Henoch–Schonlein purpura

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Summary
This review summarises the evidence from the latest published research on the epidemiology, aetiology, pathophysiology, clinical manifestations, treatment, and prognosis of Henoch–Schonlein purpura (HSP). Analysis of the literature indicates the importance of genetic and infectious aetiologic considerations in the development of HSP. And, within the last year, multiple inflammatory markers have been studied in association with the disease. Although, the common complaints associated with HSP are well known, the disease can also be associated with sequelae in multiple organ systems, as well as vasculitis throughout the body. No consensus has yet been agreed upon regarding treatment methodology of disease complications, but prognostic studies have determined that 6 months is appropriate in which to follow-up children to monitor for renal complications. Recent literature indicates the continued interest in defining the aetiology, complete clinical manifestations, treatment options and prognostic markers of HSP and the complications from the disease.

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Practice points
- Randomised control trials of treatments of HSP with steroids show no influence on long-term outcome
- Most cases of HSP are self-limiting. Therefore the unusual and unusually severe cases are written up and published
- Monitoring for renal complications in patients with HSP should last at least 6 months

Introduction
Henoch–Schonlein purpura (HSP) was first recognised by Heberden in 1801 and first described as an association between purpura and arthritis by Schonlein in 1837. Henoch added descriptions of gastrointestinal (GI) involvement in 1874 and renal involvement in 1899. HSP is a small vessel vasculitis the major manifestations of which include arthritis, non-thrombocytopenic purpura, abdominal pain, and renal disease. In 1990, the American College of Rheumatology published diagnostic criteria for HSP. These included: (1) palpable purpura—slightly raised ‘palpable’ haemorrhagic skin lesions, not related to thrombocytopenia; (2) age 20 years or younger at onset of first symptoms of the disease; (3) bowel angina—diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischaemia, usually including bloody diarrhea; and (4) wall granulocytes on biopsy—histologic changes showing granulocytes in the walls of arterioles or venules. The classification further states:

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For purposes of classification, a patient shall be said to have HSP if at least two of these four criteria are present. The presence of any two or more criteria yields a sensitivity of 87.1% and a specificity of 87.7%.  

HSP is one of the most common vasculitides of childhood and is considered to be self-limiting. One manifestation of HSP that can continue to cause lifelong problems is renal involvement. 

**Epidemiology, aetiology and pathophysiology**

Dolezalova et al. conducted a prospective epidemiologic incidence survey of childhood vasculitic disease in the Czech Republic showing an incidence of 10.2 per 100 000, whereas across the globe, a Taiwanese survey of childhood HSP epidemiological characteristics yielded an annual incidence of 12.9 per 100 000 children under the age of 17 years.  

Although the aetiology of HSP remains unclear, there are case reports of associations that are worth reviewing. In the last year, HSP has been reported in adults in association with oesophageal and lung adenocarcinoma, pulmonary Mycobacterium avium-intracellulare complex, familial Mediterranean fever, comadurin exposure, and intravesical administration of bacillus Calmette Guerrin (BCG) for the management of bladder cancer. In children, HSP has been reported in association with protein-losing enteropathy and severe esophagitis, varicella, and invasive meningococcal disease. In all cases, HSP was nonfatal and prolonged renal involvement was rare. Most cases of disease-associated HSP presented after the primary diagnosis was made. 

A number of studies evaluated the relationship between HSP and inflammatory markers, the studies document involvement of anti-neutrophil antibodies (ANCAs) both P and C, the rare interleukin (IL)-1β (-511) T allele, transforming growth factor-β, the C4 null allele, increased production of IL-8 but no increase in expression of ICAM-1, tumour necrosis factor (TNF)-α, and the lectin pathway complement activation in the progression of renal disease in HSP. There are conflicting articles about the role of nitric oxide synthase polymorphisms in susceptibility of developing HSP. 

**Clinical manifestations**

Characteristic clinical manifestations associated with HSP include GI complaints, non-thrombocytopenic rash, arthritis, and nephritis. Multiple case reports and research articles over the past year have expounded upon these characteristic symptoms to discuss the extent of symptomology and report involvement of other organ systems. 

