Treatment of Henoch–Schönlein purpura: what evidence do we have?

The clinical features of Henoch–Schönlein purpura (HSP) are now well recognized; however, there remains uncertainty and a lack of consensus regarding treatment. Considerable concern has been expressed regarding the importance of identifying an improved, well-studied therapeutic protocol for use in the treatment of HSP. This article will focus on published studies, specifically randomized controlled trials, and aims to provide an evidence-based approach to the evaluation of therapy in children with HSP. We do have evidence that steroids do not protect against the development of kidney disease in patients with HSP. However, there is a clear lack of robust clinical trials for the treatment of moderate and severe HSP nephritis. At the present time, treatment of HSP nephritis is not guided by evidence from properly designed randomized controlled trials. We also lack consensus for the definition of outcome measures. Adequately powered, well-designed, multicenter, randomized controlled trials with follow-up periods of at least 5 years are particularly needed in children with HSP nephritis.

KEYWORDS: evidence based ■ Henoch–Schönlein purpura ■ randomized controlled trials ■ treatment

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Henoch–Schönlein purpura (HSP) is defined as a small vessel vasculitis with IgA-dominant immune deposits typically involving the skin, gut and glomeruli, and associated with arthralgias or arthritis [1]. HSP typically affects children between the age of 3 and 10 years with an estimated annual incidence of 20.4 per 100,000 children [2]. The course of HSP is often self-limiting, although it may be associated with early gastrointestinal morbidity and may cause long-term renal morbidity. The clinical course and long-term outcome vary according to the cohorts examined, especially when unselected cohorts are compared with children followed by pediatric nephrology units. Variations in the prevalence of renal involvement among different series may also depend on the methods of detection of nephritis. In a systematic review of studies of unselected patients, renal involvement was reported in 34% of patients; 80% had isolated hematuria and/or proteinuria, and 20% had acute nephritis or nephritic syndrome [3]. Renal involvement is the most serious long-term complication of HSP. Persistent renal involvement occurs in 2.0–5.5% of patients overall, but the incidence varies with the severity of the kidney disease at presentation [4,5].

The concept of evidence-based medicine, the philosophical origins of which extend back to mid-19th century Paris and earlier, remains a hot topic for clinicians. Principals of evidence-based medicine have only recently been used to systematically evaluate treatment of HSP and glomerular disease in children [6–8]. The clinical features of HSP are now well recognized; however, there remains uncertainty and a lack of consensus regarding treatment. In this article, we will provide an evidence-based approach to the evaluation of therapy in children with HSP. However, randomized trials in HSP are few and variability in the spectrum of renal disease included in the relevant trials is significant. The long time period from clinical onset of disease until progression to end-stage renal disease (ESRD) and its remitting/relapsing course are the other important points that could potentially affect appropriate conclusions with regards to therapeutic efficacy.

Most children with HSP have mild renal involvement and these patients do not require immunosuppressive treatment. However, this is not always the case. The outcome of HSP nephritis (HSPN) has become clearer in the last decade. Recent studies highlight the adverse renal prognosis in patients with HSP, especially in those with heavy proteinuria and crescents [9]. In a long-term follow-up of a HSP cohort, almost 10% developed chronic renal failure at 23 years. Heavy proteinuria, impaired renal function at presentation and the extent of crescents on renal biopsy seem to be the critical determinants of renal survival. In fact, as Narchi has discussed in his recent review, 20% of HSP patients with crescents develop persistent renal disease whereas only 1.8% of overall HSP patients do so [3]. Thus, a renal biopsy is indicated in HSP patients with

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marked proteinuria and elevated serum creatinine. It should be noted that a uniform approach was lacking in the presented papers on indications of biopsy, which was a major drawback in the studies dealing with treatment of HSPN.

Methods

Randomized and quasi-randomized trials and relevant studies on the topic were retrieved from the Cochrane Central Registry of Controlled Trials, PubMed and EMBASE electronic databases. The search was limited to pediatric age groups and focused on 'Henoch–Schönlein purpura', 'Henoch–Schönlein purpura nephritis', 'anaphylactoid purpura', 'leukocytoclastic vasculitis' and 'treatment options'. Reference lists of nephrology textbooks, review articles and relevant trials were also searched. A search was conducted over the period January 1989–May 2010 with papers written in English only.

