Impaired GFR: <80 ml/min/1.73 m^2. [e]Severe persistent proteinuria: >250 mg/mmol for at least 4 weeks. Note: for those that use different units, these conversions can be used to determine equivalent cut-off scores: 1 g/day of proteinuria (in 24 h urine collection) = UP:UC (early morning UP:UC ratio) of 100 mg/mmol = UA:UC (early morning UA:UC ratio) of 70 mg/mmol. This approximates to urine dipstick testing for proteinuria of 150 mg/dl but does not replace laboratory UP:UC or UA:UC. IgAV: IgA vasculitis; GFR: glomerular filtration rate; UP:UC: urine protein:urine creatinine ratio; UP:UC: urine albumin:urine creatinine ratio.

Diagnostic work-up for gastrointestinal involvement of IgAV

IgAV is associated with a wide range of associated gastrointestinal features including gastritis, duodenitis, gastrointestinal mucosal ulceration and purpura [45]. Periumbilical and/or epigastric pain is common, especially with meals, and bleeding is generally occult, although it can be associated with melena. However, intussusception is by far the most serious and common surgical complication, usually either ileo-ileo, or ileo-colic [45]. For this reason, the panel agreed that in cases of severe abdominal pain, an US should be performed by an ultrasonographer with paediatric expertise to exclude intussusception.

Treatment recommendations for IgAV

Table 3 summarizes the SHARE recommendations regarding the general management of IgAV.

Use of analgesia

Arthralgia and/or acute arthritis occur in about 78% of children [26]. In the acute phase, the pain can be significant, and yet concern about renal toxicity often limits the use of anti-inflammatory analgesics. The panel agreed that NSAIDs and/or paracetamol are not contraindicated in the absence of nephritis in IgAV, or in the presence of microscopic haematuria as the sole renal finding in IgAV nephritis, since this is benign. There was insufficient evidence for the panel to make any firm recommendation regarding the risk of gastrointestinal bleeding from NSAID in IgAV, but pragmatically (and in general) the use of NSAID is contraindicated in the presence of active gastrointestinal bleeding. Diffuse abdominal pain may occur in up to 60% of children [26] and may require analgesia, which should be instituted without undue delay while assessing for potential surgical complications (see above).

Treatment with CS

In general, most patients with IgAV only require supportive treatment and adequate analgesia. However, some children may require CS for select indications. Aside from IgAV nephritis (see below), key complications of IgAV where CS should be considered include: orchitis, cerebral vasculitis, pulmonary haemorrhage and severe gastrointestinal involvement [9, 46–49]. Organ- or life-threatening involvement may also require the addition of cytotoxic immunosuppressants or even plasma exchange as suggested by the SHARE group for rare systemic vasculitides [18].

In patients with severe abdominal pain and/or rectal bleeding, CS treatment could also be considered (see above) [45], although the panel recognized the paucity of robust data to guide this recommendation. Clinical trial data have demonstrated that CS may reduce the intensity and duration of abdominal pain in early IgAV [50]. However, other studies reported no clear advantage of prednisone over supportive treatment such as nasogastric decompression, parenteral nutrition and antibiotics [46, 51].

Recommended doses of oral CS are prednisolone 1–2 mg/kg/day (e.g. for 1–2 weeks with weaning over the subsequent fortnight). For severe cases (e.g. severe cerebral, pulmonary or gastrointestinal involvement), pulsed i.v. methylprednisolone 10–30 mg/kg with a maximum of 1 g/day for three consecutive days may be considered [46].

Prophylactic CS treatment to prevent the development of IgAV nephritis is not indicated [31, 52, 53] since controlled studies have shown that patients who received CS at the early stage of the disease developed kidney involvement as frequently as those who did not.

Therapeutic recommendations for IgAV nephritis

Table 3 and Fig. 1 summarize the SHARE recommendations regarding the treatment of IgAV nephritis.

General recommendations

Since a key priority is to avoid permanent renal damage [35, 40], and high-quality evidence is currently lacking regarding the treatment of IgAV nephritis, the panel highlighted the urgent need for randomized controlled trials for the treatment of IgAV nephritis.

