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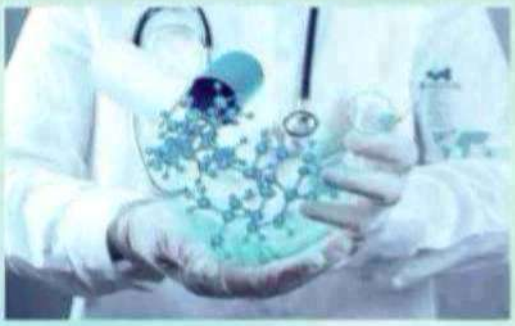

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DIAGNOSTIC CHALLENGES AND EVOLVING APPROACHES IN SCHÖNLEIN - HENOCH PURPURA AMONG CHILDREN

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✓ ***Resume***

Henoch-Schönlein Purpura (HSP), or IgA vasculitis, is the most prevalent small-vessel vasculitis in the pediatric population, with variable clinical manifestations including palpable purpura, arthralgia, abdominal pain, and renal involvement. Despite the widespread use of the EULAR/PRINTO/PRES criteria, current diagnostic strategies often fall short in atypical or renal-predominant cases. This review critically examines global diagnostic approaches, highlighting traditional clinical criteria, laboratory biomarkers, imaging modalities, and histopathological confirmation methods. Furthermore, it explores emerging tools such as urinary cytokines, immunogenetic markers, and machine learning-based diagnostic algorithms. By synthesizing findings from recent studies, this review emphasizes the need for standardized, evidence-based, and regionally adaptable diagnostic models to improve early detection and personalized care in children with HSP

Keywords: Henoch-Schönlein Purpura (HSP); IgA vasculitis; pediatric vasculitis; diagnosis; renal biopsy; biomarkers; IL-17; immunogenetics; EULAR/PRINTO/PRES criteria; nephritis; machine learning; urinary cytokines

BOLALARDA GEMORRAGIK VASKULIT DIAGNOSTIKASIDAGI MUAMMOLAR VA ZAMONAVIY YONDOSHUVLAR

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✓ ***Rezyume***

Gemorrgaik vaskulit (GV), Henoch-Schönlein purpurasi (HSP), yoki IgA vaskuliti, bolalarda eng ko‘p uchraydigan kichik qon tomirlari vaskuliti hisoblanadi. Uning klinik belgilari xilma-xil bo‘lib, teridagi purpuralar, artralgiya, qorin og‘rig‘i va buyrak shikastlanishi bilan namoyon bo‘ladi. EULAR/PRINTO/PRES mezonlarining keng qo‘llanishiga qaramay, mavjud diagnostik yondashuvlar noodatiy va nefrit-dominant holatlarda samarasiz bo‘lib qolmoqda. Ushbu sharh maqolada global diagnostika strategiyalari tahlil qilinib, klinik mezonlar, laboratoriya biomarkerlari, tasvirlash usullari va gistopatologik tasdiq jarayonlari yoritib berilgan. Shuningdek, yallig‘lanish sitokinlari, immunogenetik markerlar va sun’iy intellekt asosidagi algoritmlar kabi yangi instrumentlarga ham e’tibor qaratilgan. Ilmiy manbalar tahlili asosida maqola bolalarda GVni erta aniqlash va individual yondoshuvni ta’minlash uchun standartlashtirilgan, dalillarga asoslangan, mintaqaviy moslashuvchan diagnostik modellarga ehtiyoj borligini ta’kidlaydi

Kalit so‘zlar: Henoch-Schönlein purpurasi (HSP), IgA vaskuliti, gemorragik vaskulit, diagnostika, buyrak biopsiyasi, biomarkerlar, IL-17, immunogenetika, EULAR mezonlari, nefrit, sun’iy intellekt, sitokinlar

