

Chapter 11: Henoch-Schönlein purpura nephritis

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INTRODUCTION

This chapter will focus on the treatment of HSP nephritis in adults and children. The cost implications for global application of this guideline are addressed in Chapter 2.

11.1: Treatment of HSP nephritis in children

11.1.1: We suggest that children with HSP nephritis and persistent proteinuria, >0.5-1 g/d per 1.73 m², are treated with ACE-I or ARBs. (2D)

11.1.2: We suggest that children with persistent proteinuria, >1 g/d per 1.73 m², after a trial of ACE-I or ARBs, and GFR >50 ml/min per 1.73 m², be treated the same as for IgAN with a 6-month course of corticosteroid therapy (see Chapter 10). (2D)

11.2: Treatment of crescentic HSP nephritis in children

11.2.1: We suggest that children with crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for crescentic IgAN (see Recommendation 10.6.3). (2D)

BACKGROUND

HSP is an acute small-vessel vasculitis, characterized clinically by a nonthrombocytopenic purpuric rash, nondeforming arthritis, gastrointestinal involvement, and nephritis.⁵⁵⁴ The incidence of HSP is about 10 cases per 100,000 per year. It affects all ages, but 90% of cases are found in those less than 10 years of age, with the median age at presentation being 6 years.⁵⁵⁴ Kidney involvement occurs in 30–50% of patients.^{554–556} Microscopic hematuria is the most common finding. In a systematic review of 12 studies of 1133 unselected children with HSP, abnormal urinalysis occurred in 34% with the majority (79%) having isolated hematuria with or without proteinuria.⁵⁵⁵ Only 21% of those with kidney involvement (or 7.2% of all cases) developed a nephritic and/or nephrotic syndrome. Ninety percent of children had developed kidney involvement by 8 weeks after acute presentation, while 97% developed kidney involvement by 6 months. Recurrence of rash and other symptoms occur in one-third of patients.⁵⁵⁶ Nephritis is associated with older age at presentation, persistent rash, and recurrence of HSP, while proteinuria >20 mg/m²/h was associated with recurrence and severe abdominal pain.⁵⁵⁷ Only 1–3% of patients progress to ESRD.⁵⁵⁴ Long-term prognosis correlates with kidney presentation at onset. Compared to 1.6% of children with isolated hematuria with/without proteinuria, 19.5% of

children with nephritic or nephrotic syndromes at initial presentation have nephrotic-range proteinuria, hypertension, and/or reduced GFR at long-term follow up.⁵⁵⁵ Among 78 patients managed in specialized pediatric kidney units, 44% of those with a nephritic or nephrotic presentation had hypertension and/or impaired kidney function at a mean follow-up of 23.4 years, while 82% of those presenting with hematuria with or without proteinuria had normal urinalysis, kidney function, and blood pressure.⁵⁵⁸ A recent study of 103 children found that, at final follow up, GFR correlated with GFR and proteinuria at onset and 1 year, with ISKDC pathology grade and interstitial fibrosis. Multivariate analysis identified that proteinuria at 1 year and ISKDC grade were most useful in identifying patients with a poor prognosis.⁵⁵⁹ However, one long-term study found that severity of findings on first kidney biopsy did not correlate with the risk of a poor outcome (hypertension, persistent proteinuria, ESRD).⁵⁶⁰

RATIONALE

- There is no evidence for the use of RAS blockade in HSP nephritis in children, but an RCT in children and young adults with IgAN demonstrated the benefit of this therapy in reducing proteinuria and maintaining GFR.
- There is no evidence for the use of oral corticosteroids in HSP nephritis, but data from RCTs in adults with IgAN have demonstrated a benefit in reducing proteinuria and maintaining GFR.
- There is very low-quality evidence for the benefit of high-dose corticosteroids and immunosuppressive agents in HSP nephritis with deteriorating kidney function.

There is no evidence available for the use of RAS blockade in HSP nephritis. However, an RCT in 66 children and young adults with IgAN with moderate proteinuria (>1 to <3.5 g/d per 1.73 m²) and GFR >50 ml/min per 1.73 m² demonstrated the benefit of ACE-I in reducing proteinuria and maintaining GFR.⁴⁷⁸ There are very limited data to support the use of corticosteroids in children with established nephritis of any severity,⁵⁶¹ though corticosteroids are widely used in children presenting with nephrotic-range proteinuria or acute nephritis. In a post-hoc analysis of one placebo-controlled RCT,⁵⁶² nephritis resolved more rapidly in children treated with prednisone compared to placebo. Seven of 36 children (19%) in the prednisone group still had kidney involvement at 6 months compared to 15 of 35 (43%) in the placebo group. The trial only provided outcome data to 6 months after randomization, so it is unclear whether prednisone treatment reduced the number of patients with

persistent HSP nephritis overall, or promoted more rapid resolution of kidney disease compared to placebo.

