

EUROPEAN CONSENSUS-BASED RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT OF IgA VASCULITIS – THE SHARE INITIATIVE

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Key messages

1. IgA Vasculitis is the commonest cause of systemic vasculitis in childhood.
2. These are the first international, evidence-based recommendations concerning the management of childhood IgA Vasculitis.
3. All IgA Vasculitis patients need proactively investigated for renal involvement, at diagnosis and throughout follow-up.

Keywords:

Childhood / paediatric; IgA Vasculitis (Henoch-Schönlein Purpura); Systemic vasculitis; Diagnosis; Management; Recommendations

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ABSTRACT

Objectives

IgA Vasculitis (IgAV, formerly known as Henoch-Schönlein Purpura, HSP) is the commonest 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 European League Against Rheumatism 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 $\geq 80\%$ 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 workup and imaging. Treatment recommendations included: the importance of appropriate analgesia and ACE-inhibitor use and non-renal indications for corticosteroid use, as well as a structured approach to treating IgAV nephritis, including appropriate use of corticosteroids and second-line agents in mild, moderate and severe disease along with use of ACE-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.

Introduction

IgA Vasculitis (IgAV; formerly known as Henoch-Schönlein Purpura, HSP[1]) is the commonest 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 which 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 (ESRD) 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 antiphospholipid syndrome, juvenile dermatomyositis, familial Mediterranean fever, auto-inflammatory diseases, childhood-onset lupus and lupus nephritis 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 randomised 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 and the rarer childhood systemic vasculitides will be published separately (currently in press).

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 (EU)-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 (BF). The SHARE methods have previously been described in detail[15, 16] including use of the European League Against Rheumatism (EULAR) standardised operating procedure for developing best practice recommendations[17].

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. Whilst these latter did not directly inform the recommendations, they were included in the manuscript commentary to provide up-to-date face validity and contextualisation. 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[18] (Tables S1 and S2 respectively). The comprehensive literature review was undertaken inclusive of these other forms of systemic vasculitis to ensure 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 (NdG, NG) and full text checked when necessary to determine eligibility. Disagreement was resolved by a third reviewer (MWB); 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 standardised data extraction and predefined scoring forms for demographics, diagnostic[19] and therapeutic studies. Discrepancies were resolved by a third expert (MWB) to reach consensus. Adapted classification tables for diagnostic[20] and therapeutic[21] studies were used to determine the level of evidence and strength of each recommendation (see Tables S3, S4).

Establishment of recommendations

Data from the included articles were extrapolated to develop provisional statements regarding diagnosis and treatment of IgAV (NdG, NG, PB, SO, SK and MWB). These provisional statements were presented to the expert committee (n=14/16) using **an online survey** (with 100% response rate)[22]. 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** [23] was used to reach consensus as used across all SHARE recommendations (see above), final recommendations accepted only if ≥80% agreement was reached among experts.

RESULTS

Literature search and guideline formulation

The overall vasculitis literature search yielded 8,077 articles (Figure S1), of which 7,766 articles remained after removal of duplications. A total of 5,183 articles were then excluded as they did not meet the inclusion criteria (Figure S1). A total of 272 articles pertaining to IgAV were identified and along with

a parallel detailed evidence synthesis review of the management of IgAV [9], together 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 (Figure S1).

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 summarises 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 American College of Rheumatology (ACR) classification criteria[24], and the Chapel Hill Consensus Conference (CHCC) definition[1]. The expert panel recognised the strengths of each of these but agreed unanimously that the *European League Against Rheumatism (EULAR) / Paediatric International Trials Organisation (PRINTO) / Paediatric Rheumatology European Society (PReS)*-endorsed Ankara 2008 criteria should be used to classify IgAV[25]. 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[26].

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 [27]. 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[28-32]. 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[33]. 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, 34, 35]. Although children with mild renal involvement carry a risk for severe long-term complications, the risk of progression to chronic kidney disease is between 5% and 20% of children with more than 50% crescentic glomerulonephritis[8, 36, 37].

