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Advances and Challenges in Pediatric *Helicobacter pylori*-Negative Eosinophilic Gastritis: From Th2-Driven Pathogenesis to Precision Medicine Management

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Abstract:

Helicobacter pylori-negative eosinophilic gastritis (EoG) in children remains a diagnostic and therapeutic challenge due to heterogeneous presentation and lack of standardized management. Recent studies have elucidated a Th2-skewed immunopathogenesis driven by key cytokines (IL-5, IL-13) and epithelial-derived chemokines (eotaxin-3, TSLP), which orchestrate eosinophil recruitment and disrupt mucosal integrity. Multimodal diagnostic frameworks that combine quantitative histology (≥30 eos/HPF), high-resolution endoscopic assessment, and molecular biomarkers (e.g., EGDP18 transcript levels, serum TSLP) have enhanced both sensitivity and specificity. Current treatment strategies, including dietary elimination, corticosteroids, and emerging biologics, show variable efficacy and require individualized combination approaches based on severity, tolerability, and safety. However, the field still faces major limitations in standardized outcome metrics, long-term safety data, and guidance for personalized therapy. This review integrates current insights into pediatric EoG immunopathogenesis, diagnostic standardization, treatment paradigms, and translational obstacles, and outlines priorities for future research toward evidence-based, precision medicine strategies. Emerging biomarker panels and multi-omics approaches receive focus for refining patient stratification and monitoring therapeutic responses. Long-term safety assessments and multidisciplinary collaboration are emphasized as essential for advancing novel targeted therapies.

Keywords: Eosinophilic gastritis; EoG; TSLP.

1. Introduction

Epidemiological data suggest that the annual incidence of eosinophilic gastritis (EoG) in children is approximately 5–10 per 100,000 children, and has been increasing in recent years, both due to the improved diagnostic capacity of pediatric gastroscopy and suggesting that the true burden of the disease in the pediatric population may be underestimated [1]. Multiple cohorts and retrospective studies reported significant differences in age of onset, sex ratio, and geographic distribution, with differences in prevalence between specific regions (e.g., North America/Europe and Asia) suggesting a combination of factors such as genetic predisposition, environmental exposures, and lifestyle influencing the epidemiological profile of the disease. Eosinophilic gastritis (EoG) in children, as an independent subtype of *Helicobacter pylori*-negative gastritis, has attracted much attention due to its diverse clinical manifestations and lack of specificity. Typical symptoms include recurrent abdominal pain, vomiting, dyspepsia, and growth retardation, and some children have peripheral eosinophilia or atopic diseases (e.g., asthma, eczema, food allergies), while only mild mucosal hyperemia, edema, or erosion are often seen endoscopically, further making early diagnosis more difficult [2]. Current diagnosis is still based on pathologic criteria: a high-power field eosinophil count of ≥ 30 eos/HPF on gastric mucosal biopsy is required after infectious and other secondary causes have been ruled out [3]. It is important to note that there are slight differences in this threshold in different studies, and it needs to be standardized to improve diagnostic consistency. EoG originated from sporadic case reports, and with the deepening of research on eosinophilic gastroenterological diseases (EGIDs), it has been included in the spectrum of non-esophageal EGIDs, which belong to the same Type 2 T helper cell-dominant immune-associated subtype as eosinophilic enteritis and colitis; compared with adults, pediatric EoG patients differed in lesion location, immune cell infiltration pattern, and cytokine expression profile, and there were age-specific differences in response to diet, hormonal and other treatments, suggesting the need to develop a dedicated pediatric management strategy [4].