A prospective but uncontrolled study of 38 consecutive children with mean follow-up period of 5 years and 7 months showed resolution of severe nephritis (nephrotic syndrome and/or >50% crescents on biopsy) in 27 of 38 children treated with three pulses of methylprednisolone followed by oral prednisone for 4 months.⁵⁶³ Seven children had residual abnormalities and four progressed to ESRD. Two recent RCTs in adults with IgAN, proteinuria ≥ 1 g/d, and GFR ≥ 30 -50 ml/min per 1.73 m² have demonstrated the benefit of 6-8 months of prednisone and ACE-I, compared to ACE-I alone, on reducing the rate of kidney functional deterioration and reducing proteinuria during follow-up periods of up to 48 months⁵¹¹ or 96 months.⁵¹⁰

In the absence of sufficient long-term data in HSP nephritis, we suggest that persistent HSP nephritis can be treated as isolated IgAN (see Recommendation 10.3.1). However, there are no data to determine when prednisone should be commenced in children with HSP nephritis, and for how long ACE-I or ARB therapy should be administered before commencing prednisone. Foster *et al.*⁵⁶⁴ noted that the chronicity score (interstitial fibrosis, tubular atrophy, fibrosed crescents) on initial kidney biopsy increased with increasing delay between onset of kidney involvement and time of biopsy. Most children in their series of 20 patients were biopsied within 3 months, with a median of 30 days. Treatment with prednisone and azathioprine resulted in improvement in acuity score but not chronicity score. Therefore, in HSP nephritis, it may be appropriate to commence prednisone therapy earlier than in IgAN.

There are limited data on immunosuppressive agents, so it remains unclear whether these have any role in HSP nephritis. In a single RCT of 56 children with significant HSP nephritis (nephrotic range proteinuria, reduced kidney function, ISKDC* grades III-V on kidney biopsy [crescents <50% to >75%]) treated within 3 months of onset of HSP and followed for 5-6 years, there was no significant difference in the risk for persistent kidney involvement of any severity between cyclophosphamide and supportive treatment (RR 1.07; 95% CI 0.65-1.78).⁵⁶⁵ Corticosteroids were not administered to these children. A nonrandomized comparative study of 37 children with HSP nephritis and >50% crescents (ISKDC grades IV-V) on kidney biopsy found that none of 17 treated with cyclophosphamide plus corticosteroids, compared to four of 20 treated with corticosteroids alone, had persistent nephropathy (proteinuria >20 mg/m²/h with/without GFR <40 ml/min per 1.73 m²) at 6-8 years of follow-up.⁵⁶⁶ A small RCT, in children with nephrotic-range proteinuria and/or ISKDC grades III-V on kidney biopsy, found that all of 10 children treated with cyclosporin achieved remission compared to five of nine children treated with methylprednisolone.⁵⁶⁷ However, at the 2-year follow-up of

23 children, seven of 11 children treated with cyclosporin and seven of 12 treated with methylprednisolone had persistent proteinuria with/without decreased GFR.⁵⁶⁸

One nonrandomized comparative study involving 20 children with nephrotic-range proteinuria and ISKDC grades II-III on kidney biopsy reported that none of 10 children treated with azathioprine and prednisone, compared to four of 10 treated with prednisone alone, had nephrotic-range proteinuria and/or GFR <60 ml/min per 1.73 m² after 4-5 years of follow-up.⁵⁶⁹ Observational studies have reported good outcomes with corticosteroids combined with azathioprine,⁵⁶⁴ cyclophosphamide,⁵⁷⁰ cyclosporine,^{571,572} and plasma exchange.^{573,574} There are no data, other than small observational studies, examining the treatment of crescentic HSP nephritis with rapidly progressive kidney failure. In the absence of data, we suggest treating such patients similarly to patients with ANCA vasculitis.

A single small RCT⁵⁷⁵ comparing 1 year of treatment with MMF to azathioprine has enrolled 17 children (ISKDC grade II and III) to date. Proteinuria resolved in all of 10 children treated with MMF, and six of eight treated with azathioprine. Seven patients treated with MMF and five treated with azathioprine showed regression of histological changes at 1 year. Children received prednisone for 6 months, but were not treated with ACE-I. These data are insufficient to draw any conclusions on the value of MMF in HSP nephritis in children.