ДИАГНОСТИЧЕСКИЕ ТРУДНОСТИ И СОВРЕМЕННЫЕ ПОДХОДЫ ПРИ ПУРПУРЕ ШЕНЛЕЙНА — ГЕНОХА У ДЕТЕЙ

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✓ ***Резюме***

Геморрагический васкулит (ГВ), Пурпура Геноха-Шенлейна, или IgA-васкулит, является самым распространённым васкулитом мелких сосудов у детей. Заболевание проявляется разнообразными клиническими признаками, включая пальпируемую пурпуру, артралгию, абдоминальные боли и поражение почек. Несмотря на широкое применение критериев EULAR/PRINTO/PRES, существующие диагностические подходы часто оказываются недостаточными при атипичных или почечно-доминирующих формах заболевания. В данном обзоре критически рассмотрены мировые стратегии диагностики, включая клинические критерии, лабораторные биомаркеры, методы визуализации и гистопатологическое подтверждение. Также обсуждаются новые инструменты, такие как мочевые цитокины, иммуногенетические маркеры и алгоритмы, основанные на машинном обучении. Обобщая современные исследования, обзор подчёркивает необходимость создания стандартизированных, доказательных и регионально адаптированных диагностических моделей для раннего выявления, и персонализированного ведения детей с ГВ

Ключевые слова: Геморрагический васкулит, Пурпура Геноха-Шенлейна, IgA-васкулит, васкулит у детей, диагностика, почечная биопсия, биомаркеры, IL-17, иммуногенетика, критерии EULAR, нефрит, цитокины

Relevance

Henoch-Schönlein Purpura (HSP), also known as IgA vasculitis, represents the most common form of systemic small-vessel vasculitis in the pediatric population. It is characterized by immune complex deposition, primarily IgA, in small blood vessels, leading to a constellation of clinical manifestations including palpable purpura (typically on the lower limbs), arthralgia or arthritis, abdominal pain, and varying degrees of renal involvement [3,8,11,18,22]. While many cases resolve spontaneously, some can progress to long-term complications, most notably chronic kidney disease, which has significant implications for a child's health and quality of life [1,5,6,14,18,22].

The relevance of studying diagnostic approaches to HSP stems from its clinical heterogeneity and overlap with other pediatric diseases, such as systemic lupus erythematosus, meningococcemia, and infectious purpuras. These similarities can lead to delayed or inaccurate diagnoses, which may result in inappropriate management decisions [2,8,9,23]. For instance, renal involvement can initially be asymptomatic, yet if missed; it may lead to irreversible kidney damage. Similarly, gastrointestinal complications such as intussusception or gastrointestinal bleeding can become life threatening if not identified early.

Moreover, current diagnostic criteria, particularly the EULAR/PRINTO/PRES guidelines, while widely adopted, may not be sufficiently sensitive in atypical presentations, such as those with isolated renal or gastrointestinal symptoms. This underscores the need for more refined and sensitive diagnostic tools, especially those tailored to pediatric physiology and immune response patterns [22].

Another dimension adding to the urgency of this research is the lack of standardized global protocols. Different countries and regions adopt varying diagnostic algorithms—some prioritizing imaging, others relying heavily on laboratory markers or clinical criteria. This inconsistency not only complicates international research but also hinders the development of unified treatment strategies and long-term patient follow-up systems.

Additionally, with recent advances in immunogenetics and molecular diagnostics, there is a growing potential to personalize diagnostic strategies based on individual genetic risk factors and biomarker profiles. Understanding which children are at higher risk for severe or relapsing disease could pave the way for targeted surveillance and earlier intervention, ultimately improving outcomes.

Therefore, the study of diagnostic approaches to HSP in children is both timely and essential. It not only addresses current clinical gaps but also aligns with broader goals in pediatric medicine—improving diagnostic precision, reducing long-term complications, and promoting equitable healthcare outcomes across different populations.