All children with suspected IgAV must therefore be proactively investigated for renal involvement, at diagnosis and throughout follow-up. Importantly, the introduction of a standardised pathway for the monitoring of IgAV can facilitate the safe and effective monitoring of children[38]. 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[39, 40]. Urinalysis should include determining the presence of haematuria and quantification of albuminuria and/or proteinuria (with early morning (first sample of day) urine albumin:creatinine or urine protein:creatinine ratio (UA:UC or UP:UC ratio)[41]. Furthermore, blood pressure measurement and urinalysis needs 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[38]. 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 (ISKDC) histological classification of IgAV nephritis[42]. However, for moderate proteinuria (UP:UC ratio 100-250 mg/mmol, in an early morning urine sample), and/or impaired eGFR (<90 mls/min/1.73m²), 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 ISKDC histological classification, with more than 50% crescent formation[42].

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[43]. 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 commonest surgical complication, usually either ileo-ileo, or ileo-colic[43]. For this reason, the panel agreed that in cases of severe abdominal pain, an ultrasound should be performed by an ultrasonographer with paediatric expertise to exclude intussusception.

Treatment recommendations for IgAV

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

Use of Analgesia

Arthralgia and/or acute arthritis occur in about 78% of children[25]. 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 non-steroidal anti-inflammatory drugs (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 GI 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[25] and may require analgesia, which should be instituted without undue delay whilst assessing for potential surgical complications (see above).

Treatment with Corticosteroids

In general, most patients with IgAV only require supportive treatment and adequate analgesia. However, some children may require corticosteroids for select indications. Aside from IgAV nephritis (see below), key complications of IgAV where corticosteroids should be considered include: orchitis, cerebral vasculitis, pulmonary haemorrhage, and severe gastrointestinal involvement[44-46] [9, 47]. 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 (manuscript submitted[48]).

In patients with severe abdominal pain and/or rectal bleeding, corticosteroid treatment could also be considered (see above)[43] although the panel recognised the paucity of robust data to guide this recommendation. Clinical trial data has demonstrated that corticosteroids may reduce the intensity and duration of abdominal pain in early IgAV[49]. However, other studies reported no clear advantage of prednisone over supportive treatment as nasogastric decompression, parenteral nutrition, and antibiotics[44, 50].

Recommended doses of oral corticosteroids 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 intravenous methylprednisolone (IVMP) 10-30 mg/kg with a maximum of 1 gram per day for three consecutive days, may be considered.[44].

Prophylactic corticosteroid treatment to *prevent* the development of IgAV-nephritis is not indicated[29, 51, 52] since controlled studies have shown that patients who received corticosteroids 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 Figure 1 summarise the SHARE recommendations regarding the treatment of IgAV nephritis.

General recommendations

Since a key priority is to avoid permanent renal damage[33, 38], and high quality evidence is currently lacking regarding the treatment of IgAV nephritis, the panel highlighted the urgent need for randomised controlled trials for the treatment of IgAV nephritis.

There is accumulating evidence supporting the beneficial effect of renin-angiotensin blockade in patients with proteinuria[53]. Therefore, in children with IgAV who have renal involvement with persistent proteinuria (more than 3 months duration) irrespective of whether they are receiving prednisolone or other immunosuppressive treatment, the panel recommended that an ACE inhibitor or ARB should be considered to prevent and/or limit secondary glomerular injury.[54].

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[55, 56]. However, it was acknowledged that some patients may have persistent proteinuria (see Table 2) that does not resolve. Addition of azathioprine (AZA) or mycophenolate mofetil (MMF)[57-60], or ciclosporin[61] may be considered as second-line treatment or corticosteroid-sparing agent. Pulsed IVMP may also be warranted, although is rarely required for those with truly mild IgA V nephritis.

Treatment of moderate IgAV nephritis

For patients with moderate IgAV nephritis, oral prednisolone or pulsed IV methylprednisolone should be used as first line treatment[62]. Addition of AZA, MMF or IV cyclophosphamide 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 evidence to recommend ciclosporin or oral cyclophosphamide 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. AAV[48], usually with high dose corticosteroids and intravenous cyclophosphamide to induce remission, and lower doses of corticosteroids combined with AZA or MMF[57-60] as maintenance treatment[63]. 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).