There is accumulating evidence supporting the beneficial effect of renin-angiotensin blockade in patients with proteinuria [54]. Therefore, in children with IgAV who have renal involvement with persistent proteinuria (>3 months

Table 3 SHARE recommendations for the treatment of IgAV

Number	Recommendations: Treatment	LoE	SoR
Analgesia			
1.	Adequate analgesia should be prescribed for IgAV-associated arthropathy[a]	4	D
2.	NSAIDs are not contraindicated if renal function is normal in IgAV	4	D
3.	Adequate analgesia should be prescribed for IgAV-associated abdominal pain	4	D
Use of CS			
4.	CS treatment is indicated in case of: • Orchitis • Cerebral vasculitis • Pulmonary haemorrhage • Other severe organ- or life-threatening vasculitis manifestations	4	D
5.	In patients with severe abdominal pain and/or rectal bleeding (in whom intestinal intussusception has been excluded), CS treatment could be considered	4	D
6.	The dose of oral CS (prednisolone/prednisone) should be 1–2 mg/kg/day	4	D
7.	If CS are indicated, pulsed i.v. methylprednisolone (e.g. 10–30 mg/kg with a maximum of 1 g/day on three consecutive days) may be considered for severe cases	4	D
8.	Prophylactic CS treatment to prevent the development of IgAV-associated nephritis is not indicated	1B	A
IgAV nephritis			
9.	When starting treatment of IgAV nephritis, a paediatric nephrologist should be consulted	4	D
10.	In the absence of robust data for evidence supporting the treatment of nephritis, a randomized controlled trial for the treatment of IgAV nephritis is urgently needed	4	D
11.	ACE inhibitors should be considered in IgAV nephritis to prevent/limit secondary glomerular injury for patients with persistent proteinuria	4	D
12.	Oral prednisolone should be used as first-line treatment in patients with mild IgAV nephritis	4	D
13.	AZA, MMF and/or pulsed methylprednisolone can be used as second-line treatment in patients with IgAV nephritis following renal biopsy	4	D
14.	Oral prednisolone and/or pulsed methylprednisolone should be used as first-line treatment in patients with moderate IgAV nephritis	4	D
15.	AZA, MMF or i.v. CYC may be used in the first- or second-line treatment of moderate IgAV nephritis	4	D
16.	Ciclosporin or oral CYC cannot be routinely recommended in moderate IgAV nephritis	4	D
17.	As in other severe systemic small vessel vasculitides, i.v. CYC with pulsed methylprednisolone and/or oral prednisolone are recommended as first-line treatment in patients with severe IgAV nephritis	4	D
18.	In combination with steroid therapy, AZA and MMF may be used as maintenance treatment in patients with severe IgAV nephritis	4	D
19.	One treatment approach for IgAV nephritis is listed below in Fig. 1	4	D

[a]Adequate fluid intake is essential when taking NSAIDs. SHARE: Single Hub and Access point for paediatric Rheumatology in Europe; LoE: level of evidence; 1A: meta-analysis of randomized controlled trials; 1B: randomized controlled study; 2A: controlled study without randomization; 2B: quasi-experimental study; 3: descriptive study; 4: expert opinion [20]; SoR: strength of recommendation; A: based on level 1 evidence; B: based on level 2 or extrapolated from level 1; C: based on level 3 or extrapolated from level 1 or 2; D: based on level 4 or extrapolated from level 3 or 4 expert opinion [17]; IgAV: IgA vasculitis; ACE: angiotensin-converting enzyme.

duration) irrespective of whether they are receiving prednisolone or other immunosuppressive treatment, the panel recommended that an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be considered to prevent and/or limit secondary glomerular injury [55].

IgAV nephritis—specific recommendations

Recommendations for mild, moderate and severe IgAV nephritis (defined in Table 2) are outlined below.