The main clinical manifestations of the disease are abdominal pain, vomiting, anemia, malnutrition, and lack of weight gain, and some children may also have peripheral eosinophilia or atopic constitutions, such as asthma, eczema, or food allergies [2]. At present, the most accepted diagnostic criterion is that the eosinophil count in gastric mucosal biopsy exceeds 30 per high-power field and the diagnosis is confirmed after an infectious cause has been ruled out [1]. In recent years, with the systematic advancement of eosinophilic gastrointestinal diseases (EGIDs), its disease spectrum has gradually become clear, and it has been included in non-esophageal EGIDs, which together with eosinophilic enteritis and colitis constitute immune-related subtypes of gastrointestinal involvement. Compared with adults, children with EoG differ in pathogenesis, lesion location, and immune background, and there are age-specific differences in response to diet, hormonal and other treatments, suggesting an urgent need to establish an independent clinical management framework for pediatric EoG [4]. There are currently three main strategies for the treatment of EoG in children: dietary interventions, glucocorticoid therapy, and emerging biologics. Dietary interventions focus on the elimination of possible allergenic foods, and the common methods include the Six Categories of Food Elimination (SFED) and targeted elimination diet. Studies have shown that dietary therapy can achieve clinical or histologic remission in about 70% of children, but its long implementation cycle, high compliance requirements, and risks such as nutritional imbalance limit its long-term application [1]. Corticosteroids remain the most commonly used drug therapy option for EoG. Systemic hormones (such as prednisone) are suitable for moderate to severe active periods, but there are adverse reactions such as growth inhibition and immunosuppression; Topical hormones (such as budesonide oral suspension) have fewer side effects while ensuring efficacy, and are suitable for long-term maintenance therapy in children. However, hormonal drugs generally have problems such as high recurrence rate and limited long-term safety. In recent years, biologics targeting the Th2 inflammatory pathway have opened up new directions for pediatric EoG therapy. For example, anti-IL-4Rα dupilumab has been approved by the FDA for the treatment of eosinophilic esophagitis and has shown the potential to inhibit eosinophilic infiltration in non-esophageal EGIDs; Lirentelimab, an anti-Siglec-8 antibody, has also demonstrated a favorable gastrointestinal histological response in multiple clinical trials [2]. Although biologics provide a new therapeutic pathway for refractory EoG, their use is costly, long-term safety data are insufficient, and more large randomized controlled studies are needed to validate them. The purpose of this study was to systematically evaluate the efficacy and limitations of dietary interventions, glucocorticoid therapy and novel biologics in children with eosinophilic gastritis, and to explore the limitations and optimization directions of each strategy, in order to provide evidence-based reference for clinical practice and clarify the direction of future individualized and mechanism-oriented treatment research.

2. Immunopathological mechanisms of eosinophilic gastritis in children

2.1 Th2-driven immune response

The onset of EoG begins when antigen-presenting cells (e.g., dendritic cells) in the gastric mucosa capture food

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or environmental antigens and transport them to the proximal lymph nodes, activating $CD4^+$ T cell differentiation into the Th2 phenotype. Mature Th2 cells release key cytokines such as IL-4, IL-5, and IL-13 in response to specific antigen stimulation. IL5 is a major factor promoting eosinophil proliferation, differentiation, and peripheral mobilization, while IL13 and IL4 induce the expression of eotaxin-3 (i.e., CCL26) in gastric epithelial cells and microvascular endothelial cells, which significantly enhances eosinophil migration to the gastric mucosa through CCR3[2]. In addition, gastric epithelial cells also release „upstream alarm factors“ such as TSLP and IL-33 after antigen exposure, which not only activate type 2 innate lymphoid cells (ILC2), but also synergize with Th2 cells to form multi-level positive feedback and amplify the local inflammatory response.

2.2 Eosinophilic infiltration and mucosal damage

The accumulation of chemokines causes a large number of eosinophils to accumulate in the gastric mucosal layer and release major basic proteins (MBPs), eosinophilic peroxidase (EPO), and eosinophilic neurotoxins (EDNs), which together induce apoptosis and disrupt tight junctions. At the same time, activated eosinophils produce excess reactive oxygen species (ROS) and matrix metalloproteinases (MMP-9), which exacerbate oxidative stress and matrix degradation, which in turn leads to mucosal erosion [2]. As the disease progresses, activated eosinophils also release TGFβ to work with IL-13 to stimulate collagen synthesis in fibroblasts, promoting fibrotic remodeling and mucosal thickening in the chronic phase. This process not only presents a typical eosinophilic infiltrate in histological sections, but is also closely associated with systemic complications such as protein-losing gastropathy and hypoalbuminemia.