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

Discussion

These SHARE recommendations, whilst 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, emphasising an important unmet need for high level control 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[64]. The KDIGO group has also suggested ACEI for persistent proteinuria because of its beneficial effects on proteinuria and the mesangial cell. However, Davin and Coppo have stressed that the use of ACEIs 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[64]. Whilst

the kidney pathology may be similar, the nephritis of IgAV is an acute damage to the endothelium and is different than the slowly progressive IgA nephritis, and thus warrants acute anti-inflammatory therapy[65]. Thus, we recommend corticosteroids 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 cyclophosphamide for >50% crescents[64]. 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[29, 56, 62, 63]. 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[64].

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 corticosteroids and compare AZA to 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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Contributors

NW and BV designed the SHARE initiative. NdG and NG performed the systematic literature review, supervised by MWB and SK. Validity assessment of selected papers was done by SO, PB, LM, AvR and MWB. Recommendations were formulated by NdG, NG, PB, SO, SK and MWB. The expert committee consisted of SO, PB, SDM, TA, BB-M, PD, IK-P, PL, LM, CP, AR, AvR, YU, NW, SK and MWB; they completed the online surveys and/or participated in the subsequent consensus meetings. NdG, NG, SK and MWB prepared the consensus meetings and NdG and NG took minutes. AR and BMF facilitated the associated consensus meetings using nominal group technique. MWB initially drafted the manuscript. SO, SDM and PB all contributed to writing the manuscript, with contribution and approval of all co-authors. MWB oversaw all aspects as senior author.

References

- 1 Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65(1):1-11.
- 2 Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* 2002;360(9341):1197-202.
- 3 Nielsen HE. Epidemiology of Schonlein-Henoch purpura. *Acta Paediatr Scand* 1988;77(1):125-31.
- 4 Piram M, Mahr A. Epidemiology of immunoglobulin A vasculitis (Henoch-Schonlein): current state of knowledge. *Curr Opin Rheumatol* 2013;25(2):171-8.
- 5 Brogan P, Eleftheriou D, Dillon M. Small vessel vasculitis. *Pediatr Nephrol* 2010;25(6):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(9):916-20.
- 7 Altugan FS, Ozen S, Aktay-Ayaz N, et al. Treatment of severe Henoch-Schonlein nephritis: justifying more immunosuppression. *Turk J Pediatr* 2009;51(6):551-5.
- 8 Bogdanovic R. Henoch-Schonlein purpura nephritis in children: risk factors, prevention and treatment. *Acta Paediatr* 2009;98(12):1882-9.
- 9 Bayrakci UB, E. Özen, S. . Treatment of Henoch Schonlein Purpura: What evidence do we have? *Int J Clin Rheumatol* 2010;5(6):669-76.
- 10 Wulfraat NM, Vastert B, consortium S. Time to share. *Pediatr Rheumatol Online J* 2013;11(1):5.
- 11 Enders FB, Bader-Meunier B, Baidam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis* 2017;76(2):329-40.
- 12 Giancane G, Ter Haar NM, Wulfraat N, et al. Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever. *Ann Rheum Dis* 2015;74(4):635-41.
- 13 ter Haar NM, Oswald M, Jeyaratnam J, et al. Recommendations for the management of autoinflammatory diseases. *Ann Rheum Dis* 2015;74(9):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(10):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(11):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(12):1965-73.
- 17 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(9):1172-6.
- 18 Leclercq E, Leeflang MM, van Dalen EC, Kremer LC. Validation of search filters for identifying pediatric studies in PubMed. *J Pediatr* 2013;162(3):629-34 e2.
- 19 Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. *Ann Intern Med* 2004;140(3):189-202.
- 20 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 (ESCSIT). *Ann Rheum Dis* 2006;65(10):1301-11.
- 21 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 (ESCSIT). *Ann Rheum Dis* 2006;65(10):1312-24.

