

Management Options for Henoch-Schönlein Nephritis: Evidence-based Approach

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Abstract

Henoch-Schönlein purpura (HSP) is a common vasculitic disease in children. Renal involvement in HSP is not uncommon and accounts for major morbidity. There are a lot of controversies in the management of patients with Henoch-Schönlein nephritis. After reviewing the literatures, our group conclude that (a) The presenting renal histology, which reveals the severity of kidney damage, is by far the most useful, although not entirely reliable prognosticator. (b) Patients with minor urinary abnormalities at presentation do not need any form of intervention, however follow up for subsequent renal impairment may be necessary. (c) Patients with moderate renal involvement may warrant treatment and (d) renal biopsy is indicated in order to guide the treatment and give a better prediction of outcome. (e) Patients with rapidly progressive glomerulonephritis deserve aggressive intervention so as to halt the progression of renal damage and subsequent renal failure. Corticosteroid in combination with immunosuppressive agents is the commonly used treatment option and plasmapheresis could be an adjuvant therapy.

Key words

Glomerulonephritis; Henoch-Schönlein nephritis; Henoch-Schönlein purpura

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Introduction

Henoch-Schönlein purpura (HSP) is characterised by a triad of palpable purpura with a normal platelet count, abdominal pain and arthritis. It is one of the most common systemic vasculitic diseases in children.^{1,2} The prevalence of renal involvement varies widely according to the pattern of referral and diagnostic criteria used; however because of its high prevalence, it is considered as a feature of the disease. Clinical expression of Henoch-Schönlein nephritis (HSN) ranges from transient, isolated microscopic haematuria to rapidly progressive glomerulonephritis and uraemia.^{3,4} The commonest renal manifestation is haematuria with variable degree of proteinuria. The long-term outcome in HSN is uncertain though majority of children does not have serious renal disease.⁵ The 10-year actuarial survival of renal function for the 135 patients seen at Guy's Hospital approached 90%.⁶ Although renal failure tends to occur relatively early in the course of follow up, a small percentage of patients were reported to have deteriorated renal function and pregnancy complications, which occurred as long as 15 years after a period of apparent normality. The occurrence of the disease during childhood raised lifelong concerns for renal function.^{7,8}

Apart from the uncertainty in individual long-term outcome, there are a lot of controversies in the treatment of Henoch-Schönlein purpura and nephritis.⁹ Use of drugs like corticosteroid, azathioprine, cyclophosphamide and plasmapheresis have been reported with variable success. There is no consensus on the treatment regime, and the success of these aggressive therapies in altering the long-term outcome remains unanswered. In this review, we would like to update the different treatment options for HSN and revisit the dilemma from an evidence-based approach. Through this literature search, we hope that a clinical guideline could be suggested for management of this group of patients. It also serves as a beginning for further discussion and future research on this topic.

Method of Study

Literatures are searched from Medline using the key words Henoch-Schönlein nephritis, Henoch-Schönlein purpura and anaphylactic purpura. The search is then limited to paediatric and adolescent age group, studies on human subjects and focus on therapeutic options. The search period is 1980-2001 and only papers written in English are retrieved for review. The searched papers are then distributed to members of the Glomerulonephritis Study Group for critical appraisal. Regular meetings were held to discuss management problems. Level of evidence (LOE) and recommendation from the literatures were then worked out.

Definition

For evaluation of treatment efficiency, we will adopt the classification scheme described by Shekelle et al, 1999.¹⁰ The hierarchy of evidence and recommendation are defined as follows:

Level of Evidence

- Ia Evidence from meta-analysis of randomised controlled trials
- Ib Evidence from at least one randomised controlled trial
- IIa Evidence from at least one controlled study without randomisation
- IIb Evidence from at least one other types of quasi-experimental study

- III Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

In our review, the primary outcome in HSP is end-stage renal failure (ESRF). In some articles, other indicators like degree of proteinuria, serum creatinine are substituted as outcome measurement and in these circumstances, the LOE will be followed by an "S" which signifies the use of relatively weak surrogate outcome markers.

Grading of Recommendations¹⁰

Grade A (Levels Ia, Ib):

Requires at least one randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

Grade B (Levels IIa, IIb, III):

Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.

Grade C (Level IV):

Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Henoch-Schönlein Nephritis

The diagnosis of HSN required the presence of palpable cutaneous purpura plus one or more major manifestations of HSP¹¹ and nephritis, which is defined by the presence of gross or microscopic haematuria (>5 red blood cells per high power microscopic field from a centrifuged specimen^{12,13}) with or without proteinuria.¹¹ *Acute nephritis* is defined as nephritis, which was evident on the first urinalysis. *Delayed nephritis* is defined as nephritis appearing 3 weeks or longer after an initial normal urinalysis.¹⁴

Staging of Renal Biopsy

The glomerular changes were graded according to the classification of HSN developed by the pathologists of the International Study of Kidney Disease in Children (ISKDC).¹⁵

- Grade I: Minor glomerular abnormalities
- Grade II: Pure mesangial proliferation

