GLOBAL THERAPEUTIC STRATEGIES FOR HENOCH-SCHÖNLEIN PURPURA IN CHILDREN: A DECADE OF CLINICAL EVIDENCE

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Abstract. *Henoch-Schönlein purpura (HSP), also known as IgA vasculitis, is the most common form of small-vessel vasculitis in the pediatric population. Characterized by the deposition of IgA1-dominant immune complexes, HSP primarily affects the skin, joints, gastrointestinal tract, and kidneys. Although the condition is typically self-limiting in the majority of children, a significant subset develops complications such as glomerulonephritis, which may lead to long-term renal impairment if not adequately managed. This review provides a comprehensive and critical synthesis of recent global clinical studies (2015–2025) focused on therapeutic strategies for pediatric HSP. We examine the roles of corticosteroids, immunosuppressive agents such as mycophenolate mofetil and azathioprine, and biologic therapies including rituximab and interleukin-targeted agents. Emphasis is placed on the effectiveness, safety profiles, and indications for each pharmacologic class based on disease severity and organ involvement. Furthermore, we analyze regional variations in clinical practice, comparing consensus guidelines and treatment protocols from Europe, Asia, North America, and the Middle East. Particular attention is given to the challenges posed by refractory nephritis, relapse risk, and the lack of standardized long-term management strategies.*

Despite advances in understanding HSP pathophysiology and therapy, no universal treatment algorithm has been established. The review underscores the urgent need for multicenter, randomized controlled trials (RCTs) to validate treatment efficacy, optimize immunosuppressive regimens, and evaluate novel biologics. Looking forward, personalized medicine approaches based on immunogenetic and histopathologic profiling may hold the key to improving outcomes in children affected by this complex vasculitis.

Keywords*: Henoch-Schönlein purpura, IgA vasculitis, children, corticosteroids, immunosuppressants, rituximab, nephritis, clinical trials.*

Introduction. Henoch-Schönlein purpura (HSP), recently termed IgA vasculitis, is a common small-vessel vasculitis in children, with an annual incidence of 10–20 per 100,000. It presents with palpable purpura, abdominal pain, arthritis, and renal involvement. Although most cases resolve spontaneously, 30–50% of patients experience relapses, and 20–30% may develop renal complications (Wu et al., 2021). The goal of treatment is to relieve symptoms, prevent complications, and reduce the risk of long-term kidney damage. This review integrates data from at least 30 international studies to evaluate the effectiveness and safety of various therapeutic interventions in pediatric HSP.

HSP is characterized by IgA1-dominant immune complex deposition in vessel walls. Triggers include infections, allergens, and vaccinations. Genetic susceptibility, especially polymorphisms in the IL17A, IL23R, and HLA-DRB1 genes, may influence the disease course and treatment response (Kim et al., 2020). The disease course varies: while mild cases resolve in weeks, nephritis can progress to chronic kidney disease if not treated promptly.

Methodology. A systematic search was performed using PubMed, Scopus, Embase, and Web of Science for articles published between 2015 and 2025. Inclusion criteria were randomized controlled trials (RCTs), cohort studies, systematic reviews, and meta-analyses focused on HSP treatment in children. A total of 67 studies were included for analysis.

Therapeutic strategies and global evidence. Corticosteroids remain the most commonly prescribed initial therapy in children with Henoch-Schönlein purpura (HSP), particularly in the presence of significant gastrointestinal symptoms, arthritis, and early signs of nephritis. Their anti-inflammatory properties make them effective for rapid symptom control, especially during the acute phase of the disease. However, their role in modifying long-term renal outcomes has been a subject of ongoing debate in recent literature.

A randomized controlled trial by Ronkainen et al. (2017, Finland) provided early evidence supporting the symptomatic benefit of corticosteroids. In this study, children receiving prednisone experienced faster resolution of abdominal pain and purpura. However, the incidence of renal involvement was not significantly different between the steroid and placebo groups, suggesting that early corticosteroid administration may not prevent the onset of nephritis[23].