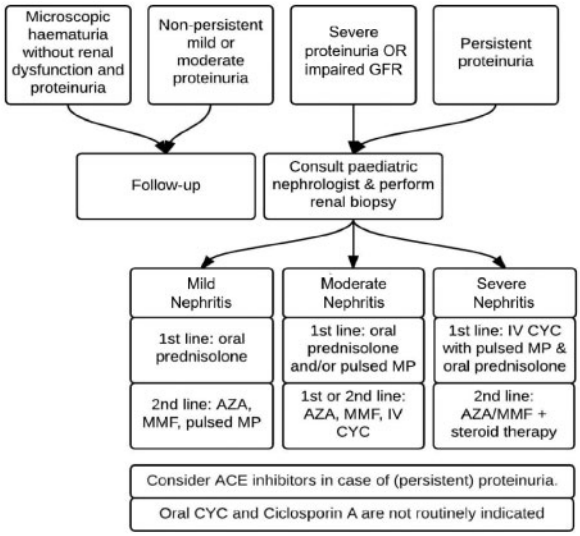
Treatment of mild IgAV nephritis

For patients with mild IgAV nephritis, oral prednisolone should be used as first-line treatment [56, 57]. However, it was acknowledged that some patients may have persistent proteinuria (see Table 2) that does not resolve. Addition of AZA or MMF [58–61], or ciclosporin [62], may be considered as second-line treatment or CS-sparing agent. Pulsed i.v. methylprednisolone may also be warranted, although is rarely required for those with truly mild IgAV nephritis.

Treatment of moderate IgAV nephritis

For patients with moderate IgAV nephritis, oral prednisolone or pulsed i.v. methylprednisolone should be used as first-line treatment [63]. Addition of AZA, MMF or i.v. CYC may also be used in the first- or second-line treatment of moderate nephritis according to the histopathological findings in the renal biopsy [7]. There was insufficient

Fig. 1 Guideline for the management of IgA vasculitis-associated nephritis



For definitions of severity of proteinuria, see Table2. For IgA vasculitis-associated crescentic glomerulonephritis, please see section on crescentic glomerulonephritis. IV: intravenous; MP: methylprednisolone; ACE: angiotensin-converting enzyme.

evidence to recommend ciclosporin or oral CYC routinely in the treatment of moderate IgAV nephritis.

Treatment of severe IgAV nephritis

Severe IgAV nephritis is treated similarly to systemic small vessel vasculitis with kidney involvement, e.g. ANCA-associated vasculitides (AAV) [18], usually with high-dose CS and i.v. CYC to induce remission, and lower doses of CS combined with AZA or MMF [58–61] as maintenance treatment [64]. Since there is a lack of evidence to support this approach, treatment of such severely affected individuals is recommended only under expert supervision, particularly regarding duration of induction and maintenance phases of treatment, how and when to wean treatment, and how to monitor therapeutic response (or lack thereof).

Fig. 1 summarizes such a treatment approach for IgAV nephritis, encompassing all these recommendations/caveats.

Discussion

These SHARE recommendations, while acknowledging a lack of high-level evidence, provide international, expert, consensus recommendations for the diagnosis and treatment of IgAV and IgAV nephritis. A total of 7 recommendations for diagnosis and 19 for treatment were accepted with 100% agreement.

The therapeutic recommendations are largely based on expert opinion, emphasizing an important unmet need for high-level controlled therapeutic trials for severe IgAV nephritis. Kidney Disease: Improving Global Outcomes (KDIGO) has previously suggested recommendations for the treatment of the nephritis of IgAV, again mainly based on expert opinion [54]. The KDIGO group has also suggested angiotensin-converting enzyme inhibitor for persistent proteinuria because of its beneficial effects on proteinuria and the mesangial cell. However, Davin and Coppo [65] have stressed that the use of angiotensin-converting enzyme inhibitors should not delay the initiation of an effective anti-inflammatory treatment for the underlying pathology, and emphasize that the KDIGO recommendations are mainly based on experience of IgA nephritis rather than IgAV *per se* [54]. While the kidney pathology may be similar, the nephritis of IgAV is an acute damage to the endothelium and is different from the slowly progressive IgA nephritis, and thus warrants acute anti-inflammatory therapy [65]. Thus, we recommend CS and a variety of immunosuppressive agents for IgAV nephritis, based on the few paediatric reports available (recommendations 15 and 16). It is interesting that KDIGO does not suggest the use of immunosuppression, except for the use of CYC for >50% crescents [54]. However, the literature search and expert opinion emphasize the need for effective immunosuppression in the acute stages of this (acute) vasculitis, in order to prevent chronic kidney disease including renal failure [32, 57, 63, 64]. We thus believe that our recommendations will be more widely applicable for paediatric practice. For severe IgAV nephritis, both KDIGO and we have suggested a treatment similar to glomerulonephritis in ANCA-associated vasculitides [54].