Diagnostic Criteria and Clinical Practice Variability. The most widely accepted diagnostic framework for Henoch-Schönlein Purpura (HSP), also referred to as IgA vasculitis, is the EULAR/PRINTO/PRES criteria introduced in 2008 [8,22]. These criteria stipulate that a diagnosis of

HSP can be established when a patient presents with palpable purpura (in the absence of thrombocytopenia) and at least one of the following additional clinical signs: abdominal pain, arthritis or arthralgia, renal involvement (typically hematuria and/or proteinuria), or histologically confirmed IgA deposition in vessel walls.

Materials and methods

While this system has been instrumental in standardizing HSP diagnosis across pediatric rheumatology, emerging clinical evidence suggests that it may not adequately capture the full spectrum of HSP presentations, particularly in atypical or renal-predominant cases. A pivotal study by Cimaz et al. (2018) systematically assessed the diagnostic accuracy of the EULAR criteria in such non-classical cases and concluded that a significant number of patients could be underdiagnosed or misclassified if clinicians rely solely on the criteria without considering regional variations and atypical features [8].

For example, renal-dominant presentations, in which skin involvement is minimal or delayed, challenge the criteria's reliance on palpable purpura as a primary requisite. This poses a diagnostic risk, as renal symptoms may emerge subtly, yet their progression could lead to irreversible damage if not identified and treated early. Ronkainen et al. (2017) also noted that certain patients present with isolated hematuria or proteinuria weeks before any purpura develops, emphasizing the need for flexible diagnostic thinking [23].

Adding to the complexity, diagnostic approaches vary significantly across geographic regions, often shaped by healthcare infrastructure, cultural medical practices, and local disease prevalence patterns. In European countries, especially in Northern and Western regions, protocols emphasize early renal monitoring. Routine urine testing is commonly implemented even in mild cases to detect silent renal involvement. This proactive strategy has been associated with better long-term renal outcomes, as early detection allows for timely initiation of nephrology referral and treatment.

Conversely, East Asian countries, particularly Japan, South Korea, and Taiwan, tend to employ more comprehensive diagnostic workups that integrate abdominal ultrasonography and fecal occult blood tests. Yamashita et al. (2021) reported that in Japan, abdominal imaging is routinely used even when gastrointestinal symptoms are mild or absent, allowing for the early detection of bowel wall edema, mesenteric vasculitis, and even preclinical signs of intussusception [33]. Morimoto et al. (2021) further demonstrated the diagnostic value of fecal occult blood testing, showing that nearly one-third of patients with gastrointestinal involvement had no overt symptoms but tested positive on fecal occult screening [17].

These regional differences highlight the lack of a unified global standard and raise questions about the applicability of the EULAR/PRINTO/PRES criteria in diverse clinical settings. In areas with limited access to advanced imaging or laboratory diagnostics, reliance on clinical observation may lead to underdiagnosis. On the other hand, over-investigation in low-risk cases may cause unnecessary stress, costs, or interventions.

Taken together, recent research underscores the urgent need to reevaluate and refine existing diagnostic criteria. There is growing consensus in the pediatric rheumatology community that a more nuanced, flexible, and regionally adaptable diagnostic model—potentially incorporating biomarkers, imaging, and genetic data—could improve diagnostic sensitivity and specificity. Ultimately, this would ensure that children with HSP are accurately identified and treated, regardless of where or how they present.

Laboratory Markers and Emerging Biomarkers. Laboratory evaluation plays a pivotal role in the diagnostic workup of Henoch-Schönlein Purpura (HSP) in children, particularly in supporting clinical suspicion, detecting systemic involvement, and monitoring disease progression. While the diagnosis is often made based on clinical features, laboratory tests provide critical supplementary information—especially in cases with atypical or severe presentations [2,20,31].

The most commonly used laboratory tests in HSP include inflammatory markers and basic urine analysis. Elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are frequently observed, reflecting systemic inflammation. These markers, although non-specific, help confirm the presence of active inflammation and can guide initial treatment strategies.

In addition, complete blood count (CBC) may reveal leukocytosis, and in some cases, mild thrombocytosis, particularly in the acute phase. Urinalysis is essential to detect hematuria and

proteinuria, both of which signal renal involvement—a major determinant of long-term prognosis in HSP.