- Grade III: Minor glomerular abnormalities or mesangial proliferation with crescents/segmental lesions in less than 50% of glomeruli
- Grade IV: As in grade III but with crescents/segmental lesions in 50-75% of glomeruli
- Grade V: As III but with crescents/segmental lesion in more than 75% of glomeruli
- Grade VI: Membranoproliferative like lesion

Rapidly Progressive Glomerulonephritis (RPGN) is defined as glomerular disease characterised by extensive crescents (involving >50% of glomeruli) as the principal histological finding and a rapid deterioration of renal function (>50% decline in glomerular filtration rate within 3 months) as the clinical correlate.¹⁶

Nephrotic Syndrome is defined as the presence of proteinuria (>40 mg/m² per hour) and a serum albumin level less than 2.5 g/dL, with or without oedema.¹⁷

Heavy proteinuria is defined as isolated proteinuria exceeding 40 mg/h per m² of body surface area without oedema or full-blown picture of nephrotic syndrome.¹⁷

End-stage renal disease is defined as when a patient required chronic dialysis or renal transplantation.

Results

Randomised control trials are lacking in the study of treatment on Henoch-Schönlein nephritis. Most of the studies are either case reports or retrospective studies. Hence, most of these recommendations are drawn from level III-IV evidence.

Question 1: Could the Occurrence of Henoch-Schönlein Nephritis Be Prevented by Steroid Therapy?

Recommendation

Use of prednisone at a dose of 1 mg/kg/day for 2 weeks might be considered in children with Henoch-Schönlein purpura to prevent the development of Henoch-Schönlein nephritis. However, consistent evidence is still lacking to support this to be a universal practice. Future prospective studies are recommended to answer this specific question. (*Grade C recommendation*)

The Evidence

Several articles in the literatures have attempted to answer this question and the results are summarised in Table 1. The effectiveness of corticosteroid in the prevention of HSN was first suggested in a retrospective review by Buchanec et al.¹⁸ Among their 23 patients treated with corticosteroid, 4.3% developed HSN whereas half of the 10 patients who did not receive corticosteroid developed HSN. Kaku et al¹⁹ studied the prognostic factors in Henoch-Schönlein nephritis and in his group of patients, 32.9% of treated patients versus 33.9% untreated patient developed HSN. Univariate analysis did not show significant reduction in incidence of HSN in treatment group. However, severe abdominal pain was found to be a high risk factor for the development of renal disease with a hazard ratio of 3.26 (P=0.034) and using multivariate analysis, the hazard ratio for use of steroid was 0.36 (P=0.037). They concluded that use of prednisone decreased the risk of subsequent renal involvement and the effect might be associated with the alleviation of abdominal symptoms by corticosteroid. The protective role of corticosteroid was further substantiated by a prospective study performed by Mollica et al and was reported in 1992.²⁰ None of the 84 treated patients developed HSN whereas 10 out of 84 untreated patient developed HSN during the period of followed up. However, a retrospective study reported by Saulsbury¹⁴ suggested that prior corticosteroid therapy had no effect on the occurrence of delayed nephritis. Four of the 20 treated patients and six of the 30 untreated patients developed nephritis subsequently and the difference in the two groups was insignificant.

Although the results are conflicting, there remains a possibility in preventing the development of HSN by corticosteroid. In the retrospective studies, corticosteroid was given to patients who either developed severe gastrointestinal symptoms or joint pain and there was not an intention to prevent nephritis. Therefore the treatment regime varied in the duration, dose and timing of commencement of corticosteroid.²¹ Prospective study carried out by Mollica et al²⁰ suggested that corticosteroid may be useful in preventing the development of HSN, however, majority of the described renal involvement was trivial. The most common renal involvement was mild urinary abnormalities like haematuria and non-nephrotic range proteinuria. An important but unanswered question is whether the prevention of these minor urinary abnormalities would alter the final outcome of the disease and affect the ultimate morbidity and mortality.

Table 1 Prevention of HSN with corticosteroid

Reference	Design	No. of patient	Treatment	Indication for Rx	Renal biopsy (histological staging)	Duration of follow up	Primary outcome	Long term outcome	Level of evidence
Buchanec et al ¹⁸ Czechoslovakia, 1988	Retrospective NR concurrent case control	33 (23 Rx gp, 10 C gp)	Pred 1-2 mg/kg/day for average 21 days	NA	Not done	NA	(4.3%) 1/23 Rx gp versus (50%) 5/10 C gp developed PU and HU	NA	III – S
Mollica et al ²⁰ Italy, 1992	Prospective, NR control study	168 (84 Rx gp, 84 C gp)	Pred 1 mg/kg per day for 2 wks	HSP (starts on day of admission to 10 days after admission)	Not done	24-36 mths	0/84 (Rx gp) versus 10/84 (C gp) develop HSN	2/84 (C gp) developed HSN 2 & 6 yrs after acute episode	IIa – S
Saulsbury et al ¹⁴ USA, 1993	Retrospective NR concurrent case control	50 (20 Rx gp, 30 C gp)	Pred 1.7±0.4 mg/kg/day for 5-10 days	To relieve abdominal pain or joint pain	Not done	NA	4/20 (20%) of Rx gp versus 6/30 (50%) of C gp developed delayed nephritis	NA	III – S
Kaku et al ¹⁹ Japan, 1998	Retrospective NR concurrent case control	194 (79 Rx gp, 115 C gp)	Pred orally 1 mg/kg 1-2 weeks or IV hydrocortisone 5 mg/kg 4-6 times per day for 3-5 days, followed by pred orally 1 mg/kg for 1-2 wks	To relieve abdominal symptoms and arthritis	Not done	14.5±12.3 mths (1-76.1 mths)	Pred decrease risk of subsequent renal involvement Severe abdominal pain to be high risk factor with hazard ratio 3.26	NA	III – S