- 22 McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm* 2016;38(3):655-62.
- 23 Harvey N, Holmes CA. Nominal group technique: an effective method for obtaining group consensus. *Int J Nurs Pract* 2012;18(2):188-94.
- 24 Mills JA, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schonlein purpura. *Arthritis Rheum* 1990;33(8):1114-21.
- 25 Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010;69(5):798-806.
- 26 Hunder GG. The use and misuse of classification and diagnostic criteria for complex diseases. *Ann Intern Med* 1998;129(5):417-8.
- 27 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(5):813-22.
- 28 Chan H, Tang YL, Lv XH, et al. Risk Factors Associated with Renal Involvement in Childhood Henoch-Schonlein Purpura: A Meta-Analysis. *PLoS One* 2016;11(11):e0167346.
- 29 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(11):877-82.
- 30 de Almeida JL, Campos LM, Paim LB, Leone C, Koch VH, Silva CA. Renal involvement in Henoch-Schonlein purpura: a multivariate analysis of initial prognostic factors. *J Pediatr (Rio J)* 2007;83(3):259-66.
- 31 Kaku Y, Nohara K, Honda S. Renal involvement in Henoch-Schonlein purpura: a multivariate analysis of prognostic factors. *Kidney Int* 1998;53(6):1755-9.
- 32 Shin JI, Park JM, Shin YH, Hwang DH, Kim JH, Lee JS. Predictive factors for nephritis, relapse, and significant proteinuria in childhood Henoch-Schonlein purpura. *Scand J Rheumatol* 2006;35(1):56-60.
- 33 Ronkainen J, Nuutinen M, Koskimies O. The adult kidney 24 years after childhood Henoch-Schonlein purpura: a retrospective cohort study. *Lancet* 2002;360(9334):666-70.
- 34 Butani L, Morgenstern BZ. Long-term outcome in children after Henoch-Schonlein purpura nephritis. *Clin Pediatr (Phila)* 2007;46(6):505-11.
- 35 Coppo R, Andrulli S, Amore A, et al. Predictors of outcome in Henoch-Schonlein nephritis in children and adults. *Am J Kidney Dis* 2006;47(6):993-1003.
- 36 Goldstein AR, White RH, Akuse R, Chantler C. Long-term follow-up of childhood Henoch-Schonlein nephritis. *Lancet* 1992;339(8788):280-2.
- 37 Koskimies O, Mir S, Rapola J, Vilska J. Henoch-Schonlein nephritis: long-term prognosis of unselected patients. *Arch Dis Child* 1981;56(6):482-4.
- 38 Watson L, Richardson AR, Holt RC, Jones CA, Beresford MW. Henoch schonlein purpura--a 5-year review and proposed pathway. *PLoS One* 2012;7(1):e29512.
- 39 Mian AN, Schwartz GJ. Measurement and Estimation of Glomerular Filtration Rate in Children. *Adv Chronic Kidney Dis* 2017;24(6):348-56.
- 40 Salvador CL, Tondel C, Rowe AD, et al. Estimating glomerular filtration rate in children: evaluation of creatinine- and cystatin C-based equations. *Pediatr Nephrol* 2018.
- 41 Foster HB, P. *Oxford Handbook of Paediatric Rheumatology*. 2nd Edition ed: Oxford University Press; 2018.
- 42 Koskela M, Ylinen E, Ukonmaanaho EM, et al. The ISKDC classification and a new semiquantitative classification for predicting outcomes of Henoch-Schonlein purpura nephritis. *Pediatr Nephrol* 2017;32(7):1201-9.
- 43 Ebert EC. Gastrointestinal manifestations of Henoch-Schonlein Purpura. *Dig Dis Sci* 2008;53(8):2011-9.
- 44 Ronkainen J, Koskimies O, Ala-Houhala M, et al. Early prednisone therapy in Henoch-Schonlein purpura: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2006;149(2):241-7.