11.3: Prevention of HSP nephritis in children

11.3.1: We recommend not using corticosteroids to prevent HSP nephritis. (1B)

BACKGROUND

At first presentation with HSP, nephritis may be clinically mild or even absent. Therefore, treatment strategies at the time of presentation have been developed with the goal of preventing nephritis, or reducing the risk of severe persistent nephritis.

RATIONALE

- There is moderate-quality evidence to recommend that corticosteroids not be given at presentation of HSP, since they do not appear to influence the development of persistent kidney involvement.

A meta-analysis^{576,577} of five RCTs (789 children) found no significant difference in the number of children with evidence of persistent kidney disease (microscopic hematuria, proteinuria, hypertension, reduced kidney function) during follow-up between those treated with prednisone for 2-4 weeks and those not treated (RR 0.73; 95% CI 0.43-1.24). There were no significant differences in the risk of persistent kidney disease at 6 months (379 children; RR 0.54; 95% CI 0.25-1.18) and 12 months (498 children; RR 1.02; 95% CI 0.40-2.62). Three of the five trials (568 patients) were well designed, placebo-controlled trials; exclusion of poor-quality studies from the

*The histological classification of HSP nephritis proposed by the International Study of Kidney Disease in Children is still widely used.

meta-analysis removed heterogeneity without altering the findings. Two RCTs^{562,578} found no significant difference in the risk of severe nephritis (nephrotic-range proteinuria, hypertension with/without reduced kidney function) between children treated with prednisone or placebo at presentation, though the number of events was small, resulting in imprecision (261 children; RR 1.92; 95% CI 0.57-6.50). There are no data on prevention strategies for HSP nephritis in adults.

11.4: HSP nephritis in adults

11.4.1: We suggest that HSP nephritis in adults be treated the same as in children. (2D)

RATIONALE

Outcome data from HSP nephritis in adults are from retrospective series. A Spanish retrospective study of HSP in adults suggested a higher frequency of kidney involvement than children, but the final outcome of HSP is equally good in patients of both age groups.⁵⁷⁹ In an Italian cohort, the risk for progression of HSP nephritis was found greater in adults and was associated with increasing proteinuria during follow-up.⁵⁸⁰ In a UK series, the risk factors for ESRD were: proteinuria ≥ 1 g/d during follow-up, hypertension at presentation and during follow-up, kidney impairment at presentation—very similar to the prognostic indicators in IgAN in adults.⁵⁸¹

In a Finnish series, kidney survival 10 years after biopsy was 91%.⁵⁸² A recent cohort of HSP nephritis in Chinese adults showed a higher risk of progression to kidney impairment compared to children.⁵⁸³ The biggest retrospective cohort of 250 adults with HSP was from France.⁵⁸⁴ After a median follow-up of 14.8 y, 32% of the patients showed kidney impairment (CrCl < 50 ml/min), usually associated with proteinuria and/or hematuria.

There are very few RCTs investigating the treatment of HSP nephritis in adults. A recent 12-month, multicenter, prospective, open-label trial (CESAR study) was performed using steroid therapy without or with cyclophosphamide in 54 adults with severe HSP including proliferative GN and severe visceral manifestations.⁵⁸⁵ The study did not include patients with rapidly progressive GN. All patients received

steroids while 25 were randomized to also receive cyclophosphamide. There was no additional benefit of cyclophosphamide compared to steroids alone. The investigators commented that the small population size did not permit definitive conclusions.

We suggest that treatment for HSP nephritis in adults should use the approach proposed for HSP in children (see Sections 11.1 and 11.2). Current evidence does not suggest using additional immunosuppressive agents other than steroids in HSP nephritis in adults.

RESEARCH RECOMMENDATIONS

- An RCT comparing a 6- to 12-month course of corticosteroids to shorter-duration corticosteroids (28 days) should be performed in children with moderately severe HSP nephritis (acute nephritic syndrome or nephrotic syndrome with normal kidney function and $< 50\%$ crescents or sclerosing lesions on biopsy).
- RCTs are required to determine whether immunosuppressive agents (cyclosporine, azathioprine, MMF) and corticosteroids are effective in treating children with severe HSP nephritis (acute nephritic syndrome, nephrotic syndrome with or without reduced kidney function with $> 50\%$ crescents or sclerosing lesions on biopsy).

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