A key finding reported by Kim et al. (2021) showed that approximately 50% of pediatric HSP patients present with elevated serum IgA levels. Although not diagnostic on its own, this elevation supports the immunopathogenic mechanism of the disease and may correlate with disease severity, particularly in cases with renal manifestations [14].

Recent attention has shifted toward simple, yet effective inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Tabel et al. (2020) demonstrated that NLR is significantly higher in children with HSP, particularly those with more severe disease manifestations, suggesting its utility as a prognostic marker [28]. Similarly, the CRP-to-albumin ratio has been investigated as a potential marker of systemic inflammation severity. Islek et al. (2020) proposed that this ratio could help distinguish between mild and severe cases of pediatric vasculitis, offering clinicians an inexpensive and accessible decision-support tool [12].

To enhance diagnostic precision and risk stratification, researchers have explored novel biomarkers that may better reflect the immunological underpinnings of HSP. Notably:

- Urinary IgA-fibronectin complexes have been identified as a promising early marker of renal involvement. Li et al. (2023) found that elevated levels of these complexes were significantly associated with the development of HSP nephritis, even before clinical signs of renal disease became evident [15].
- Cytokine profiling is another emerging field. Elevated levels of interleukin-6 (IL-6) and interleukin-17A (IL-17A) have been associated with disease activity. Yamamoto et al. (2021) reported that IL-17A levels correlated strongly with renal severity and could serve as a marker for identifying high-risk patients [32].
- Urinary cytokines such as MCP-1 (monocyte chemoattractant protein-1) and NGAL (neutrophil gelatinase-associated lipocalin) have also shown promise. In a study by Mitsunaga et al. (2022), these biomarkers showed superior predictive value for early HSP nephritis compared to traditional urinalysis [16].

While many of these novel biomarkers remain confined to research settings, their clinical utility is gaining traction. Non-invasive, biomarker-based diagnostics may reduce the need for invasive procedures like renal biopsy, especially in borderline or early-stage cases.

Moreover, combining traditional inflammatory markers with emerging molecular and urinary biomarkers may offer a multidimensional diagnostic approach, increasing accuracy, allowing earlier detection of complications, and supporting risk-adapted treatment strategies.

In conclusion, the evolving landscape of laboratory diagnostics in HSP—from routine blood tests to cytokine profiling and urinary biomarker analysis—offers immense potential to improve early detection, refine prognosis, and guide individualized care pathways. Ongoing validation in larger pediatric cohorts will be critical to translating these promising markers into standardized clinical practice.

Imaging and Endoscopic Evaluation. Imaging plays a critical complementary role in the diagnosis and management of Henoch-Schönlein Purpura (HSP), particularly in detecting gastrointestinal and renal complications that may not be evident on clinical examination alone [21,26]. Given the non-specific nature of some symptoms and the potential severity of internal organ involvement, radiological and endoscopic tools are increasingly used to support clinical decision-making.

Abdominal ultrasonography is widely regarded as the first-line imaging modality in pediatric HSP due to its non-invasiveness, safety, and accessibility. It is especially useful in identifying gastrointestinal involvement, which is one of the most common and potentially severe complications of the disease [4,7].

Studies have shown that HSP can cause bowel wall thickening, mesenteric edema, and intussusception—a potentially life-threatening condition in which part of the intestine folds into itself. According to Chen et al. (2019), abdominal ultrasound was instrumental in detecting early signs of intussusception in children who had only vague or mild abdominal symptoms. Their findings advocate for routine ultrasonography in HSP patients with any gastrointestinal complaints, even when classical signs like bloody stools or vomiting are absent [7].

Furthermore, ultrasound findings may correlate with disease severity. For instance, thicker bowel walls and larger mesenteric lymph nodes are more often seen in patients with extensive purpura or severe

abdominal pain. These findings can help clinicians anticipate complications and determine the need for hospitalization or surgical consultation.