- 45 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.
- 46 Sag E, Batu ED, Ozen S. Childhood systemic vasculitis. *Best Pract Res Clin Rheumatol* 2017;31(4):558-75.
- 47 Ha TS, Lee JS. Scrotal involvement in childhood Henoch-Schonlein purpura. *Acta Paediatr* 2007;96(4):552-5.
- 48 de Graeff NG, N. Brogan, P. Ozen, S. Avcin, T. Bader-Meunier, B. Dolezalova, P. Feldman, BM. Kone-Paut, I. Lahdenne, P. Marks, SD. McCann, L. Pilkington, C. Ravelli, A. van Royen, A. Uziel, Y. Vastert, B. Wulfraat, N. Kamphuis, S. Beresford, MW. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides – The SHARE initiative. Submitted - Pending Editorial decision 2018.
- 49 Alvarez-Caro F, Concha-Torre JA, Garcia-Hernandez I, et al. Massive lower gastrointestinal haemorrhage, successfully treated with corticosteroids, as main symptom of Schonlein-Henoch purpura. *Rheumatol Int* 2009;29(12):1491-4.
- 50 Chen SY, Kong MS. Gastrointestinal manifestations and complications of Henoch-Schonlein purpura. *Chang Gung Med J* 2004;27(3):175-81.
- 51 Dudley J, Smith G, Llewelyn-Edwards A, Bayliss K, Pike K, Tizard J. 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(10):756-63.
- 52 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.
- 53 Chapter 11: Henoch-Schonlein purpura nephritis. *Kidney Int Suppl* (2011) 2012;2(2):218-20.
- 54 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(6):1880-8.
- 55 Pillebout E, Alberti C, Guillevin L, Ouslimani A, Thervet E, group Cs. 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(5):495-502.
- 56 Tarshish P, Bernstein J, Edelmann CM, Jr. Henoch-Schonlein purpura nephritis: course of disease and efficacy of cyclophosphamide. *Pediatr Nephrol* 2004;19(1):51-6.
- 57 Du Y, Hou L, Zhao C, Han M, Wu Y. Treatment of children with Henoch-Schonlein purpura nephritis with mycophenolate mofetil. *Pediatr Nephrol* 2012;27(5):765-71.
- 58 Hackl A, Becker JU, Korner LM, et al. Mycophenolate mofetil following glucocorticoid treatment in Henoch-Schonlein purpura nephritis: the role of early initiation and therapeutic drug monitoring. *Pediatr Nephrol* 2018;33(4):619-29.
- 59 Mizerska-Wasiak M, Maldyk J, Demkow U, Roszkowska-Blaim M, Panczyk-Tomaszewska M. Treatment Outcomes in Children with Henoch-Schonlein Nephritis. *Adv Exp Med Biol* 2016;912:65-72.
- 60 Ren P, Han F, Chen L, Xu Y, Wang Y, Chen J. The combination of mycophenolate mofetil with corticosteroids induces remission of Henoch-Schonlein purpura nephritis. *Am J Nephrol* 2012;36(3):271-7.
- 61 Jauhola O, Ronkainen J, Autio-Harmainen H, et al. Cyclosporine A vs. methylprednisolone for Henoch-Schonlein nephritis: a randomized trial. *Pediatr Nephrol* 2011;26(12):2159-66.
- 62 Niaudet P, Habib R. Methylprednisolone pulse therapy in the treatment of severe forms of Schonlein-Henoch purpura nephritis. *Pediatr Nephrol* 1998;12(3):238-43.
- 63 Baskin E, Ozen S, Cakar N, Bayrakci US, Demirkaya E, Bakkaloglu A. The use of low-dose cyclophosphamide followed by AZA/MMF treatment in childhood lupus nephritis. *Pediatr Nephrol* 2010;25(1):111-7.
- 64 KDIGO. *KDIGO Clinical Practice Guidelines for Glomerulonephritis: Chapter 11: Henoch-Schonlein purpura nephritis*; 2012. 2(2); 1-143
- 65 Davin JC, Coppo R. Pitfalls in recommending evidence-based guidelines for a protean disease like Henoch-Schonlein purpura nephritis. *Pediatr Nephrol* 2013;28(10):1897-903.

Table 1: SHARE Recommendations for the diagnosis of IgA Vasculitis

#	Recommendations – Diagnosis	LoE	SoR
Classification criteria			
1.	The EULAR/PRINTO/PReS endorsed Ankara 2008 criteria should be used to classify IgA vasculitis (formerly known as HSP)[25]	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 IgA vasculitis.	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 IgA vasculitis patient has moderate proteinuria* and/or impaired GFR**	4	D
6.	A renal biopsy should be performed if an IgA vasculitis 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); or persistent moderate (100-250 mg/mmol) proteinuria**, or impaired GFR***.	2A	
Imaging			
7.	In severe abdominal pain, an ultrasound should be performed by an ultrasonographer with paediatric expertise to exclude intestinal intussusception.	4	D

Abbreviations: UP:UC urine protein:urine creatinine ratio; UA:UC urine albumin : urine creatinine ratio; eGRF, estimated glomerular filtration rate;

* Moderate proteinuria: UP:UC ratio 100-250 mg/mmol in an early morning urine sample

** persistent proteinuria, defined as per severity- see table 2 for full definitions; NB 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.