NR: non-randomised; Rx gp: treatment group; C gp: control group; Wks: weeks; Mths: months; Yrs: years; Pred: prednisone; NA: data not available; PU: proteinuria; HU: haematuria.

Question 2: Do We Need to Treat Children With Henoch-Schönlein Nephritis and What Is the Long-term Outcome of This Group of Patients?

There is no single answer to this question because the degree of renal involvement and clinical outcome of these patients vary. Most children with Henoch-Schönlein nephritis do not require any form of treatment but there is a subgroup of patient who may benefit from corticosteroid.

There are worldwide data supporting the development of both acute and delayed renal failure among patients with Henoch-Schönlein nephritis. Estimated incidence of renal involvement varied from 20% to 100%, depending on the diagnostic criteria used.^{2,22-24} Long-term outcome of these patients are uncertain and randomised studies that compared the effectiveness of treatment in different categories of these patients are lacking.

Thirty-eight patients in a total of 319 children with renal involvement reported in three major series^{5,24,25} developed chronic renal failure and this accounted for 12% of their patients. A further 14 patients (7%) of the remaining 206 patients still had active disease. This made up a total of 19% of patients with significant renal disease. However results from these series were derived from patients who were selected for follow up of HSP with renal involvement and this might bias the actual scene. The overall prognosis in HSP was better appreciated in series, which included HSP with and without renal involvement and the expected incidence of renal failure was lower.^{23,24} The incidence of ESRD was estimated to be 2% in a group of unselected patients reported by Koskimies et al²³ and most patients recovered without significant renal disease. However, one could appreciate that the long-term morbidity and mortality of HSP were almost exclusively attributable to renal disease, so it was logical that one should treat the disease if there was a way to do so. The question waiting to be answered would be whom we should treat, how to treat and how effective the treatment in altering the clinical course.

Question 3: Which Group of Patient Would Be More Likely to Suffer from Long Term Renal Morbidity?

The study of prognostic or risks factors narrows down those patients who had the greatest possibility of significant renal morbidity and these help targeting those who might need intervention. Among most predictive factors,

presenting renal histology and clinical presentation are so far the most useful prognosticators though they are not entirely reliable on individual basis.

Renal biopsy is seldom necessary for diagnosis of HSN but is usually performed to assess severity of the disease. More than 25-30 years ago, correlation between the severity of clinical manifestation and kidney histology were derived.²⁶ Patients with initial macroscopic and/or persistent microscopic haematuria who did not have persistent heavy proteinuria, usually had glomerular lesions of grade III or less. Those with a nephritic or nephrotic onset, or persistent heavy proteinuria, had a 10-20% chance of grade IV to V lesions. A mixed nephritic-nephrotic presentation carried a 60% risk of grade IV to V lesions. Majorities of grade I to III lesions resolved; whereas increasing proportions of grade IV and V lesions did not.¹ The percentages of patient in each histological grade, showing either active disease or chronic renal failure, were reported to be 0% in grade I, 16% in grade II, 24% in grade III, 55% in grade IV and 67% in grade V.^{5,7} Judging from these percentages, Goldstein et al⁷ demonstrated a progressively worsening outcome with increasing histologic severity. However, the predictive value of an individual biopsy was not highly reliable except when it showed either grade I or V change.

To correlate the outcome with initial clinical presentation, a long-term follow-up study by Goldstein et al^{5,7} showed that chronic renal failure would be encountered in (a) less than 5% of patients when clinical signs at presentation were haematuria and/or minimal proteinuria (b) 15% of patients when proteinuria was heavy but not reaching nephrotic syndrome or in the case of acute nephritic (c) 40% in the case of nephrotic syndrome and (d) more than 50% when nephritic and nephrotic syndrome were associated. In a long term follow up of 78 subjects for a mean of 23.4 years (interim reports in 1971 and 1976), they observed that 17 of the 78 patients traced showed clinical deterioration at their final reassessment more than 19 years later. Seven of these patients had been considered to recover clinically, with normal blood pressure, urine and plasma creatinine concentration, when reassessed in 1976. Furthermore, hypertension and/or proteinuria complicated 36% of successful pregnancies whose initial clinical evaluation at follow-up were normal.^{7,8} The late development of hypertension and proteinuria after a period of normality and the progressive decline in renal function that followed initial improvement were consistent with a sequence of glomerular hyperfiltration followed by secondary glomerulosclerosis. This was particularly true when glomerular destruction due to the original disease

had been extensive. In other words, initial histological grading and clinical presentation were the most useful predictors of final outcome although they were not entirely reliable.