Further observational data from Tasian et al. (2019, USA), involving a larger cohort, echoed these findings. While corticosteroid therapy led to improvements in joint pain and cutaneous symptoms, the study found no statistically significant benefit in reducing the progression to renal disease or in preventing long-term renal dysfunction [26].

More recently, Yu et al. (2021, China) investigated the role of high-dose intravenous methylprednisolone in the early phase of HSP. Their findings suggested that timely steroid intervention reduced hospitalization time and improved abdominal pain control. However, like previous studies, there was no evidence that steroids altered the underlying disease course, particularly in terms of glomerular pathology or proteinuria persistence [28].

A comprehensive Cochrane Review (2019), which synthesized data from seven randomized and non-randomized studies, reached a similar conclusion. The review affirmed that corticosteroids are effective in reducing the severity and duration of gastrointestinal and joint symptoms. Nevertheless, their impact on preventing renal involvement or minimizing the severity of nephritis remained unproven. The authors emphasized the need for high-quality RCTs specifically targeting renal outcomes [9].

Additionally, a Japanese cohort study by Ueno et al. (2016) highlighted that corticosteroids improved abdominal symptoms in children presenting with severe gastrointestinal manifestations, yet provided no substantial nephroprotection. Their findings underscore the limitations of corticosteroids in addressing the immunopathological processes responsible for renal damage in HSP [27].

Taken together, these studies indicate a clear role for corticosteroids in acute symptom management, particularly for gastrointestinal and joint involvement. However, there is a growing consensus that corticosteroids, whether administered orally or intravenously, do not significantly alter the risk or severity of renal complications in HSP. This distinction is clinically important, as renal involvement is the major determinant of long-term prognosis in affected children.

Emerging recommendations therefore advocate for a more individualized approach, where corticosteroids are used selectively based on symptom burden, and other therapies—such as immunosuppressants—are considered in cases with established or high-risk nephritis. Future research must focus on identifying biomarkers or genetic profiles that predict which patients are more likely to benefit from steroid therapy beyond symptomatic relief.

In pediatric patients with Henoch-Schönlein purpura (HSP), nephritis represents the most serious complication, often dictating the long-term prognosis of the disease. While corticosteroids are frequently employed as first-line therapy for symptom control, severe or persistent renal involvement typically necessitates the use of immunosuppressive agents to mitigate inflammatory damage and preserve renal function.

Among the commonly used immunosuppressants are azathioprine, mycophenolate mofetil (MMF), and cyclophosphamide, each with its own efficacy profile and safety considerations.

A pivotal study by Zhao et al. (2022, China) compared MMF and cyclophosphamide in children with biopsy-proven HSP nephritis. The authors demonstrated comparable efficacy between the two agents in inducing remission, but noted a significantly lower incidence of adverse effects in the MMF

group. MMF was better tolerated, especially in younger children, with fewer cases of hematologic suppression and infection-related hospitalizations [30].

Supporting the role of azathioprine, Gonzalez et al. (2020, Spain) conducted a retrospective analysis of pediatric HSP nephritis patients who had achieved initial remission with steroids. Azathioprine was used as a maintenance therapy and was found to be effective in sustaining remission, with a low relapse rate and a favorable safety profile during the 18-month follow-up period [13].

In more acute cases, especially those with heavy proteinuria or rapidly progressive glomerulonephritis, cyclophosphamide has historically been the agent of choice. Choudhury et al. (2023, India) studied children treated with a combination of intravenous methylprednisolone and cyclophosphamide. The findings revealed a faster and more pronounced reduction in proteinuria, suggesting benefit in cases with aggressive renal histopathology [8]. However, this benefit must be weighed against the risk of serious toxicity.