Only well-designed, multicentre studies will inform us how to treat patients with milder forms of renal involvement or gastrointestinal manifestations of IgAV. It was beyond the remit of this process to develop a comprehensive list of subsequent research priorities. However, studies to assess the validity of the use of the 'Oxford Classification of IgA Nephropathy' for IgAV nephritis are needed, in addition to well-designed studies that clarify the mode, dose and duration of CS and compare AZA with MMF in IgAV nephritis.

In conclusion, the SHARE project has resulted in recommendations on diagnosis, management and treatment of IgAV and IgAV nephritis, based on best available evidence and expert opinion. These recommendations should facilitate the optimization of the management of this condition.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Jennette JC, Falk RJ, Bacon PA. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1–11.

2 Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 2002;360:1197–202.

3 Nielsen HE. Epidemiology of Schönlein-Henoch purpura. Acta Paediatr Scand 1988;77:125–31.

4 Piram M, Mahr A. Epidemiology of immunoglobulin A vasculitis (Henoch-Schönlein): current state of knowledge. Curr Opin Rheumatol 2013;25:171–8.

5 Brogan P, Eleftheriou D, Dillon M. Small vessel vasculitis. Pediatr Nephrol 2010;25:1025–35.

6 Narchi H. Risk of long term renal impairment and duration of follow up recommended for Henoch-Schonlein purpura with normal or minimal urinary findings: a systematic review. Arch Dis Child 2005;90:916–20.

7 Altugan FS, Ozen S, Aktay-Ayaz N *et al*. Treatment of severe Henoch-Schönlein nephritis: justifying more immunosuppression. Turk J Pediatr 2009;51:551–5.

8 Bogdanovic R. Henoch-Schonlein purpura nephritis in children: risk factors, prevention and treatment. Acta Paediatr 2009;98:1882–9.

9 Bayrakci US, Baskin E, Ozen S. Treatment of Henoch Schönlein Purpura: what evidence do we have? Int J Clin Rheumatol 2010;5:669–76.

10 Wulffraat NM, Vastert B, SHARE consortium. Time to share. Pediatr Rheumatol Online J 2013;11:5.

11 Enders FB, Bader-Meunier B, Baildam E *et al*. Consensus-based recommendations for the management of juvenile dermatomyositis. Ann Rheum Dis 2017;76:329–40.

12 Giancane G, Ter Haar NM, Wulffraat N *et al*. Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever. Ann Rheum Dis 2015;74:635–41.

13 ter Haar NM, Oswald M, Jeyaratnam J *et al*. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis 2015;74:1636–44.

14 Groot N, de Graeff N, Avcin T *et al*. European evidence-based recommendations for diagnosis and treatment of paediatric antiphospholipid syndrome: the SHARE initiative. Ann Rheum Dis 2017;76:1637–41.

15 Groot N, de Graeff N, Avcin T *et al*. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. Ann Rheum Dis 2017;76:1788–96.

16 Groot N, de Graeff N, Marks SD *et al*. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. Ann Rheum Dis 2017;76:1965–73.

17 de Graeff N, Groot N, Ozen S *et al*. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease - the SHARE initiative. Rheumatology (Oxford). 2018 Dec 7. doi: 10.1093/rheumatology/key344.

18 de Graeff NG, Groot N, Brogan P *et al*. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides – the SHARE initiative. Rheumatology (Oxford) 2018; Advance Access published 7 December 2018, doi: 10.1093/rheumatology/key322.

19 Dougados M, Betteridge N, Burmester GR *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. Ann Rheum Dis 2004;63:1172–6.

20 Leclercq E, Leeflang MM, van Dalen EC, Kremer LC. Validation of search filters for identifying pediatric studies in PubMed. J Pediatr 2013;162:629–34.e2.