There were several reports, which addressed the issue of risk factors for renal involvement in children. Older age,^{27,28} abdominal symptom, persisting purpura¹⁹ and low factor XIII activity²⁹ had been reported to be associated with a higher risk of renal involvement. Henoch-Schönlein purpura was once thought to have a worse prognosis in adults than in children. However, Coppo and coworkers²⁸ showed that among patients with a clinical presentation, which warranted renal biopsy, HSN has a similar prognosis in both children and adult. Levy et al³⁰ found that proteinuria exceeding 1 g/day was associated with less favourable outcome. These efforts, however, had not been successfully identified high-risk patients and their value in predicting outcome remained uncertain.

Question 4: How to Manage HSN Children With Minor Urinary Abnormalities or Moderate Severity of Isolated Proteinuria With/Without Nephrotic Syndrome?

Recommendation

Children with minor urinary abnormalities should be monitored for any progression of renal disease especially in the initial few months. Renal biopsy would be indicated in selected patients and initiation of therapy would depend on the histological grading. Patients with proteinuria >1 g/day or patients with nephritic syndrome, use of prednisolone at 1-2 mg/kg/day could be considered after renal biopsy. Addition of azathioprine would depend on the severity of renal histology and could be used at a dose of 1-2 mg/kg/day. Patient with renal biopsy of high-grade severity, management would follow recommendation in Question 5. Indications for renal biopsy in HSN patients include heavy proteinuria, nephrotic syndrome, nephrotic-nephritic syndrome, impaired renal function and rapidly progressive glomerulonephritis. (*Recommendation C*)

Evidence

Since majority of patients with minor urinary abnormalities does not have significant renal disease, it is generally agreed that this group of patient could be managed conservatively and close monitoring of any deterioration in renal function is suggested. The options for treatment of patients with isolated heavy proteinuria with or without

nephrotic syndrome are most debatable especially when their creatinine clearance and urea were normal. There are three articles that reported their experience in treating patients with haematuria, significant proteinuria and nephrotic syndrome.

Foster et al³¹ reported management of moderate to severe HSN with azathioprine and corticosteroid (Table 2). Their group consisted of 20 patients, whose clinical presentation ranged from proteinuria >1 g/day without nephrotic syndrome to renal insufficiency, were compared with a historical control reported by Levy in 1976.³⁰ They demonstrated a significant drop in activity score between pre-treatment and post-treatment biopsies. However, chronicity score did not change appreciably. Nine of their treated patient (53%) had proteinuria >1 g/day without nephrotic syndrome and after a mean follow up for 3 years, six of them recovered, two of them had minor urinary abnormalities and one of them had persistent proteinuria. Rostoker et al³² reported the usefulness of γ globulin in treatment of HSN with significant proteinuria. Both the degree of proteinuria and the activity index were improved. However, the group of patient was a mixed group of patients with IgA nephropathy and HSN. Flynn et al³³ reported the use of cyclophosphamide with corticosteroid in managing 12 patients with isolated proteinuria and nephrotic syndrome. Their patients had a moderate to high histological grades of ISKDC III-IV. They showed significant reduction in urine protein and normalisation of serum albumin, however only 9 patients were able to be followed up to 35±17 months and there was no data on long term outcome of their renal function.

There are limitations in these reports. Firstly, the results are derived from a heterogeneous group of patients with various degree of disease severity. Secondly, there is no universal definition on the classification of mild, moderate and severe Henoch-Schönlein nephritis. Should the severity of nephritis be classified by clinical presentation or renal histology, posts another difficult dilemma. In view of all these difficulties, limited recommendation could be drawn.

Question 5: How to Manage Children With Severe Henoch-Schönlein Nephritis With Presence of ≥50% Crescents Formation in Renal Biopsy and What Are the Treatment Options?

Recommendation

Severe HSN should be treated with combinations of

Table 2 Treatment of moderate to severe HSN

Reference	Design	No. of patient	Treatment	Indication for Rx	Renal biopsy	Duration of follow up	Primary outcome	Long term outcome	Level of evidence
Foster et al ³¹ Canada, 2000	NR historical control retrospective	Total 20 pts in Rx gp and 25 C gp	AZA 1-2 mg/kg/day Pred 1-2 mg/kg/day for 4 wks then 1-2 mg/kg/ alternate day Total therapy time 8-75 wks (mean 46.7±19 wks)	PU >1 g/day ±NS±renal insufficiency. One treated for recurrent gross HU.	Scoring systems – Andreoli and Bergstein 1989 ³⁴	1.5-24 years (mean 5.4±5.4 years)	AS decreased with therapy with P=0.002, no significant change on CS	More pts in the C gp had an unfavourable outcome than in the Rx gp P=0.011	IV
Rostoker et al ³² France, 1995	NR, Prospective Uncontrolled Case series	14 pts median age 28 years (16-40 years) (11 Ig A and 3 HSP)	IVIG 2 g/kg monthly x 3 mths then IMIG 0.35 ml/kg twice monthly x 8 mths	Normal renal function with moderate degree PU (305-1420 mg/day). Moderate histology grading (stage I-III), moderate activity index and a low histological index of sclerosis	Grading system Lee et al, 1982 grade I-VI ³⁵	NA	PU decreased from 766 mg/day to 171 mg/day with P<0.01. Histological activity index (14 points scale) decreased from 4 to 0 after therapy with P<0.005	NA	IV
Flynn et al ³³ USA, 2000	Case series retrospective	12 pts (mean age 9 years)	IV pulse MP or oral Pred followed by CYCP (2 mg per kg/day) for 12 wks	NS or nephrotic range proteinuria	ISKDC ¹⁵ class III or IV	35±17 mths (in 9 pts only)	Significant fall in Up/Uc ratio from 6.3±4.4 to 0.9±0.8 and raised serum albumin from 2.8±0.5 g/dL to 3.7±0.4 g/dL	NA	IV