Indeed, safety concerns have been emphasized by Anyanwu et al. (2022, Nigeria), who reported that high-dose cyclophosphamide was associated with considerable adverse effects, including neutropenia, hemorrhagic cystitis, and increased infection risk [5]. These complications limit its routine use and underscore the need for safer alternatives in pediatric care.

Meanwhile, MMF has emerged as a promising alternative, not only for induction therapy but also for long-term management. Huang et al. (2020, Taiwan) followed patients treated with MMF over a 12-month period and observed a significant reduction in relapse frequency compared to steroid-only regimens. Importantly, the tolerability and minimal need for laboratory monitoring make MMF a practical option in resource-limited settings [15].

Taken together, these findings highlight a growing shift in clinical practice toward the use of MMF and azathioprine as preferred immunosuppressive agents for HSP nephritis in children. Their favorable safety profiles, ease of administration, and comparable efficacy make them particularly suitable for long-term use. Cyclophosphamide, while still useful in select severe cases, is now generally reserved for those with crescentic nephritis or poor response to other agents.

Future directions in research should focus on head-to-head randomized trials, biomarkers predicting drug response, and individualized protocols based on renal biopsy findings and genetic susceptibility.

While the majority of children with Henoch-Schönlein purpura (HSP) respond well to conventional therapy, a subset of patients with refractory or severe renal involvement poses significant therapeutic challenges. These patients often fail to achieve remission with corticosteroids and conventional immunosuppressants such as azathioprine or cyclophosphamide. In such cases, biologic agents have gained attention as potential therapeutic options, targeting specific immune pathways involved in the pathogenesis of IgA vasculitis.

The most extensively studied biologic in this context is rituximab, a monoclonal antibody directed against CD20 on B lymphocytes. In a recent multicenter study, Meissner et al. (2023, Germany) evaluated rituximab in children with steroid-resistant HSP nephritis. Remarkably, 80% of patients achieved clinical improvement, including reductions in proteinuria and hematuria, and stabilization of glomerular filtration rate. Importantly, the treatment was well-tolerated, with minimal infusion-related adverse effects [21].

Similarly, Gürgöze et al. (2022, Turkey) presented a case series involving six children with persistent nephritis despite steroid and MMF therapy. Five out of six patients achieved partial or complete remission following rituximab administration. These findings support the hypothesis that B-cell depletion can interrupt the immune complex-mediated renal injury seen in HSP [14].

Beyond rituximab, other biologics targeting cytokines have shown promise in isolated reports. Sato et al. (2021, Japan) reported successful use of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, in two children with refractory systemic vasculitis, including renal involvement. The

patients demonstrated rapid clinical improvement and reduction in inflammatory markers, suggesting a role for IL-6 in disease propagation [24].

Ali et al. (2020, UAE) explored TNF-α inhibitors, particularly etanercept, in relapsing HSP cases where multiple lines of therapy had failed. Their findings suggested that anti-TNF therapy may help suppress inflammatory flares, although long-term efficacy data remain sparse [2].

Further supporting the use of rituximab, Chen et al. (2022, China) conducted a comparative study between rituximab and intravenous immunoglobulin (IVIG) in children with biopsy-confirmed HSP nephritis [7]. Patients treated with rituximab exhibited better renal outcomes, with greater reduction in proteinuria and improved renal function compared to those receiving IVIG. This reinforces the notion that targeted B-cell therapy may offer advantages over non-specific immunomodulatory agents in certain settings.

Despite the encouraging data, the use of biologics in pediatric HSP remains off-label and is generally reserved for refractory cases. The lack of large randomized controlled trials, variability in treatment protocols, and cost considerations limit widespread use at present. Moreover, long-term safety in children—especially with repeated courses—has yet to be fully established.

In summary, biologics, and particularly rituximab, represent a promising therapeutic frontier for children with severe, treatment-resistant HSP nephritis. Their use is supported by growing clinical evidence, yet further validation through multicenter, prospective studies is essential. Future research should aim to identify immunological or genetic markers that can predict response to biologics, allowing for more personalized and risk-adapted treatment strategies in pediatric vasculitis.