Gastrointestinal Endoscopy. While not routinely required in all cases, endoscopic evaluation becomes crucial in children with severe or persistent gastrointestinal symptoms, especially gastrointestinal bleeding or unexplained anemia. Upper and lower GI endoscopy allows direct visualization of the mucosal lining, enabling the detection of petechiae, erosions, hemorrhagic lesions, and ulcerations.

Huang et al. (2020) demonstrated that endoscopic findings in HSP patients often reveal diffuse mucosal involvement, particularly in the duodenum and colon, even when symptoms are mild. In some cases, these lesions are the first clues pointing toward HSP when purpura or renal signs have not yet appeared, supporting its diagnostic utility in atypical cases [11].

Moreover, capsule endoscopy, although used less frequently due to cost and availability, has shown potential in visualizing deeper segments of the small intestine that conventional endoscopy cannot reach. According to Fukui et al. (2019), this technique helped identify bleeding sources in children where traditional imaging and endoscopy were inconclusive, reinforcing its value in complex or unclear presentations [10].

In cases of suspected renal involvement, renal ultrasound is often performed to rule out structural abnormalities. Although not specific for HSP nephritis, renal ultrasound may reveal increased echogenicity or subtle changes suggestive of inflammation. However, due to its limited specificity, it is mainly used as a screening or exclusion tool, rather than a definitive diagnostic method.

The integration of imaging findings with clinical and laboratory data enhances diagnostic confidence and may influence treatment decisions. For example, significant bowel wall edema on ultrasound, when coupled with elevated inflammatory markers, might justify hospital admission even in the absence of overt gastrointestinal bleeding.

In addition, Park et al. (2021) conducted a meta-analysis on imaging modalities in gastrointestinal HSP and concluded that ultrasound has the highest diagnostic sensitivity in early-stage disease, while endoscopy provides the best specificity when evaluating the extent and severity of mucosal injury [21].

In summary, imaging and endoscopic evaluations are indispensable tools in the diagnostic and prognostic assessment of HSP in children. Abdominal ultrasound serves as a rapid, non-invasive method to identify early gastrointestinal involvement and prevent serious complications like intussusception. Endoscopy provides valuable insights in severe or atypical presentations, while renal ultrasound helps assess the extent of kidney involvement. Together, these modalities support a more comprehensive and individualized diagnostic approach, enabling earlier intervention and improved outcomes for affected children.

Histopathological Confirmation. Although Henoch-Schönlein Purpura (HSP) is primarily diagnosed clinically, histopathological confirmation plays a critical role in selected cases, particularly when the presentation is atypical, when there are doubts about the diagnosis, or when complications such as persistent nephritis arise. Histopathological examination not only strengthens diagnostic accuracy but also provides valuable information regarding disease severity, prognosis, and treatment planning.

A skin biopsy is a relatively simple and minimally invasive procedure that can confirm the presence of IgA-dominant leukocytoclastic vasculitis, which is pathognomonic for HSP. Histologically, it reveals small-vessel inflammation with fibrinoid necrosis, perivascular neutrophilic infiltration, and deposition of IgA immune complexes in vessel walls, usually demonstrated via direct immunofluorescence (DIF) [6,18].

However, skin biopsy is not routinely required in all patients. Its diagnostic value is most significant in atypical presentations—for example, when the purpuric rash is absent, unusual in distribution, or confused with other conditions such as thrombocytopenic purpura or drug-induced vasculitis. Nakazato et al. (2016) emphasized the usefulness of skin biopsies in such unclear cases, helping to differentiate HSP from other dermal vasculitides and guiding targeted treatment [18].

Despite its diagnostic utility, the yield of skin biopsy depends on timing; early lesions (within 24–48 hours) offer the highest chance of detecting IgA deposition. If delayed, histologic changes may be less specific, and immune complex deposition may become harder to detect.