2.3 Genetic and environmental interactions

Children with EoG often have Th2-dominant diseases such as asthma, eczema, and food allergies, suggesting a potential genetic predisposition [1]. Shoda et al.‘s gene expression profiling of EoG mucosal tissue revealed that IL5RA, CCL26, and TSLP gene polymorphisms were associated with disease risk [5]. In particular, redox pathway genes such as PRDX2 and TXN were significantly up-regulated in the lesion mucosa, suggesting that exogenous antigen exposure may trigger Th2 inflammatory response by interfering with epithelial oxidative stress regulation. At the same time, gut microbiome imbalances, particularly changes in the ratio of firmicutes to bacteroidetes and fluctuations in their metabolites such as short-chain fatty acids, are also thought to play a role in local immune regulation. Genetic susceptibility and environmental exposure together shape the complex immunopathological profile of EoG.

3. Diagnostic criteria and challenges

3.1 Pathological diagnosis threshold and standardization issues

At present, “≥ 30 eosinophils per high-power field (eos/HPF)” in gastric mucosal biopsy is an internationally accepted pathological diagnostic criterion for EoG [3]. However, the distribution of eosinophils in the gastric mucosa is often focal-like and non-homogeneous, and single-site biopsy is prone to false negatives. Differences in HPF area definition, staining protocols, and biopsy site selection between pathology departments have led to a decrease in diagnostic consistency [4]. In addition, in some EoG patients, even if the eosinophil density does not reach the threshold, obvious epithelial damage and clinical symptoms have appeared, indicating that the current standard may have the problem of insufficient sensitivity, and it is urgent to optimize the sampling strategy and threshold setting.

3.2 Endoscopic imaging and molecular marker aids

Endoscopic findings of EoG lack specificity and common findings include mucosal edema, erythema, granular bulges, or focal erosions [4]. Therefore, gastroscopy is more to provide support for pathological materials, rather than as a direct diagnostic tool. To address this shortcoming, Shoda et al. proposed a combination of gastric mucosal gene expression model (EGDP18) and serum biomarkers (eotaxin-3, IL-5, TSLP) to achieve a highly accurate molecular diagnosis of EoG (AUC≥0.95) [5]. The study also found that some „nodular or bulging“ endoscopic phenotypes were associated with specific gene expression patterns, suggesting that endoscopic-molecular“ multimodal diagnosis may improve the EoG recognition rate in the future.

3.3 Differential diagnosis: different from other gastritis and EGIDs

EoG needs to be distinguished from many types of chronic gastritis. *Helicobacter pylori*-associated gastritis is dominated by neutrophil infiltrate, while EoG is dominated by Th2 inflammation and histologically dominated by eosinophils [1]. Autoimmune gastritis is usually accompanied by antiparietal cell or anti-intrinsic factor antibodies and mucosal atrophy, whereas EoG is usually not accompanied by antiparietal cell antibodies and does not manifest as mucosal atrophy or pyloric gland loss. In addition, it is important to distinguish specifically from other EGIDs (e.g., EoN), which typically involve a wider range of intestinal segments and require multisite biopsy to determine the extent of the lesion [2,4]. It can be seen

that accurate diagnosis depends on the comprehensive evaluation of pathology, endoscopic imaging and molecular markers to achieve accurate identification and management of various gastrointestinal lesions.

4. Treatment strategies for EoG in children

4.1 Dietary interventions

Dietary interventions, as the preferred non-pharmacological treatment for EoG in children, aim to both relieve symptoms and avoid drug side effects by excluding or reintroducing suspected allergenic foods. This approach is particularly useful for children with mild to moderate disease, a clear history of allergies, or those who wish to avoid long-term medications. One of the most representative is the „Six Categories of Food Total Elimination" (SFED), which excludes six types of high-frequency allergens such as milk, eggs, soybeans, wheat, nuts and seafood. Clinical studies by Kagalwalla et al. demonstrated that this approach resulted in histologic remission in more than 75 percent of patients and significantly reduced symptoms such as abdominal pain, nausea, and vomiting in more than 70 percent of cases [6]. In contrast, targeted food elimination diets based on IgE testing or skin prick results have an overall response rate of approximately 60 to 65 percent, although adherence is better [7].

4.2 Glucocorticoid therapy

When dietary interventions are inadequate or there is a trend towards acute exacerbations, glucocorticoids become an important bridging treatment option. Systemic hormones such as prednisone, typically used at a dose of 1 mg/kg/day for 2 to 4 weeks, significantly reduce eosinophil infiltration in the gastric mucosa and improve symptoms within one week [8]. This strategy is effective in the short term, but long-term use is prone to a series of adverse effects, including weight gain, water and sodium retention, sleep disturbance, and behavioral changes, in addition to leading to growth inhibition, osteoporosis, and increased risk of infection.