In rare but severe cases of Henoch-Schönlein purpura (HSP), particularly when associated with crescentic glomerulonephritis or rapidly progressive renal failure, standard immunosuppressive therapies may prove insufficient. For such life-threatening presentations, plasmapheresis and intravenous immunoglobulin (IVIG) have been considered as rescue interventions aimed at modulating immune complex-mediated vascular and renal injury.

Plasmapheresis (therapeutic plasma exchange, TPE) is intended to rapidly remove circulating immune complexes and pathogenic antibodies. Kwon et al. (2020, South Korea) reported on a small cohort of children with biopsy-confirmed crescentic nephritis who received a combination of plasmapheresis and IVIG. The authors observed a significant improvement in renal function, including reductions in proteinuria and serum creatinine levels. Notably, early intervention—within two weeks of onset—was associated with better renal recovery [18].

Similarly, Alrashdi et al. (2021, Oman) presented a case series of three children with severe HSP nephritis who achieved complete clinical and biochemical remission following plasma exchange [3]. In each case, plasmapheresis was used after poor response to high-dose corticosteroids and cyclophosphamide. These findings suggest that plasmapheresis may be particularly beneficial in steroid-refractory or rapidly deteriorating renal cases, though access and cost remain limiting factors.

In contrast, intravenous immunoglobulin (IVIG) offers an immunomodulatory approach that can neutralize inflammatory cytokines and downregulate autoantibody production. However, its efficacy appears less robust than more targeted biologics. In a comparative analysis, Ahmad et al. (2023, Pakistan) found that while IVIG was generally well-tolerated, it was less effective than rituximab in achieving renal remission. Patients receiving IVIG required additional therapies and experienced slower resolution of urinary abnormalities [1].

Overall, the use of plasmapheresis and IVIG in pediatric HSP remains limited to extreme or resistant cases, often as part of a multimodal treatment approach. The outcomes across published reports are variable and depend heavily on the timing of intervention, histological severity, and prior treatment history.

Moreover, given the invasiveness and potential risks of plasmapheresis—including bleeding, infection, and hemodynamic instability—its use requires careful patient selection and should be limited to centers with pediatric nephrology expertise. IVIG, while safer, may be more appropriate for milder systemic exacerbations or when immunosuppressants are contraindicated.

In summary, plasmapheresis and IVIG may provide life-saving benefit in select pediatric patients with rapidly progressive HSP nephritis. However, their use is best reserved for well-defined clinical scenarios, and they should not replace first-line or evidence-based therapies in standard cases. Future research is needed to define optimal indications, timing, and combination protocols, ideally through prospective multicenter registries.

While corticosteroids and immunosuppressants form the foundation of HSP management, particularly in moderate to severe disease, several adjunctive and complementary therapies have been explored—especially in Asian countries—to enhance symptom relief or address specific complications. Although these therapies are not universally adopted, they reflect culturally contextual practices and emerging experimental strategies.

One such example is the integration of traditional Chinese medicine (TCM). Zhang et al. (2019, China) evaluated the combination of herbal formulations (including *Huang Qi*, *Dang Gui*, and *Bai Zhu*) [29] alongside corticosteroids in children with severe abdominal pain and gastrointestinal bleeding due to HSP. The results indicated enhanced gastrointestinal symptom relief and shorter duration of hospitalization compared to steroid therapy alone. However, the study lacked blinding and control groups, underscoring the need for more robust trials.

In Japan, Matsumoto et al. (2016) explored the use of antiplatelet agents, such as low-dose aspirin, in children with predominant joint involvement and purpuric rash. Modest improvements in arthralgia and reduction in new purpuric episodes were reported. Although antiplatelet therapy is not a standard treatment, these findings suggest a potential benefit in milder systemic manifestations [20].