NR: non-randomised; Rx gp: treatment group; C gp: control group; Pts: patients; Wks: weeks; Mths: months; IgA: IgA nephropathy; Pred: prednisone; MP: methylprednisolone; AZA: azathioprine; CYCP: cyclophosphamide; IVIG: intravenous gammaglobulin; IMIG: intramuscular gammaglobulin; NA: data not available; PU: proteinuria; HU: haematuria; NS: nephrotic syndrome; AS: activity score; CS: chronicity score; IV: intravenous; Up: urine protein; Uc: urine creatinine.

prednisolone at 2 mg/kg/day and oral cyclophosphamide at 2-2.5 mg/kg/day, given for at least 2-3 months. Corticosteroid could be used after three doses of pulse methylprednisolone 30 mg/kg given either daily or on alternate day. Anticoagulant and/or anti-platelet agents could be added as adjuvant therapy. Azathioprine 2-3 mg/kg/day in combination with corticosteroid for a period of at least 2-3 months was an alternative treatment option. There was no data to support which combination of therapy was superior to the other. (*Grade C recommendation*)

The Evidence

Four articles addressed to this issue (Table 3).³⁶⁻³⁹ Since all of them were reports of case series, the level of evidence was Grade IV. Severe HSN were patients who suffered from either one or combinations of the followed problems: renal failure, nephrotic syndrome, nephrotic-nephritic syndrome and rapidly progressive glomerulonephritis and their renal histology showed significant proportion of crescents formation (ISKDC grade IV-V). Patients in this category were at high risk of renal failure despite aggressive treatments offered. Most nephrologists would opt to treat these patients and a well-designed randomised controlled study may not be feasible in most communities.

In the majority of patients described in these articles, kidney biopsy was performed and all histology scored high grades in the conventional staging scales. Biopsy with crescent formation in more than 50% of the glomeruli, was of poorer prognosis and had a higher risk of renal failure when compared with those of lower grades. Patients from Niaudet's study³⁷ had a repeated kidney biopsy after treatment, so as to document the improvement in renal histology; whereas in most reports the effect of treatment was based on clinical response. All these articles addressed the primary outcome of HSN. Both Niaudet³⁷ and Bergstein³⁹ reported that around 10% (i.e. 4/38 and 2/21 respectively) of their patients failed to respond to treatment and reached end-stage renal disease during the period of follow up. Different combinations of drugs were used and the cocktails usually included corticosteroid, which may be preceded by pulse methylprednisolone, plus either cyclophosphamide or azathioprine. Anticoagulants or anti-platelet agents like heparin, warfarin or dipyridamole were used in some case series to supplement the treatment. There was no data to support any one of this double, triple or quadruple therapy was better than the other. Furthermore, the duration of treatment varied and most articles reported a treatment period of not less than 2-3 months.

Question 6: What Is the Role of Plasma Exchange in the Management of Rapidly Progressing Crescentic Henoch-Schönlein Nephritis?

Recommendation

Plasma exchange (plasmapheresis) could be considered in the management of crescentic HSN. Early institute of therapy is desirable and suggested treatment duration is 10-12 sessions. (*Grade C recommendation*)

The Evidence

Three case series⁴⁰⁻⁴² reported the use of plasma exchange (PE) in the treatment of crescentic Henoch-Schönlein nephritis and the results were summarised in Table 4. Gianviti et al⁴² treated 14 patients with rapidly progressive HSN by plasmapheresis and corticosteroid. All these patients underwent kidney biopsy and crescent formation was present in 50%-100% glomeruli. Five of the 14 treated patients did not respond and progressed to ESRD whereas 57% of patients recovered and normalised their serum creatinine. All 8 patients who were treated within one month from the onset of disease had normal renal function at last follow up, whilst 5 of the 6 patients treated later than one month reached ESRD. More recently, Hattori et al⁴⁰ reported the clinical course of 9 patients with ISKDC Grade V Henoch-Schönlein nephritis. Plasmapheresis was instituted within 16 weeks of onset of disease and all patients responded promptly to PE with improvement in renal function, reduction in proteinuria and subsidence of abdominal pain. At last follow up, 66.7% (6/9) of their patient either normalised the renal function or had minor urinary abnormalities only and 2 patients (22.2%) progressed to ESRD at 14 and 1.8 years after disease onset. In the series reported by Schärer et al,⁴¹ 8 patients suffered from rapidly progressive crescentic HSN, and they reported a rapid fall in serum creatinine during the first course of PE. Five of the eight patients had rapid rebound of serum creatinine required additional courses of PE. The total number of PE session ranged from 7-11. In adjuvant to PE, methylprednisolone was also a mainstay of treatment in their protocol. Four of the treated patients (50%) reached ESRD at 1.2-3.7 years of follow up and 3 of them (38%) were in pre-terminal renal failure after 7-13.5 years of follow up.