21 Whiting P, Rutjes AW, Reitsma JB *et al*. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med 2004;140:189–202.

22 Zhang W, Doherty M, Pascual E *et al*. EULAR evidence based recommendations for gout. Part I: diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1301–11.

23 Zhang W, Doherty M, Bardin T *et al*. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312–24.

24 McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. Int J Clin Pharm 2016;38:655–62.

25 Harvey N, Holmes CA. Nominal group technique: an effective method for obtaining group consensus. Int J Nurs Pract 2012;18:188–94.

26 Ozen S, Pistorio A, Iusan SM *et al*. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and

childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis 2010;69:798–806.

27 Mills JA, Michel BA, Bloch DA *et al*. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. Arthritis Rheum 1990;33:1114–21.

28 Hunder GG. The use and misuse of classification and diagnostic criteria for complex diseases. Ann Intern Med 1998;129:417–8.

29 Linskey KR, Kroshinsky D, Mihm MC Jr, Hoang MP. Immunoglobulin-A-associated small-vessel vasculitis: a 10-year experience at the Massachusetts General Hospital. J Am Acad Dermatol 2012;66:813–22.

30 Chan H, Tang YL, Lv XH *et al*. Risk factors associated with renal involvement in childhood Henoch-Schönlein purpura: a meta-analysis. PLoS One 2016;11:e0167346.

31 Jauhola O, Ronkainen J, Koskimies O *et al*. Renal manifestations of Henoch-Schonlein purpura in a 6-month prospective study of 223 children. Arch Dis Child 2010;95:877–82.

32 de Almeida JL, Campos LM, Paim LB *et al*. Renal involvement in Henoch-Schönlein purpura: a multivariate analysis of initial prognostic factors. J Pediatr (Rio J) 2007;83:259–66.

33 Kaku Y, Nohara K, Honda S. Renal involvement in Henoch-Schönlein purpura: a multivariate analysis of prognostic factors. Kidney Int 1998;53:1755–9.

34 Shin JI, Park JM, Shin YH *et al*. Predictive factors for nephritis, relapse, and significant proteinuria in childhood Henoch-Schönlein purpura. Scand J Rheumatol 2006;35:56–60.

35 Ronkainen J, Nuutinen M, Koskimies O. The adult kidney 24 years after childhood Henoch-Schönlein purpura: a retrospective cohort study. Lancet 2002;360:666–70.

36 Butani L, Morgenstern BZ. Long-term outcome in children after Henoch-Schönlein purpura nephritis. Clin Pediatr (Phila) 2007;46:505–11.

37 Coppo R, Andrulli S, Amore A *et al*. Predictors of outcome in Henoch-Schönlein nephritis in children and adults. Am J Kidney Dis 2006;47:993–1003.

38 Goldstein AR, White RH, Akuse R, Chantler C. Long-term follow-up of childhood Henoch-Schönlein nephritis. Lancet 1992;339:280–2.

39 Koskimies O, Mir S, Rapola J, Vilska J. Henoch-Schönlein nephritis: long-term prognosis of unselected patients. Arch Dis Child 1981;56:482–4.

40 Watson L, Richardson AR, Holt RC, Jones CA, Beresford MW. Henoch schonlein purpura–a 5-year review and proposed pathway. PLoS One 2012;7:e29512.

41 Mian AN, Schwartz GJ. Measurement and estimation of glomerular filtration rate in children. Adv Chronic Kidney Dis 2017;24:348–56.

42 Salvador CL, Tondel C, Rowe AD *et al*. Estimating glomerular filtration rate in children: evaluation of creatinine- and cystatin C-based equations. Pediatr Nephrol 2019;34:301–311.

43 Foster HB, Brogan P. Oxford handbook of paediatric rheumatology, 2nd edn. Oxford: Oxford University Press, 2018.

44 Koskela M, Ylinen E, Ukonmaanaho EM *et al*. The ISKDC classification and a new semiquantitative classification for predicting outcomes of Henoch-Schönlein purpura nephritis. Pediatr Nephrol 2017;32:1201–9.