Two studies investigated the GI manifestations of HSP. Chang et al. used a retrospective analysis of 261 patients with the goal of assessing the diagnostic value of imaging and stool occult blood tests to identify fatal complications. This study found that 58% of patients with HSP had abdominal pain, 17.6% suffered overt GI bleed or hemepositive stools. A 3+ or greater stool occult blood had a high incidence of being associated with positive imaging findings, and abdominal ultrasound should be used to exclude intussusception or bowel perforation. Chen and Kong also used the method of retrospective chart review, but this study noted the incidence of GI complications and manifestations. Of the 162 patients, 98.1% had colicky abdominal pain (the most frequent symptom), followed by vomiting in 39.5% of patients. Interestingly, in 25.3% of reported cases, GI symptoms manifested before skin rash. Other GI manifestations reported included terminal ileum involvement as the presenting symptom of a 43-year-old male with HSP; extensive mucosal inflammation with duodenoejunaulitis as pictured by capsule endoscopy in a patient with active HSP; and multiple small bowel perforations (0.38% incidence) in a child who died from complications of septicemia secondary to perforation. The illustration of these reports highlights the importance of observing a wide differential when discussing the aetiology of abdominal complaints. 

A Swedish study reported evidence pertaining to the greatest cause of morbidity associated with HSP, renal disease. The group evaluated renal hemodynamics by measuring the glomerular filtration rate (GFR) and protein excretion rates in 73 children with HSP nephritis. The study concluded that patients with HSP nephritis had lower GFRs than controls, but that severe morphological changes, also demarcated by lower GFRs, and higher blood pressure, occurred in patients with both nephritic range, as well as mild proteinuria. From this data the authors concluded that proteinuria is a marker of renal damage in HSP nephritis, and that all patients with proteinuria should be monitored closely. Kidney biopsy should be readily performed to assess the extent of morphological damage and initiate treatment when proteinuria increases and/or persists. 

Other clinical manifestations reported over the past year include two reports of children who developed rare haemorrhagic bullae in association with HSP; a report of a 13-year-old male with proximal symmetrical muscle weakness and pain in association with HSP nephritis; and a report of a 25-week pregnant woman who developed HSP and was successfully treated with steroid therapy, resulting in disease resolution and a healthy, term infant. Also reported was the case of a 13-year-old girl who developed cerebral vasculitis and intracerebral haemorrhage, associated with vision loss, whose sight was successfully restored following plasmapheresis. 

**Treatment**

HSP, in general, is considered a self-limiting disease. However, in cases of prolonged GI pain, steroids have been reported to decrease the length of GI complaints, as well as
decrease renal complications. A study published in an April 2004 edition of *BMC Medicine* documents a randomised, controlled trial (RCT) of prednisone as an early intervention in those patients diagnosed with HSP. The 41-patient study randomised children within 7 days of symptom onset to prednisone therapy or placebo for 2 weeks. Unlike previous case reports, the study found that there was no difference in the rate of renal involvement and/or the rate of acute Gl complications between the placebo and steroid groups through 1-year of follow-up.  

As no single treatment methodology has been proven to be effective for refractory symptoms associated with HSP, multiple immunosuppressive therapies have been tried in an effort to decrease complicating symptoms. Sugiyama et al. report a case of an adult patient with HSP nephritis who was successfully treated to clinical remission with tonsillectomy followed by intravenous pulse methylprednisolone and oral prednisone therapy. In the last year, cyclosporine A has been reported to be an effective treatment of HSP nephritis, with nephritic-range proteinuria, in a child refractory to dapsone, oral prednisone and other immunosuppressive agents. Dapsone has been reported, in a small case series, to provide improvement in skin rash but no significant reduction in urinary protein excretion, no increase in hypertension. After an average of 49.2 weeks of follow-up, those patients treated with three-drug therapy had decreased urinary protein excretion, lower chronicity index of serial kidney biopsies and no progression to persistent nephropathy. 

A RCT of cyclophosphamide therapy for 56 children with histopathologically severe HSP nephritis found no differences in onset data or outcome between the trial and placebo groups. However, Kawasaki et al. reported that cyclophosphamide, when combined with methylprednisolone and urokinase pulse therapy, is beneficial for patients with severe HSP nephritis. After 6 months of therapy, the patients treated with three-drug therapy had decreased urinary protein excretion, lower chronicity index of serial kidney biopsies and no progression to persistent nephropathy.