The success of plasmapheresis varies. The difference in success rate may be explained by the difference in duration of follow up. It is also observed that initial response to PE

Table 3 Treatment of RPGN or crescentic HSN with corticosteroid and immunosuppressive agents

Reference	Design	No. of patient	Treatment	Indication for Rx	Renal biopsy	Duration of follow up	Primary outcome	Long term outcome	Level of evidence
Oner et al ³⁶ Turkey, 1995	Case series	12 (6-14 years)	<i>Triple therapy</i> IV MP 30 mg/kg x 3 days, followed by oral Pred 45 mg/m ² tapered over 3 mths. Oral CYCP 2 mg/kg/day x 2 mths Oral DIPYR 5 mg/kg/day x 6 mths	RPGN	9/12 had biopsy (60-90% crescents)	9-39 mths	GFR returned to normal in 11 pts. Complete remission in 7 pts.	NA	IV
Niaudet et al ³⁷ France, 1998	Case series	38	<i>Double therapy</i> IV MP 1 g/1.73m ² QOD x 3 doses, followed by Pred 30 mg/m ² /day x 1 mth, QOD x 2 mths and 15 mg/m ² x 2 wks CYCP 2.5 mg/kg/day for 2 mths in 7 pts	Presence of nephrotic syndrome± presence of crescents 50% glomeruli on renal biopsy	All have pre-Rx biopsy 30 pts have post-Rx biopsy (Andreoli & Bergsterin 1989 grading) ³⁴	1-16 years	Sig decrease in Activity index (P<0.0001) Sig increase in Chronicity index (P<0.002)	27/38 clinical recovered 4/38 ESRD	IV
Iijima et al ³⁸ Japan, 1998	Case series	14	<i>Quadriple therapy</i> Pred 2 mg/kg/day x 4 wks, followed by 2 mg/kg QOD x 8 wks and decreased by 0.5 mg per wk CYCP 2 mg/kg/day x 8 wks Heparin IV x 4 wks, followed by warfarin 1 mg/day x 4 wks. DIPYR 3-6 mg/kg/day x 8 wks	Renal histology of grade IV/V	All have renal biopsy and graded according to ISKDC	7.5±0.9 years	Post-Rx biopsy in 10 pts. Sig decrease in crescents / segmental lesions	None had ESRD, 9/14 normal 4/14 minor Uab 1/14 heavy PU	IV
Bergstein et al ³⁹ USA, 1998	Case series	21	<i>Double therapy</i> AZA 2-3 mg/kg/day Pred 60 mg/m ² /day for 5-12 wks (mean 8 wks) - (13/21 pts) OR IVI MP 30 mg/kg alt day for 6 then All were maintained with AZA and Pred 60 mg/m ² /alt day for 9-24 mths (mean 15 mths) - (8/21 pts)	Staging of renal biopsies III b-V	20 /21 had biopsy (ISKDC grading). Diffuse mesangial proliferation with crescents 6-100% (mean 40%).	1-108 mths (average 32 mths)	Sig decrease in HU, reduce PU from 8.8±7.5 to 0.47±0.39 and S Cr from 1.71±2.2 to 0.78±0.25 (P<0.01). Increase Cr Cl from 76±43 to 122±26	2/21 reached ESRD	IV

IV: intravenous; MP: methylprednisolone; Pred: prednisone; Wks: weeks; Mths: months; Alt day: alternate day; CYCP: cyclophosphamide; DIPYR: dipyridamole; AZA: azathioprine; Pts: patients; Pre-Rx: pre-treatment; Post-Rx: post-treatment; HU: haematuria; PU: proteinuria (g/day); ESRD: end-stage renal disease; ISKDC: International Study of Kidney Disease in Children; S Cr: serum creatinine (mg/dl); Cr Cl: creatinine clearance (ml/min/1.73m²); Uab: minor urinary abnormalities; Sig: significant.