***Impaired GFR: <80 mls/min/1.73m²;

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[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]

Table 2: Definitions of severity of IgA Vasculitis (IgAV) Nephritis

Severity of IgAV nephritis	Definition
Mild	Normal GFR ¹ and mild ³ or moderate ⁴ proteinuria
Moderate	<50% crescents on renal biopsy and impaired GFR ² or severe persistent proteinuria ⁵ [42]
Severe	>50% crescents on renal biopsy and impaired GFR ⁴ or persistent proteinuria ⁵ [42]
Persistent proteinuria ⁵ modified from [41]	<ul style="list-style-type: none"> • UP:UC ratio (early morning urine protein : creatinine ratio) > 250 mg/mmol for four weeks • UP:UC ratio > 100 mg/mmol for three months • UP:UC ratio > 50mg/mmol for six months

Footnotes:

¹ Normal GFR: >80 mls/min/1.73m²;

² Impaired GFR: <80 mls/min/1.73m²;

³ Mild proteinuria: UP:UC ratio < 100 mg/mmol (in an early morning urine sample);

⁴ Moderate proteinuria: UP:UC ratio 100-250 mg/mmol (in an early morning urine sample);

⁵ Severe persistent proteinuria: > 250 mg/mmol for at least 4 weeks

NB: for those that use different units, these conversions can be used to determine equivalent cutoff scores:

1 gram/day of proteinuria (in 24 hour urine collection)

= UP:UC (early morning urine protein : creatinine ratio) of 100mg/mmol

= UA:UC (early morning urine albumin : creatinine ratio) of 70mg/mmol

This approximates to urine dipstick testing for proteinuria of 150mg/dl but does not replace laboratory UP:UC or UA:UC

Abbreviations: IgAV, IgA vasculitis; GFR, Glomerular filtration rate; UP:UC urine protein:urine creatinine ratio;

Table 3: SHARE Recommendations for the treatment of IgA Vasculitis

#	Recommendations – Treatment	LoE	SoR
Analgesia			
1.	Adequate analgesia should be prescribed for IgA vasculitis-associated arthropathy*	4	D
2.	NSAIDs are not contraindicated if renal function is normal in IgA vasculitis	4	D
3.	Adequate analgesia should be prescribed for IgA vasculitis-associated abdominal pain	4	D
Use of Corticosteroids			
4.	Corticosteroid treatment is indicated in case of: <ul style="list-style-type: none"> • 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), corticosteroid treatment could be considered	4	D
6.	The dose of oral corticosteroids (prednisolone/prednisone) should be 1-2 mg/kg/day	4	D
7.	If corticosteroids are indicated, pulsed IV methylprednisolone (e.g. 10-30 mg/kg with a maximum of 1 gram per day on 3 consecutive days) may be considered for severe cases.	4	D
8.	Prophylactic corticosteroid treatment to <i>prevent</i> the development of IgA vasculitis-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 randomised 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