All randomized controlled trials (RCTs), semi-RCTs and case series of interventions including corticosteroids, anticoagulants, antiplatelet agents, immunosuppressive agents, angiotensin-converting enzyme inhibitors (ACEIs), and plasma exchange compared with placebo, no specific treatment or another intervention in patients with HSP with or without renal manifestations (e.g., hematuria, proteinuria, nephritis or nephritic syndrome) were included. Abstracts have been excluded because they often contain data that are not detailed enough to be properly evaluated.

Persistent renal disease likely represents the most important end point to define treatment failure. Change in the rate of renal deterioration, improvement or stability of renal biopsy findings, or decline in the amount of proteinuria and/or hematuria were also accepted as primary outcomes. Significant deterioration in renal function (i.e., 50% reduction of glomerular filtration rate or doubling of serum creatinine level) is the surrogate end point that is most closely associated with progression to ESRD [6].

For evaluation of treatment efficacy, we have used the same guidelines that were utilized for pediatric IgA nephropathy by Wyatt *et al.* [6]. The level of evidence is used to determine the strength of the recommendation [6,10–12]:

- Level 1: the highest level or 'gold standard' of evidence is an RCT that demonstrates a statistically significant difference for the primary outcome measure. The primary outcome measure must be stated before the study begins and a surrogate marker for outcome is not acceptable unless it correlates highly and unequivocally with the true outcome of progression to ESRD. A study fails to fulfil the criteria for this level if the sample size is not sufficiently adequate to detect a difference in outcome with sufficient power (usually $\alpha = 0.8$), and significance (usually $\alpha < 0.05$, two-tailed) is not achieved [6];
- Level 2: an RCT that does not reach the standards set for level 1. Often this is a small trial with uncertain results and a moderate to high risk of error. A trial with an interesting positive trend that is not statistically significant (α error) or one that, owing to small numbers of subjects, concluded that an outcome was not significant when it would have been with a larger sample size (β error) could support this level of evidence [6];
- Level 3: a nonrandomized concurrent cohort comparing treated patients and patients who received no therapy or another form of therapy [6];
- Level 4: a nonrandomized historical comparison between currently treated patients and former patients who received no therapy or another form of therapy. The control patients may be from the same study site, from another institution(s) or from the literature [6];
- Level 5: a case series of at least ten patients without controls [6];
- Level 6: a case series of less than ten patients without controls [6].

Recommendations for treatment range from grades A to D, with grade A representing the highest recommendation. One or more studies at level 1 are required to support the grade A recommendation. The systematic review of RCTs by Chartapisak *et al.* provides level 1 evidence [8]. The grade B recommendation requires at least one level 2 study and the grade C at least one level 3 study. The grade D recommendation is supported by lower levels of evidence and may include 'expert opinion'. Studies with level 4, 5 and 6 evidence do not provide satisfactory confirmation for the data they provide. Finally, if the outcome measure employed does not correlate adequately with the primary outcome of progression to ESRD, an 'S' follows the grading of the level of evidence to designate the employment of an intermediate outcome marker [6,7]. The pathological grading of HSPN in the presented papers has been based on the criteria as described in the International Study of Kidney Disease in Children [9].

Results

Literature search

The electronic search revealed 1029 studies related to the treatment of HSP. Four trials were identified by full-text review to be RCTs [13–15]. Three RCTs were identified from the reference lists of review articles [16,17]. Trials that were only available in abstract form were not included. All included trials were published in English.

Prevention of HSPN

The overall prognosis of HSP is excellent and supportive care suffices in most patients. However, in the long term, the development of nephritis leads to significant morbidity. Thus, prevention of nephritis would have obvious benefits in terms of the long-term prognosis of HSP. In 1988, Buchanec *et al.* proposed that early use of corticosteroids in children with HSP could prevent chronic renal disease [18]. Chartapisak *et al.* recently systematically reviewed all the published papers on the subject; RCTs that evaluated prednisone therapy at the presentation of HSP revealed that the risk of renal involvement with prednisone treatment does not significantly differ from that associated with placebo [8]. There have been many retrospective and prospective studies following this observation and discussing the effect of early steroid treatment in preventing the development of HSPN [13,14,16,18–22]. The largest RCT in this field was conducted by Dudley *et al.*; however, this study is only available in abstract form [23]. Table 1 provides an overview of studies related to the prevention of nephritis in childhood HSP. The available data do not support the use of prophylactic corticosteroid treatment to prevent renal disease (grade A recommendation).