Plasmapheresis has also been reported to be effective for patients with nephritis. A Taiwanese case report discusses the case of a 33-year-old man with crescentic glomerulonephritis refractory to steroid and oral cyclophosphamide therapy. The patient had successful recovery after nine sessions of simple double-filtration plasmapheresis and remained free of vasculitic events at 18 months follow-up. In a case series of six Japanese children with rapidly progressive HSP nephritis, the authors report treatment with five courses of plasmapheresis followed by multiple drug therapy, including methylprednisolone and urokinase pulse therapy, oral prednisolone, cyclophosphamide, dipyridamole and warfarin. After 6 months, each patient had significantly reduced urinary protein excretion, no increase in crescentic and sclerosed glomeruli, and no patient progressed to renal insufficiency. 

The most original treatment study reported a cohort of five children with biopsy-proven HSP and repeated episodes of haematuria and proteinuria treated with fish oil and angiotensin-converting enzyme inhibitor (ACEI) therapy for hypertension. After an average of 49.2 weeks of follow-up, the protein excretion rate and average blood pressure had both significantly decreased with no study participant requiring ACEI therapy. Also, the GFR and serum creatinine of all study patients remained stable. It is evident from these treatment studies that a clear consensus regarding therapy has yet to be determined, however, many different treatment strategies can be used to aid patients with complications from HSP.

### Prognosis

In general, the prognosis for most children diagnosed with HSP is very good. As HSP is considered a self-limiting disease with a low percentage of complications, most children recover without permanent sequelae. The most significant cause of morbidity associated with HSP is renal insufficiency. Two studies have discussed prognostic factors relating to HSP and renal involvement. 

Rigante et al. prospectively examined a cohort of paediatric patients diagnosed with HSP to look at the possible relationship between renal involvement or disease relapse with regard to multivariate analysis. Those patients who were treated with steroid therapy or who had renal complications at the onset of disease were excluded from the analysis. The study revealed that persistent rash, greater than 1 month, was significantly related to renal involvement. A second prognostic meta-analysis was undertaken with the goal of determining the duration of recommended follow-up for children diagnosed with HSP without significant renal complications at the time of diagnosis. The study included 12 studies with a total cohort of 1133 children. The results indicated that children should be followed-up using urinalysis for at least 6 months because 97% of children who will have abnormal urine findings will present in that time period. Encouragingly, children with normal urinalysis at presentation were found to have no long-term renal impairment. However the risk of long-term renal impairment is 12 times higher if the patient presents with nephritic or nephritic syndrome. Those children that have abnormal urinalysis at presentation or develop abnormal urinalysis within the first 6 months should be followed-up by measurements of serum urea and creatinine.

### Conclusion

Although HSP has been described for well over a century, we are still struggling to determine the aetiology of this most common vasculitis of childhood, and the best treatment for the most severe outcomes. Most children with HSP have no significant sequelae, but renal involvement can result in lifelong problems. Through review of the most recent year’s literature, the continued interest in this disease, its aetiology, and its outcome can be appreciated.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as: *Of special interest; **Of outstanding interest.


*Case report of familial association of HSP presenting in the same environment.


*Sera from children with HSP induce expression of IL-8 but not ICAM-1.


*Retrospective study analyzing the correlation between incidence of URI in conjunction with the diagnosis of HSP.


*Study of 73 children and the clinical findings, including proteinuria and GFR, that relate to significant renal pathology. Surprisingly even mild to moderate proteinuria can be associated with severe morphological changes seen on biopsy.


**RCT with data indicating that early intervention with prednisone therapy has no effect on outcome of GI or renal complications.**


**Study of five patients with HSP and renal complications treated with fish oil and ACEI therapy. The cohort had significant reductions in renal complications.**


**Prospective multivariant analysis of factors related to prolonged renal involvement in children diagnosed with HSP. The study found that the only predictive variable of renal involvement is prolonged classic HSP rash greater than 1 month.**


**Further reading**