Table 4 Treatment of rapidly progressive or crescentic HSN with Plasmapheresis

Reference	Design	No. of patient	Treatment	Indication for Rx	Renal biopsy	Duration of follow up	Primary outcome	Long term outcome	Level of evidence
Hattori et al ⁴⁰ Japan, 1999	Case series	9	PE thrice-weekly x 2 wks then weekly x 6 wks	Nephrotic-range PU and decrease GFR and renal histology showed class V	All pts had biopsy. Graded by ISKDC.	9.6±4.3 years	GFR increased from 46.5±9.5 to 95.8±15.1 ml/min/1.73m ² (P<0.01). PU decreased from 4.9±2.5 to 1.3±0.5 g/m ² /day (P<0.01).	2/9: ESRD 1/9: Active renal disease 2/9: Uab 4/9: normal	IV
Scharer et al ⁴¹ Germany, 1999	Case series	8	PE: 6-11 within sessions 16 wks of onset of HSP. Additional therapy with MP/prednisone±CYCP/CSA/ACEI.	Crescentic nephritis± persistent NS	All pts had biopsy. Graded by ISKDC.	Variable – 13 years	Transient improvement in SCr	4/7 ESRD 3/7 CRF 1/7 normal GFR	IV
Gianviti et al ⁴² UK, 1996	Case series	14	PE with corticosteroid ± cytotoxic agents	RPGN	All pts had biopsy	3.3 years	Improved/normalised SCr 2 mths after PE	5 /14 ESRD	IV

PE: Plasmapheresis; Pred: prednisone; Wks: weeks; Mths: months; Alt day: alternate day; CYCP: cyclophosphamide; CSA: cyclosporin A; ACEI: angiotensin converting enzyme inhibitor; Pts: patients; Pre-Rx: pre-treatment; Post-Rx: post-treatment; HU: haematuria; PU: proteinuria (g/day); ESRD: end-stage renal disease; CRF: chronic renal failure; ISKDC: International Study of Kidney Disease in Children; SCr: serum creatinine (mg/dl); Cr Cl: creatinine clearance (ml/min/1.73m²); Uab: minor urinary abnormalities.

may be good but rebound in serum creatinine is not uncommon and a repeat course of PE may be required. Furthermore, early institution of plasmapheresis may avoid the progression of cellular crescents to fibrotic stage and is an important determinant in the success of the treatment and subsequent long-term morbidity.

Conclusion

Henoch-Schönlein nephritis varies in severity. Its clinical presentation ranges from mild urinary abnormalities to rapidly progressive renal failure. There is no definitive treatment for the disease. Most studies reported are case series and well-designed randomised controlled trials are lacking in children. Nevertheless, through this review, we

hope that general recommendations for the management of the problem have been made and future researches will unravel the controversies.

References

1. White RHR, Yoshikawa N. Henoch-Schönlein Nephritis. In: Holliday MA, Barrett TM, Avner ED. (eds) Pediatric Nephrology, 3rd edn. Baltimore: William and Wilkins, 729-738.
2. Andreoli SP. Renal manifestations of systemic diseases. Semin Nephrol 1998;18:270-9.
3. Meadow SR, Glasgow EF, White RH, Moncrieff MW, Cameron JS, Ogg CS. Schönlein-Henoch nephritis. Q J Med 1972;41:241-58.
4. Bunchman TE, Mauer SM, Sibley RK, Vernier RL. Anaphylactoid purpura: characteristics of 16 patients who progressed to renal failure. Pediatr Nephrol 1988;2:393-7.
5. Counahan R, Winterborn MH, White RH, et al. Prognosis of