Effects of antiplatelet agents

Treatment with antiplatelet agents (e.g., dipyridamole with or without cyproheptadine and aspirin) did not prevent development of HSPN (grade B recommendation). There was no significant difference in the risk of renal disease during follow-up in children with or without treatment with antiplatelet agents [8,17]. However, the available trials examining these agents for prevention of HSPN are very small, and thus the results cannot offer firm conclusions.

Treatment of moderately severe HSPN

Patients with less than 50% crescents on renal biopsy, suboptimal glomerular filtration rate and heavy proteinuria, which is not necessarily in the nephrotic range, are included in this group [1]. Studies regarding treatment of moderately severe HSPN are all hampered by several limitations making it difficult to reach an evidence-based conclusion. Zaffenello *et al.* has concluded that the data obtained from the literature are insufficient to support specific treatments such as intravenous γ-globulins and ACEIs [7]. However, they suggest that structured studies comparing long-term ACEI treatment in children with mild HSPN must be emphasized [7]. Indeed, the satisfactory results obtained with IgA nephropathy

Table 1. Overview of studies related to the prevention of nephritis in childhood Henoch–Schönlein purpura.

Study (year)	Study design	Subjects (n)	Follow-up (range)	Outcome	Level of evidence	Ref.
Ronkainen (2006)	Prospective, double-blind, placebo-controlled trial	T: 84, C: 87	6 months	5% T versus 3% C had severe HSPN	1-S	[14]
Huber (2004)	Randomized, double-blind, placebo-controlled trial	T: 21, C: 16	1 year	14% T versus 12% C had renal involvement	2-S	[13]
Mollica (1992)	Retrospective, case–control study	T: 84, C: 84	2–6 years	0% T versus 12% C developed HSPN	3-S	[16]
Kaku (1998)	Retrospective study	T: 79, NoT: 18	15 ± 12 months (1–76 months)	Reduced risk of PU and HU	3-S	[20]
Saulsburry (1993)	Retrospective, controlled study	T: 20, C: 30	3–8 weeks	20% T versus 20% C developed HSPN	Failed at 3-S	[19]
Bayrakci (2007)	Retrospective study	T: 61, NoT: 96	10 months (3–60 months)	28% T versus 19% C did not develop HSPN	4-S	[22]
Reinehr (2000)	Retrospective, case study	T: 55, NoT: 44	<1.5 years	8% T versus 52% C did not develop HSPN	4-S	[21]
Buchanec (1988)	Retrospective, controlled study	T: 23, C: 10	-	4.3% T versus 50% C developed PU and HU	4-S	[18]

C: Control group; HSP: Henoch–Schönlein purpura; HSPN: Henoch–Schönlein purpura nephritis; HU: Hematuria; NoT: No treatment group; PU: Proteinuria; T: Treatment group.

may indicate that ACEIs have an increased efficacy in delaying mild-to-severe HSPN progression in cases featuring comparable renal involvement [7].

Dixit *et al.* have claimed that ACEIs combined with fish oil led to a significant reduction in protein excretion rate after a few weeks of treatment [24]. However, the study was composed of only five patients, only three of whom received fish oil and ACEIs. In patients with a 6-month duration of proteinuria, an ACEI may be indicated to limit secondary glomerular injury, although again the evidence to support this therapy is poor [7].

Many papers advocate steroids for the treatment of HSPN. Orally administered prednisone and methylprednisolone pulse therapy were the most frequently used therapeutic options. In an Italian collaborative study involving adults with IgA nephropathy, level 1 evidence was shown to support the efficacy of a 6-month intensive treatment regimen, which incorporated high-dose intravenous methylprednisolone [25]. The extrapolation of these results together with other studies to a pediatric population with moderately severe IgA nephropathy revealed grade C recommendation for treatment with prednisolone alone [6]. Considering the nature of both diseases, it may be possible for one to extrapolate these results to the patients with HSPN. Steroids have been administered in combination with, or in substitution for, other immunosuppressive drugs following unsatisfactory therapeutic results when steroids were used alone. However, as concluded by earlier reviews [7,8], further studies should be performed to evaluate the efficacy of cyclosporine A (CSA), azothioprine (AZA) and mycophenolate mofetil (MMF) in this disease.

There are no established outcome definitions from clinical trials to guide therapy for moderately severe presentation. HSPN that is not rapidly progressive may be treated with 8 weeks of oral cyclophosphamide (CYCP; 2 mg/kg/day) along with corticosteroids, and converting to alternate-day prednisolone and AZA for a total of 12 months [1,26,27]. Published evidence for the efficacy of this approach is lacking; however, this may be a reasonable option, bearing in mind the adverse prognosis of children with HSP who have a nephritic/nephrotic phenotype [1].