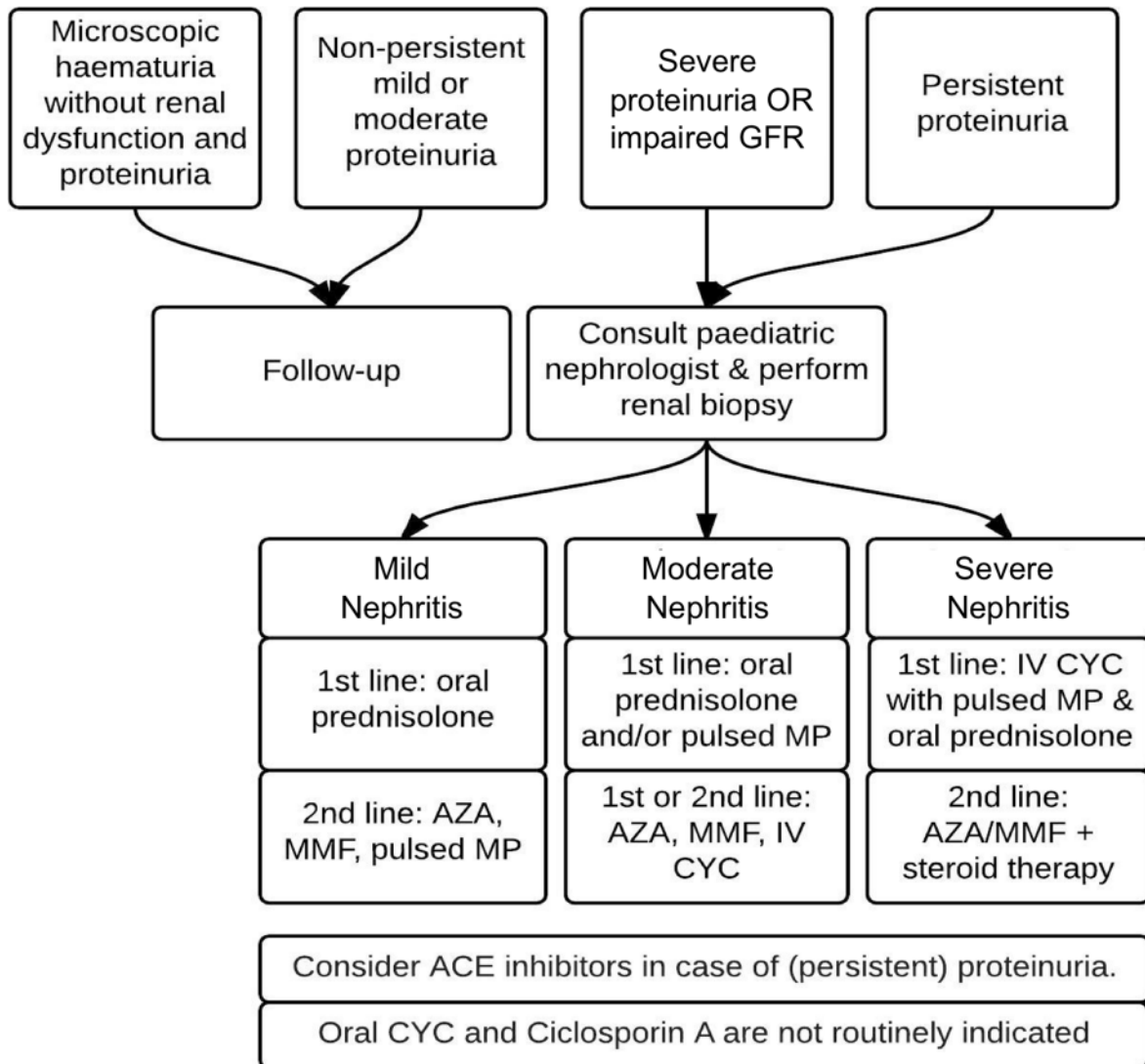
14.	Oral prednisolone and/or pulsed methylprednisolone should be used as first line treatment in patients with moderate IgAV nephritis.	4	D
15.	AZA, MMF or IV cyclophosphamide may be used in the first or second-line treatment of moderate IgAV nephritis.	4	D
16.	Ciclosporin or oral cyclophosphamide cannot be routinely recommended in moderate IgAV nephritis.	4	D
17.	As in other severe systemic small vessel vasculitides, intravenous cyclophosphamide 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 Figure 1	4	D

**Adequate fluid intake is essential when taking NSAIDs.*

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; IV, intravenous; IgAV, IgA vasculitis-associated; ACE, angiotensin-converting enzyme; AZA: azathioprine; MMF: mycophenolate mofetil

LoE, level of evidence: 1A, meta-analysis of randomised controlled trials; 1B, randomised controlled study; 2A, controlled study without randomisation; 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]

Figure 1: Guideline for the management of IgA Vasculitis-associated nephritis



Footnote: For definitions of severity of proteinuria, see Table 2. For IgA vasculitis-associated crescentic glomerulonephritis, please see section on crescentic glomerulonephritis.

Abbreviations: IV, intravenous; MP = Methylprednisolone; AZA = Azathioprine; MMF = Mycophenolate Mofetil; CYC = Cyclophosphamide; ACE, angiotensin-converting enzyme.