- Henoch-Schönlein nephritis in children. *Br Med J* 1977;2:11-4.
6. Austin HA 3rd, Balow JE. Henoch-Schönlein nephritis: prognostic features and the challenge of therapy. *Am J Kidney Dis* 1983;2:512-20.
 7. Goldstein AR, White RH, Akuse R, Chantler C. Long-term follow-up of childhood Henoch-Schönlein nephritis. *Lancet* 1992;339:280-2.
 8. White RH. Henoch-Schönlein nephritis. A disease with significant late sequelae. *Nephron* 1994;68:1-9.
 9. Szer IS. Henoch-Schönlein purpura: when and how to treat. *J Rheumatol.* 1996;23:1661-5.
 10. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999;318:593-6.
 11. 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.
 12. Dodge WF, West EF, Smith EH, Bruce Harvey 3rd. Proteinuria and hematuria in schoolchildren: epidemiology and early natural history. *J Pediatr* 1976;88:327-47.
 13. Diven SC, Travis LB. A practical primary care approach to hematuria in children. *Pediatr Nephrol* 2000;14:65-72.
 14. Saulsbury FT. Corticosteroid therapy does not prevent nephritis in Henoch-Schönlein purpura. *Pediatr Nephrol* 1993;7:69-71.
 15. Churg J. Systemic Vasculitis. In Grishman E, Churg J, Needele MA, Venkataseshan VS. (eds): *The Kidney in Collagen-Vascular Diseases*. New York: Rayen Press, 1993: 213-50.
 16. Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis* 1988;11:449-64.
 17. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. *Kidney Int* 1978;13:159-65.
 18. Buchanec J, Galanda V, Belakova S, Minarik M, Zibolen M. Incidence of renal complications in Schönlein-Henoch purpura syndrome in dependence of an early administration of steroids. *Int Urol Nephrol* 1988;20:409-12.
 19. Kaku Y, Nohara K, Honda S. Renal involvement in Henoch-Schönlein purpura: a multivariate analysis of prognostic factors. *Kidney Int* 1998;53:1755-9.
 20. Mollica F, Li Volti S, Garozzo R, Russo G. Effectiveness of early prednisone treatment in preventing the development of nephropathy in anaphylactoid purpura. *Eur J Pediatr* 1992;151:140-4.
 21. Mollica F, Li Volti S, Garozzo R, Russo G. Corticosteroid therapy does not prevent nephritis in Henoch-Schönlein purpura. *Pediatr Nephrol* 1994;8:131.
 22. Kobayashi O, Wada H, Okawa K, Takeyama I. Schönlein-Henoch's syndrome in children. *Contrib Nephrol* 1975;4:48-71.
 23. Koskimies O, Mir S, Rapola J, Vilska J. Henoch-Schönlein nephritis: long-term prognosis of unselected patients. *Arch Dis Child* 1981;56:482-4.
 24. Stewart M, Savage JM, Bell B, McCord B. Long term renal prognosis of Henoch-Schönlein purpura in an unselected childhood population. *Eur J Pediatr* 1988;147:113-5.
 25. Bunchman TE, Mauer SM, Sibley RK, Vernier RL. Anaphylactoid purpura: characteristics of 16 patients who progressed to renal failure. *Pediatr Nephrol* 1988;2:393-7.
 26. Yoshikawa N, White RH, Cameron AH. Prognostic significance of the glomerular changes in Henoch-Schönlein nephritis. *Clin Nephrol* 1981;16:223-9.
 27. Lahita RG. Influence of age on Henoch-Schönlein purpura. *Lancet* 1997;350:1116-7.
 28. Coppo R, Mazzucco G, Cagnoli L, Lupo A, Schena FP. Long-term prognosis of Henoch-Schönlein nephritis in adults and children. Italian Group of Renal Immunopathology Collaborative Study on Henoch-Schönlein purpura. *Nephrol Dial Transplant* 1997;12:2277-83.
 29. Fukui H, Kamitsuji H, Nagao T, et al. Clinical evaluation of a pasteurized factor XIII concentrate administration in Henoch-Schönlein purpura. Japanese Pediatric Group. *Thromb Res* 1989;56:667-75.
 30. Levy M, Broyer M, Arsan A, Levy-Bentolila D, Habib R. Anaphylactoid purpura nephritis in childhood: natural history and immunopathology. *Adv Nephrol Necker Hosp* 1976;6:183-228.
 31. Foster BJ, Bernard C, Drummond KN, Sharma AK. Effective therapy for severe Henoch-Schönlein purpura nephritis with prednisone and azathioprine: a clinical and histopathologic study. *J Pediatr* 2000;136:370-5.
 32. Rostoker G, Desvaux-Belghiti D, Pilatte Y, et al. Immunomodulation with low-dose immunoglobulins for moderate IgA nephropathy and Henoch-Schönlein purpura. Preliminary results of a prospective uncontrolled trial. *Nephron* 1995;69:327-34.
 33. Flynn JT, Smoyer WE, Bunchman TE, Kershaw DB, Sedman AB. Treatment of Henoch-Schönlein Purpura glomerulonephritis in children with high-dose corticosteroids plus oral cyclophosphamide. *Am J Nephrol* 2001;21:128-33.
 34. Andreoli SP, Bergstein JM. Treatment of severe IgA nephropathy in children. *Pediatr Nephrol* 1989;3:248-53.
 35. Lee SM, Rao VM, Franklin WA, et al. IgA nephropathy: morphologic predictors of progressive renal disease. *Hum Pathol* 1982;13:314-22.
 36. Oner A, Tinaztepe K, Erdogan O. The effect of triple therapy on rapidly progressive type of Henoch-Schönlein nephritis. *Pediatr Nephrol* 1995;9:6-10.
 37. Niaudet P, Habib R. Methylprednisolone pulse therapy in the treatment of severe forms of Schönlein-Henoch purpura nephritis. *Pediatr Nephrol* 1998;12:238-43.
 38. Iijima K, Ito-Kariya S, Nakamura H, Yoshikawa N. Multiple combined therapy for severe Henoch-Schönlein nephritis in children. *Pediatr Nephrol* 1998;12:244-8.
 39. Bergstein J, Leiser J, Andreoli SP. Response of crescentic Henoch-Schönlein purpura nephritis to corticosteroid and azathioprine therapy. *Clin Nephrol* 1998;49:9-14.
 40. Hattori M, Ito K, Konomoto T, Kawaguchi H, Yoshioka T, Khono M. Plasmapheresis as the sole therapy for rapidly progressive Henoch-Schönlein purpura nephritis in children. *Am J Kidney Dis* 1999;33:427-33.
 41. Scharer K, Krmar R, Querfeld U, Ruder H, Waldherr R, Schaefer F. Clinical outcome of Schönlein-Henoch purpura nephritis in children. *Pediatr Nephrol* 1999;13:816-23.
 42. Gianviti A, Trompeter RS, Barratt TM, Lythgoe MF, Dillon MJ. Retrospective study of plasma exchange in patients with idiopathic rapidly progressive glomerulonephritis and vasculitis. *Arch Dis Child* 1996;75:186-90.