Treatment of severe HSP with rapidly progressive or crescentic glomerulonephritis

Henoch–Schönlein pupura nephritis, presenting as rapidly progressive or crescentic glomerulonephritis, requires an effective intervention. Crescents in 50% of glomeruli and nephrotic range proteinuria have been shown to carry an unfavorable prognosis [1]. A number of studies have shown that the risk of deteriorating kidney disease is much higher than originally appreciated in patients with severe proteinuria and crescents on biopsy. Thus, there is an urgent need for evidence-based data regarding treatment of severe HSPN.

Unfortunately, to date, there is only one published RCT that has evaluated the benefit of treatment with only CYCP [15]. However, current protocols and uncontrolled series have suggested the use of a single specific immunosuppressant therapy with steroids, CSA or CYCP, while some other protocols suggested more than one immunosuppressant, such as steroid plus CYCP, steroid and AZA, and steroid plus CSA or steroid plus CSA plus ACEI [7]. Triple immunosuppressant therapy was also suggested with steroid plus CYCP switching to AZA and steroid plus AZA or MMF [7]. The only RCT on the subject studied 28 patients treated daily with CYCP compared with 28 controls [15]. A period of 6 weeks of CYCP at a rather high dose (3 mg/kg/day) was used in the study (while the preferred dose was 2 mg/kg/day for 8–12 weeks in other studies) for 6 weeks. Only five out of 28 patients with nephrotic levels of proteinuria and severe-onset histopathology recovered fully in this study. No patient with crescents in 50% or more of glomeruli fully recovered. The authors claim that their results do not support the use of CYCP alone [15].

A case series published by Oner *et al.* revealed 58% complete remission with triple therapy including pulse methylprednisolone, prednisone and CYCP [28]. Watanabe *et al.* found that urokinase therapy was effective in improving the prognosis of severe HSPN patients with at least grade III [29]. Niaudet and Habib described the beneficial effect of methylprednisolone pulse therapy in the treatment of severe HSPN [26]. Combination of methylprednisolone and urokinase pulse therapy was reported by Kawasaki *et al.*, who noted a 100% renal survival rate and a decrease in acuity index. However, there was no significant effect on the chronicity [30]. Kawasaki *et al.* combined this treatment with CYCP in a group of patients in 2004 and reported a decrease both in activity index and in the chronicity index of patients [31].

Cyclosporine A proved to be effective in a small series with steroid-resistant HSPN [7]. Ronkainen *et al.* reported a case series of seven patients followed-up for 6 years [32]. The treatment was effective in reducing proteinuria and led to stable remission for 6 years in four patients. Shin *et al.* reported seven patients treated with

pulse or oral prednisone and CSA with or without ACEI cilazapril, with a marked efficacy in reversing nephrotic range proteinuria and reversing histological grading [33].

In a retrospective investigation, 21 children with biopsy grade IIIb–V, diffuse mesangial proliferation who were treated with AZA and steroids displayed an effective clinical outcome. All treated patients had decreased hematuria, proteinuria and serum creatinine level. Unfortunately, the considerable variability of the histological patterns and the lack of a control group hampers interpretation of the results obtained [34]. A nonrandomized concurrent cohort study was performed by Shin *et al.*, comparing treatment with steroids and AZA versus steroids alone [35]. The study found a significant decrease in activity index in the group treated with AZA and steroids while the chronicity index increased [35]. The authors claimed that combination of AZA and steroids may ameliorate the progression of immunologic renal injury and histopathologic changes in severe HSN [35]. However, the evidence is not yet enough to recommend this treatment (level 4 evidence).

Altugan *et al.* treated 18 patients presenting with severe HSPN with a combination of oral prednisolone and oral CYCP, and subsequently continued with AZA [36]. All patients had crescents in their renal biopsies. They reported complete remission of proteinuria and normal glomerular filtration rate in all patients at the end of the 4-year follow-up period. Another retrospective study investigated the outcome of 27 children with HSPN of grade IIIb or higher treated with long-term immunosuppressive therapy [37]. The treatment protocol was similar to that of Altugan *et al.* and was comprised of daily steroids and CYCP for 8–12 weeks followed by AZA and a reducing regimen of alternate-day steroids for 8–12 months [36]. After a mean follow-up period of 6 years, 37% made complete recovery, 40.7% had persistent proteinuria and 14.8% had progressed to ESRD.