In contrast to skin biopsy, renal biopsy is of much higher clinical importance, especially in children with persistent proteinuria, hematuria, or signs of nephrotic/nephritic syndrome. While not indicated in all cases, it becomes essential when:

- Urinary abnormalities persist beyond 4–6 weeks,
- There is significant proteinuria (e.g., >1g/day),
- Hypertension or decreased glomerular filtration rate is observed,
- Or there are signs of rapid progression toward renal dysfunction.

Renal biopsy in HSP not only confirms the diagnosis by showing mesangial IgA deposition on immunofluorescence microscopy, but it also provides prognostic value through standardized classification systems. The most commonly used is the International Study of Kidney Disease in Children (ISKDC) classification, which grades the severity of glomerular involvement from I to VI based on the presence and extent of crescent formation, sclerosis, and interstitial fibrosis.

Results and discussions

Calvo-Rio et al. (2016) demonstrated that patients with ISKDC grade III or higher had significantly worse renal outcomes, including increased risk of chronic kidney disease and reduced long-term renal function. Similarly, Ozaltin et al. (2018) highlighted the prognostic significance of immunohistochemical staining patterns in biopsy samples, suggesting that stronger IgA and C3 deposition correlated with more aggressive nephritis phenotypes [6].

Biopsy findings also guide therapeutic decisions. For instance, cases with extensive crescent formation or tubulointerstitial inflammation may warrant immunosuppressive therapy (e.g., corticosteroids, cyclophosphamide), whereas milder histological grades might be managed conservatively with close monitoring.

Despite the critical role of renal biopsy in diagnosing and managing Henoch-Schönlein Purpura (HSP) nephritis, its use is not without limitations. Being an invasive procedure, renal biopsy carries inherent risks and demands careful clinical judgment regarding its necessity, timing, and potential impact on therapeutic decisions.

Renal biopsy, particularly in pediatric patients, is associated with several procedural risks, albeit infrequent in experienced hands. These include:

- Post-biopsy bleeding, which may range from minor hematuria to rare but serious retroperitoneal hemorrhage.
- Infection risk, especially in immunocompromised or previously treated children.
- Pain and anxiety, which may necessitate sedation or general anesthesia in younger children.

These concerns necessitate a cautious approach, where the benefit of obtaining histological clarity is weighed against the risk of harm, especially when alternative non-invasive monitoring (e.g., urinary biomarkers, imaging) may suffice in milder cases.

A major area of ongoing debate in pediatric nephrology is the optimal timing of renal biopsy in HSP. This is particularly relevant in patients with persistent but sub-nephrotic proteinuria, isolated hematuria, or mild renal dysfunction. The community remains divided:

- Proponents of early biopsy argue that histopathological insights allow for earlier disease stratification and the initiation of targeted therapy, especially in those with potentially aggressive histologic lesions that are not clinically obvious. This approach may prevent irreversible renal scarring, particularly in cases with silent crescents or subclinical glomerular inflammation.
- On the other hand, advocates for a conservative approach highlight that a significant proportion of HSP nephritis cases resolve spontaneously or respond to supportive care without requiring immunosuppression. For them, serial monitoring of urine protein levels, blood pressure, and renal function offers a safer, non-invasive path that avoids unnecessary biopsies in self-limiting cases.

A middle-ground strategy is often adopted in practice, where biopsy is deferred unless certain thresholds are crossed, such as:

- Persistent proteinuria beyond 4–6 weeks,
- Nephrotic-range proteinuria,
- Hypertension,
- Reduced glomerular filtration rate,

- Or the presence of systemic symptoms suggesting severe vasculitis.

In addition to clinical factors, family preference and psychosocial considerations also influence the decision-making process. Parents may express concern over the invasiveness of the procedure, especially if the child appears otherwise well. Clear communication about the potential benefits of biopsy—in terms of prognosis, guiding therapy, and avoiding overtreatment—is crucial to obtain informed consent and maintain trust in the care process.