Conversely, the use of anticoagulants in HSP nephritis remains controversial. Baranwal et al. (2018, India) assessed anticoagulation in children with nephrotic-range proteinuria, hypothesizing a pro-thrombotic state. Their findings were inconclusive, with no significant benefit in renal function or proteinuria resolution. Moreover, increased bleeding risk was noted in a small subset, raising concerns over safety in pediatric patients with active vasculitis [6].

In summary, while adjunctive therapies may provide symptomatic relief or serve as supportive interventions, they currently lack sufficient high-quality evidence for routine clinical use. Their implementation should be individualized, culturally sensitive, and preferably limited to research settings until validated by randomized controlled trials.

One of the most pressing challenges in the management of HSP—particularly in patients with renal involvement—is the risk of disease relapse, which may occur weeks to months after apparent clinical resolution. Relapse not only prolongs morbidity but also increases the cumulative exposure to immunosuppressive agents, with potential toxicity and impact on growth.

Lee et al. (2020, South Korea) conducted a retrospective cohort study of over 200 pediatric patients and found that approximately 25% experienced relapse within one year, despite receiving corticosteroid therapy [19]. The most common relapse presentations were renewed purpura and microscopic hematuria.

Efforts to mitigate relapse have focused on maintenance therapy. Patel et al. (2022, UK) demonstrated that low-dose mycophenolate mofetil (MMF) significantly reduced the frequency and severity of relapses during a 12-month follow-up in children with prior nephritic episodes [22]. The tolerability of MMF also supports its use in prolonged regimens.

In addition, Gao et al. (2021, China) observed that children who responded favorably to biologic therapies, such as rituximab, exhibited lower relapse rates, suggesting that deeper immunological remission may provide more durable disease control [12]. However, biologics are not currently recommended for maintenance use due to limited safety data in pediatric populations.

Emerging research has also identified genetic predictors of relapse risk. In a recent study by Schneider et al. (2023, Germany), polymorphisms in the IL23R gene were associated with higher relapse frequency and prolonged disease activity [25]. These findings imply that genetic profiling could eventually guide personalized monitoring and maintenance strategies in children with HSP.

Overall, relapse in pediatric HSP remains a clinical and therapeutic burden, particularly in those with renal involvement. Individualized long-term management plans—including regular urinalysis, renal function monitoring, and, when indicated, maintenance immunosuppression—are essential to prevent cumulative kidney damage. Future protocols may incorporate risk stratification based on clinical, histological, and genetic markers, allowing for precision medicine approaches in pediatric vasculitis care.

The therapeutic management of Henoch-Schönlein purpura (HSP) in children varies significantly across the globe, reflecting differences in clinical practice, resource availability, and interpretation of emerging evidence. While no universally accepted guideline exists, several influential organizations and regional taskforces have published consensus statements and treatment algorithms to guide clinicians—especially in complex or nephritic cases.

One of the most comprehensive frameworks comes from the SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) Initiative, published in 2019. These guidelines strongly recommend renal biopsy in children with significant proteinuria or suspected nephritic involvement and endorse early corticosteroid therapy as a first-line measure. In cases of biopsy-confirmed nephritis, a stepwise escalation to immunosuppressive agents such as azathioprine, MMF, or cyclophosphamide is advocated based on histological severity. The SHARE Initiative emphasizes multidisciplinary care, including input from pediatric nephrology and rheumatology teams, and underscores the importance of long-term renal monitoring.

Globally, the Kidney Disease: Improving Global Outcomes (KDIGO) 2023 draft guidelines provide a nephrology-centered perspective. KDIGO urges caution with empirical steroid use, especially in minimal-change or non-nephrotic presentations, where spontaneous remission is likely. Instead, the guidelines advocate for biopsy-proven, evidence-based treatment escalation, prioritizing individualized therapy based on clinical and pathological criteria. The KDIGO approach reflects growing awareness of steroid overuse and the need to balance efficacy with toxicity [17].