Unfortunately, the experience with MMF in HSPN is limited to few case reports or small case series [7]. However, reports are emerging for IgA nephropathy and a recent meta-analysis on MMF was published by Xu *et al.* [38]. This study included only four RCTs, which had enrolled a total of 168 patients. Three of the four studies compared MMF with placebo, and one compared MMF with steroids. In three RCTs, patients also received conventional treatment with ACEIs. The study revealed that the use of MMF did not result in a significant reduction in proteinuria or serum creatinine level at the end of the treatment period. The need for renal replacement therapy did not differ between the groups either. Thus, they have concluded that the currently available evidence does not support the routine use of MMF in patients with IgA nephropathy [38].

Table 2 provides an overview of the selection of the available case series and studies treating rapidly progressive or crescentic glomerulonephritis of HSP.

Henoch–Schönlein purpura is probably the most common cause of rapidly progressive glomerulonephritis in childhood; more aggressive therapeutic approaches have been employed in some cases [1]. Shenoy *et al.* reported on 14 children with severe HSPN treated successfully with plasma exchange alone [39]. Plasma exchange could potentially be important in selected cases, although the outcome is not yet supported by RCTs [1,7].

The studies in this section are complicated by the fact that they lack homogenetiy in the histopathological group and, thus, the severity of the underlying kidney damage. Most of the studies use patients with both International Study of Kidney Disease in Childhood (ISKDC) grade III pathology (<50% crescents) and those with grade IV and V pathology. However, a number of case series have investigated predominantly grade III with few included patients having more than 50% crescents [32,35,36]. Similarly, in other case series, half or more of the included patients had more than 50% crescents [26,30,31].

Recommendation: one RCT study [15] did not recommend the use of CYCP in treating severe HSPN; however, the number of patients enrolled in the study was rather small and the treatment period was 6 weeks through an oral route only and steroids were not used (grade B). At the present time, insufficient data are available to recommend the use of pulse and oral steroids, AZA, CSA or MMF, and there is no consensus on the selection or dose of immunosuppressives to be used in such patients. Another limiting step in the evaluation of these studies is the heterogeneity of the histopathological class and the lack of well-defined end points. Furthermore, the heterogeneity in clinical presentation makes it difficult to reach a firm conclusion with the small series. Thus, it is not possible to make recommendations for the treatment of severe HSPN, as of yet.

Conclusion

In this article we present the evidence showing lack of the preventive effect of steroids for renal involvement and we have tried to summarize the therapeutic options used in the treatment of HSPN. The main conclusion of this article

Table 2. Overview of studies related to the treatment of rapidly progressive or crescentic glomerulonephritis of Henoch–Schönlein purpura.

Study	Study design	Subjects (n)	Treatment	Follow-up	Outcome	Evidence	Ref.
Tarshish (2004)	Randomized controlled trial	T: 28, C: 28	CYCP	Up to 14 years	No difference in the rate of ESRD	2	[15]
Kawasaki (2004)	Retrospective controlled study	T: 20, C: 17	iv. MP, pulse UK, prednisone, DIPYR, warfarin, CYCP	24 months	AI decreased in both C and T, CI decreased more in T	4	[31]
Shin (2005)	Retrospective cohort study	T: 10, C: 10	AZA and pulse MP versus steroid alone	4.8 years	AI decreased, CI increased, IgA deposition reduced	4	[35]
Altugan (2009)	Retrospective study	T: 18	Oral prednisone, CYCP, AZA	4 years	Improvement in PU and in GFR, no ESRD	5	[36]
Shenoy (2007)	Retrospective study	T: 27	Steroids, pulse MP, CYCP, AZA	7 ± 2.5 years	Full recovery: 37%, ESRD: 14.8%, majority had persistent renal abnormalities	5	[39]
Bergstein (1998)	Retrospective study	T: 21	AZA, prednisone or iv. MP	1–108 months	Decreased HU, PU and serum creatinine	5	[34]
Niaudet (1998)	Prospective study	T: 14	Pulse MP, prednisone, CYCP	5.6 years	Recovery: 71%, ESRD: 10.5%, decreased AI, increased CI	5	[26]
Kawasaki (2003)	Retrospective uncontrolled study	T: 56	Pulse MP, pulse UK, prednisone, DIPYR, warfarin	9.7 ± 6 years	Recovery rate for IIIb: 84%; for IVb: 62%; for Vb: 25%, decreased AI, renal survival: 100%	5	[30]
Oner (1995)	Case series	T: 12	Pulse MP, prednisone, CYCP, DIPYR	9–39 months	Complete remission: 58%, one chronic diffuse sclerosing GN	5	[28]
Shin (2005)	Case series	T: 7	Oral prednisone and/or pulse iv. MP, ACEI, CSA	5.5 years	Decreased AI, stable CI	6	[33]
Ronkainen (2003)	Case series	T: 7	CSA	6 years	Remission from PU: 50%, 43% relapsed and became CSA dependent	6	[32]