Emerging non-invasive biomarkers, such as urinary cytokines (e.g., NGAL, MCP-1) and IgA-fibronectin complexes, are being explored to identify patients at risk for severe nephritis. If validated through larger clinical studies, these tools may in the future reduce reliance on invasive diagnostics, offering a safer pathway for early risk stratification without a biopsy. However, as of now, biopsy remains the gold standard in cases where clinical indicators suggest significant renal involvement.

While renal biopsy provides indispensable histological insight in HSP nephritis, its use must be carefully individualized [5,6,18]. The balance between clinical necessity and procedural risk, coupled with ongoing debate about timing, makes biopsy decisions nuanced and context-dependent. As diagnostic tools evolve, future algorithms may integrate clinical parameters, laboratory trends, biomarkers, and imaging to better guide when biopsy is truly warranted—offering a more refined and patient-centered approach to managing HSP in children.

In summary, histopathological confirmation serves as a cornerstone in the diagnosis and management of complex or severe HSP cases. While skin biopsy confirms IgA vasculitis in uncertain cases, renal biopsy remains critical for evaluating the extent of nephritis, predicting prognosis, and tailoring treatment. As our understanding of HSP evolves, histopathology continues to offer irreplaceable insights into the immunopathologic mechanisms of the disease and supports a more personalized approach to patient care.

Genetic and Immunogenetic Diagnostics. The pathogenesis of Henoch-Schönlein Purpura (HSP), or IgA vasculitis, is believed to involve a complex interplay of genetic predisposition, environmental triggers, and immune dysregulation [9,19]. While HSP has traditionally been diagnosed based on clinical and histological findings, emerging evidence suggests that genetic and immunogenetic factors may not only influence disease susceptibility but also modulate severity, organ involvement, and risk of recurrence. This growing field holds significant promise for personalized diagnostics and targeted management strategies in pediatric patients.

Multiple studies have identified specific gene polymorphisms associated with an increased risk of developing HSP. Among the most prominent genetic markers are variations in:

- IL-17A: A key pro-inflammatory cytokine implicated in vasculitis pathophysiology. Tanaka et al. (2020) demonstrated that polymorphisms in the IL-17A gene were significantly associated with increased susceptibility to HSP in children, and possibly with more severe renal involvement [29].
- IL-23R: A gene encoding the interleukin-23 receptor, which is involved in Th17-mediated immune responses. Schneider et al. (2023) found that IL-23R polymorphisms were linked to a higher risk of relapse, suggesting a role in chronic or recurrent disease patterns [25].
- HLA-DRB1: Human leukocyte antigen (HLA) genes, which are crucial for antigen presentation and immune system activation, have also been implicated. Certain HLA-DRB1 alleles appear to increase susceptibility to HSP, potentially by influencing the strength and character of the IgA-mediated immune response.

These findings highlight the immune-genetic foundation of HSP, particularly the role of Th17 cell activation and cytokine dysregulation. However, these markers are not yet part of routine clinical diagnostics, as their predictive value and utility across diverse ethnic populations are still under investigation.

Genetic profiling may eventually help predict which patients are at greater risk of severe complications, such as nephritis or systemic relapse. For example, Schneider et al. (2023) emphasized that IL23R polymorphism was associated not only with relapse but also with poor response to conventional therapy. Such insights could guide more intensive monitoring or early initiation of immunosuppressive therapy in genetically high-risk patients [25].

Similarly, Yamamoto et al. (2021) showed that elevated levels of IL-6 and IL-17A, both genetically influenced cytokines, correlated strongly with disease activity and renal injury severity [32]. This

suggests that integrating genetic and cytokine profiling could offer a dual-layered diagnostic strategy, enhancing early risk stratification beyond clinical symptoms alone.

As genetic data becomes more accessible and affordable through next-generation sequencing, there is growing interest in integrating genomic analysis into pediatric vasculitis management. The goal is to shift from a "one-size-fits-all" approach to a personalized medicine model, in which diagnosis, monitoring, and treatment are tailored to the patient's molecular profile.