45 Ebert EC. Gastrointestinal manifestations of Henoch-Schonlein Purpura. Dig Dis Sci 2008;53:2011–9.

46 Ronkainen J, Koskimies O, Ala-Houhala M *et al*. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. J Pediatr 2006;149:241–7.

47 Sohagia AB, Gunturu SG, Tong TR, Hertan HI. Henoch-schonlein purpura-a case report and review of the literature. Gastroenterol Res Pract 2010;2010:597648.

48 Sag E, Batu ED, Ozen S. Childhood systemic vasculitis. Best Pract Res Clin Rheumatol 2017;31:558–75.

49 Ha TS, Lee JS. Scrotal involvement in childhood Henoch-Schönlein purpura. Acta Paediatr 2007;96:552–5.

50 Alvarez-Caro F, Concha-Torre JA, García-Hernández I *et al*. Massive lower gastrointestinal haemorrhage, successfully treated with corticosteroids, as main symptom of Schönlein-Henoch purpura. Rheumatol Int 2009;29:1491–4.

51 Chen SY, Kong MS. Gastrointestinal manifestations and complications of Henoch-Schonlein purpura. Chang Gung Med J 2004;27:175–81.

52 Dudley J, Smith G, Llewelyn-Edwards A *et al*. Randomised, double-blind, placebo-controlled trial to determine whether steroids reduce the incidence and severity of nephropathy in Henoch-Schonlein Purpura (HSP). Arch Dis Child 2013;98:756–63.

53 Huber AM, King J, McLaine P, Klassen T, Pothos M. A randomized, placebo-controlled trial of prednisone in early Henoch Schonlein Purpura [ISRCTN85109383]. BMC Med 2004;2:7.

54 KDIGO. Chapter 11: Henoch-Schönlein purpura nephritis. Kidney Int Suppl (2011) 2012;2:218–20. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-GN-Guideline.pdf.

55 Coppo R, Peruzzi L, Amore A *et al*. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. J Am Soc Nephrol 2007;18:1880–8.

56 Pillebout E, Alberti C, Guillevin L, Ouslimani A, Thervet E, CESAR study group. Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schonlein Purpura. Kidney Int 2010;78:495–502.

57 Tarshish P, Bernstein J, Edelmann CM Jr. Henoch-Schönlein purpura nephritis: course of disease and efficacy of cyclophosphamide. Pediatr Nephrol 2004;19:51–6.

58 Du Y, Hou L, Zhao C, Han M, Wu Y. Treatment of children with Henoch-Schönlein purpura nephritis with mycophenolate mofetil. Pediatr Nephrol 2012;27:765–71.

59 Hackl A, Becker JU, Körner LM *et al*. Mycophenolate mofetil following glucocorticoid treatment in Henoch-Schönlein purpura nephritis: the role of early initiation and

therapeutic drug monitoring. Pediatr Nephrol 2018;33:619–29.

60 Mizerska-Wasiak M, Małdyk J, Demkow U, Roszkowska-Blaim M, Pańczyk-Tomaszewska M. Treatment outcomes in children with Henoch-Schönlein nephritis. Adv Exp Med Biol 2016;912:65–72.

61 Ren P, Han F, Chen L *et al*. The combination of mycophenolate mofetil with corticosteroids induces remission of Henoch-Schönlein purpura nephritis. Am J Nephrol 2012;36:271–7.

62 Jauhola O, Ronkainen J, Autio-Harmainen H *et al*. Cyclosporine A vs. methylprednisolone for Henoch-Schönlein nephritis: a randomized trial. Pediatr Nephrol 2011;26:2159–66.

63 Niaudet P, Habib R. Methylprednisolone pulse therapy in the treatment of severe forms of Schönlein-Henoch purpura nephritis. Pediatr Nephrol 1998;12:238–43.

64 Baskin E, Ozen S, Cakar N *et al*. The use of low-dose cyclophosphamide followed by AZA/MMF treatment in childhood lupus nephritis. Pediatr Nephrol 2010;25:111–7.

65 Davin JC, Coppo R. Pitfalls in recommending evidence-based guidelines for a protean disease like Henoch-Schönlein purpura nephritis. Pediatr Nephrol 2013;28:1897–903.