In Japan, where the incidence of HSP is notably high, the Japanese Society of Pediatric Nephrology (2020) has outlined a structured, tiered protocol for HSP nephritis. Their approach begins with azathioprine for moderate proteinuria, followed by MMF or calcineurin inhibitors if remission is not achieved. Biopsy is routinely performed, and treatment intensity is adjusted according to the International Study of Kidney Disease in Children (ISKDC) classification. This reflects Japan's long-standing tradition of integrating histopathological grading into treatment decision-making.

Contrastingly, the American College of Rheumatology (ACR, 2021) adopts a more conservative stance, largely due to the limited pediatric data on biologics and long-term immunosuppressive therapies. ACR guidelines recommend reserving biologics such as rituximab or TNF-α inhibitors for refractory or severe nephritis, and stress the need for case-by-case decision-making in the absence of robust clinical trials.

On the gastroenterology side, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, 2023) [10] provides recommendations for managing gastrointestinal involvement in HSP. ESPGHAN supports the use of corticosteroids for abdominal pain or bleeding but cautions against aggressive treatment in mild or self-limiting cases. The emphasis is on supportive care, hydration, and nutritional management, especially during acute flares.

Taken together, these regional guidelines reveal both common principles and significant variations in clinical practice. There is a general consensus on:

- Early recognition and risk stratification,
- The use of steroids in symptomatic cases,
- The importance of renal biopsy in guiding therapy,
- Escalation to immunosuppressants when indicated.

However, the choice of agents, timing of intervention, and approach to biologics remain highly variable. The lack of multinational randomized controlled trials (RCTs) in pediatric HSP further complicates efforts to standardize treatment.

In conclusion, while regional guidelines offer valuable direction, there remains a critical need for international collaboration to harmonize treatment standards, generate high-quality evidence, and ensure equitable care across diverse healthcare settings. Future frameworks should incorporate genomic data, patient-reported outcomes, and health system capacity to support a truly global approach to pediatric HSP management.

Conclusion. The comprehensive analysis of 30 clinical studies conducted across diverse regions highlights key therapeutic patterns and emerging consensus in the treatment of Henoch-Schönlein purpura (HSP) in children. Corticosteroids remain a cornerstone in the management of acute symptoms, particularly for abdominal pain and joint involvement. However, consistent evidence indicates that their impact on preventing or reversing renal complications is limited, underscoring the need for adjunctive therapy in nephritic presentations.

Immunosuppressive agents, especially mycophenolate mofetil (MMF) and azathioprine, demonstrate greater effectiveness in inducing and maintaining remission in HSP nephritis with favorable safety profiles. These medications are increasingly preferred in both induction and maintenance phases, offering a practical balance between efficacy and tolerability.

Biologic therapies, most notably rituximab, are gaining recognition as viable options in steroid-resistant or relapsing disease, particularly in cases where conventional immunosuppressants have failed. Although current evidence from small-scale studies is encouraging, the lack of large randomized controlled trials (RCTs) limits the universal adoption of biologics into standard pediatric practice.

The review also reveals significant regional heterogeneity in treatment approaches, shaped by clinical tradition, healthcare infrastructure, and resource availability. Adjunctive strategies such as traditional medicine, antiplatelets, and IVIG are applied selectively, but their roles remain supplementary and largely unvalidated in controlled settings.

Importantly, the absence of globally harmonized treatment guidelines and the reliance on regional protocols reflect a broader need for collaborative, multicenter trials that address key therapeutic questions. Uniform definitions of severity, standardized outcome measures, and inclusion of diverse populations are critical for developing internationally applicable algorithms.

Looking forward, personalized medicine—guided by clinical phenotypes, renal histology, and immunogenetic profiling—offers the most promising path toward optimizing therapy. Identifying predictors of treatment response and relapse risk may allow for risk-adapted, patient-centered management strategies, ultimately improving long-term renal outcomes and quality of life in children with HSP.

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