Such strategies could potentially:

- Identify children who are at higher risk for nephritis or recurrence,
- Predict response to immunomodulatory therapies,
- Guide long-term follow-up and screening intensity,
- Reduce unnecessary treatments in low-risk patients.

However, this vision is still in its early stages. Larger, multicenter studies across diverse populations are needed to validate existing genetic associations, standardize testing protocols, and determine the cost-effectiveness and feasibility of implementing such tools in routine pediatric care.

Nonetheless, the rapid evolution of immunogenetic research and its integration into clinical models may soon redefine how HSP is diagnosed and managed. As more robust data become available, clinicians may eventually be able to use genetic profiles as a core component of precision diagnostics, particularly for children with atypical or severe forms of HSP.

Despite their widespread use, EULAR/PRINTO/PRES criteria may fall short in specific subtypes or age groups. Invasive procedures like biopsy remain the diagnostic gold standard, yet there is growing momentum toward non-invasive tools. AI-assisted algorithms and machine learning models have recently shown promise in enhancing diagnostic accuracy (Zhu et al., 2023) [35].

Diagnosis of HSP in children primarily relies on clinical presentation, supported by laboratory, imaging, and sometimes histopathological findings. While the EULAR criteria provide a functional framework, they are not universally sufficient. Advances in biomarker identification and immunogenetics offer hope for more precise, individualized diagnostics. International collaboration is key to refining diagnostic strategies and establishing standardized, evidence-based protocols suitable for diverse pediatric populations.

Conclusion

Diagnosing Henoch-Schönlein Purpura (HSP) in children remains a nuanced clinical challenge due to its variable presentation, overlapping symptoms with other pediatric diseases, and the potential for serious complications—particularly renal involvement. While current diagnostic frameworks, most notably the EULAR/PRINTO/PRES criteria, offer a practical baseline for clinical evaluation, they fall short in cases with atypical features, such as isolated renal symptoms, gastrointestinal-predominant manifestations, or delayed purpura.

The expanding body of evidence underscores that a purely clinical diagnosis may not be sufficient in all scenarios. Supportive investigations, including laboratory testing (e.g., inflammatory markers, IgA levels, NLR), imaging (abdominal ultrasound, renal ultrasound), and endoscopy, serve to confirm diagnosis, assess systemic involvement, and identify early complications. Furthermore, in select cases, histopathological examination—especially renal biopsy—remains a cornerstone for diagnosis and prognostic evaluation, guiding therapeutic decisions and long-term care strategies.

Importantly, the field is witnessing a paradigm shift toward precision diagnostics, driven by advances in biomarker research and immunogenetic profiling. The identification of urinary cytokines, IgA-fibronectin complexes, and gene polymorphisms in IL-17A, IL-23R, and HLA-DRB1 are opening new avenues for individualized care. These tools offer the potential to predict disease severity, risk of relapse, and response to therapy—even before clinical symptoms fully manifest.

However, despite these scientific advancements, a global consensus on diagnostic algorithms remains lacking. Regional disparities in diagnostic practices, resource availability, and healthcare infrastructure mean that children across different countries may receive vastly different levels of care. This inconsistency highlights the urgent need for standardized, evidence-based protocols that incorporate both traditional and emerging diagnostic modalities.

Moving forward, international collaboration is vital. Multicenter studies and global data-sharing initiatives can help validate novel biomarkers, standardize genetic testing guidelines, and optimize the

timing and indications for invasive diagnostics like renal biopsy. Additionally, the integration of machine learning and AI-assisted diagnostic models shows promise in enhancing early recognition and decision support, especially in resource-limited settings.

In conclusion, improving the diagnosis of HSP in children demands a multifaceted and adaptive approach—one that combines clinical acumen with scientific innovation. Through the convergence of conventional methods, advanced biomarkers, and genetic insight, the future of HSP diagnostics lies in precision medicine—offering each child the right diagnosis, at the right time, with the right tools.

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