ACEI: Angiotensin-converting enzyme inhibitor; AI: Activity index; AZA: Azathioprine; C: Control group; CI: Chronicity index; CSA: Cyclosporine A; CYCP: Cyclophosphamide; DIPYR: Dipyridamole; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; GN: Glomerulonephritis; HU: Hematuria; iv.: Intravenous; MP: Methylprednisolone; PU: Proteinuria; RPGN: Rapidly progressive glomerulo-nephritis; T: Treatment group; UK: Urokinase.

is the lack of robust clinical trials for the treatment of moderate and severe HSPN. At the present time, treatment of HSPN is not guided by evidence from adequately designed RCTs with level 1 evidence. We also lack consensus for the definition of outcome measures. The majority of studies that are available should be interpreted with upmost caution, since selection bias, small number of patients and lack of control patients make it difficult to interpret and compare the results. Reasons for the lack of RCTs include the high cost, long-term commitment required and the ethical issues, such as the reluctance of a physician to accept placebo therapy for a child with more than a mild disease.

Although severe forms of HSPN are rare, it is the most frequent cause of rapidly progressive glomerulonephritis in children. Thus, aggressive immunosuppressive therapies seem justified. Adequately powered, well-designed, multicenter RCTs with homogeneous groups and at least 5-year follow-up periods are especially needed in children with HSPN [8]. These studies may compare treatment arms instead of using a placebo.

Future perspective

Multicenter pediatric studies should be designed in order to provide evidence for:

- HSPN with non-nephrotic proteinuria and with low grade crescent formation on histopathology;
- Rapidly progressive HSPN with heavy proteinuria and 50% crescents.

These studies should be double blind and controlled with clear end points. Extrapolation from IgA nephropathy suggests that ACEIs are probably a part of treatment in all stages of HSPN. This task is necessary in order to offer the best management for children with HSP, and to avoid overtreatment.

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Executive summary

Prevention of Henoch–Schönlein purpura nephritis

- Available data do not support the use prophylactic corticosteroid treatment to prevent the development of Henoch–Schönlein purpura (HSP) nephritis (grade A recommendation).

Effects of antiplatelet agents

- Treatment with antiplatelet agents does not prevent development of HSP nephritis (grade B recommendation).

Treatment of moderately severe HSP nephritis

- The number of the studies in this area is very small and they are hampered by several limitations. Thus, it is difficult to reach an evidence-based conclusion.
- Angiotensin-converting enzyme inhibitors may be indicated to limit secondary glomerular injury.
- Studies regarding steroid usage in IgA nephritis revealed grade C recommendation. Although there is insufficient data regarding steroid usage in patients with moderately severe HSP nephritis, results regarding IgA nephropathy could be extrapolated to children with HSP nephritis.
- Further studies should be performed to evaluate the efficacy of steroids and their combination with other immunosuppressive drugs (e.g., azothioprine [AZA], cyclosporine A and mycophenolate mofetil).

Treatment of severe HSP with rapidly progressive or crescentic glomerulonephritis

- Sufficiently powered data on the use of immunosuppressives for patients with severe HSP is lacking. However, in one randomized controlled trial study, cyclophosphamide was not proven to be successful at 6 weeks (grade B).
- The combination of AZA and steroids may be useful (level 4 evidence); however, data is not sufficient for any recommendation level.
- The combination of methyl prednisolone, urokinase pulse therapy and cyclophosphamide decreases both activity index and chronicity index. However, the data is not sufficient for any level of recommendation (level 4 evidence).
- The combination of oral prednisolone and oral cyclophosphamide, followed by AZA and alternate-day steroids could be beneficial. However, the data is not sufficient to recommend this treatment as of yet.
- Insufficient data are available to recommend pulse and oral steroids, AZA, cyclosporine A and mycophenolate mofetil. There is not even consensus on the selection or the dose of immunosuppressive to be used.
- Plasma exchange could potentially be important in selected cases, although the outcome is not yet supported by randomized controlled trials.

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