To reduce systemic exposure, the topically acting budesonide suspension acts directly on the gastric mucosa by oral swallowing, thereby achieving local anti-inflammatory effects and significantly reducing systemic absorption. Comparable rates of histological improvement to systemic hormones have been shown in small studies and better safety tolerability [9]. However, due to the limited local hormone research on EoG, more long-term prospective trials are needed to verify its dose optimization, mucosal adsorption efficiency and long-term safety.

4.3 Novel biologics

With the deepening of the understanding of Th2-driven immune mechanisms, targeted biologics have gradually become the focus of research on refractory EoG. Dupilumab is a monoclonal antibody targeting IL4Rα that blocks the IL4 and IL13-mediated signaling pathways, thereby inhibiting eotaxin-3-induced eosinophil recruitment and adhesion. In a phase III clinical trial in patients with eosinophilic esophagitis, dupilumab demonstrated significant tissue relief and symptom reduction, and its potential indication in non-esophageal EGIDs has also attracted attention [10]. Early data suggest that Dupilumab can also control gastric mucosal inflammation in some children with hormone-dependent or recurrent EoG, with adverse effects being limited to mild reactions at the injection site.

Another drug candidate, lirentelimab, induces programmed death of eosinophils by activating the Siglec-8 signaling pathway, significantly reducing tissue eosinophil counts and maintaining long-term remission in gastric and small intestinal eosinophilic diseases, while being safe and well tolerated [11]. Although these biologics offer new hope for severe or recurrent cases, the high cost and lack of long-term follow-up data remain major barriers to their widespread adoption.

5. Current challenges

At present, the clinical research of eosinophilic gastritis (EoG) in children still faces multiple evaluation and monitoring problems. First of all, the current criteria for efficacy evaluation are not uniform. Different studies often use different clinical symptom scales (e.g., PGIS, EoE-QoL children's version, etc.), and there is often a lack of synchronization between the histological "complete remission" of the gastric mucosa (significant reduction in eosinophilic infiltration) and the improvement of patients' subjective symptoms (e.g., abdominal pain, dyspepsia), resulting in a decrease in the comparability and reproducibility of efficacy evaluation results. Second, most clinical trials and longitudinal cohort studies have a follow-up period of ≤ 12 months, which does not fully reflect the long-term efficacy, recurrence rate and safety, especially for the long-term adverse reaction risk of topical hormones and biologics, which still lacks systematic monitoring.

There are also significant challenges in the construction of a framework for precision treatment and multidisciplinary collaboration. To date, there are no evidence-based guidelines for stratifying patients based on clinical phenotype, molecular characteristics, or genetic markers (e.g., peripheral Th2 cell subsets, serum lactoperoxidase levels); Most of the relevant efficacy prediction models are in retrospective cohort analysis, which has not been verified by prospective clinical trials, and it is difficult to provide reli-

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able decision-making support for individualized treatment plans. Finally, the standardized management of EoG relies on a multidisciplinary collaboration system, but the current multi-link collaboration mechanism such as nutrition, pathology, endoscopy, and molecular experiments is still imperfect, and the information sharing mechanism is lacking. In particular, the high cost of equipment procurement and reagents for advanced technologies such as ultra-minimally invasive endoscopic biopsy, accurate histological evaluation and high-throughput genetic testing platform and limited coverage rate further restrict the optimization of clinical pathways and the improvement of the whole process management level.

6. Conclusions

Helicobacter pylori-negative eosinophilic gastritis in children is a disease in which Th2-dominated immune response is the core, and eosinophils cause chronic inflammation of the gastric mucosa and damage the epithelium through the release of granulin proteins. The current multimodal integration strategy based on histological diagnostic criteria (≥30 eos/HPF) combined with endoscopic morphology, molecular markers (e.g., eotaxin-3, TSLP, IL-5) and EGDP18 expression models is expected to significantly improve the diagnostic sensitivity and specificity of EoG, early identification and accurate stratification. At the therapeutic level, dietary interventions, glucocorticoids and targeted biologics have their own adaptations and limitations at different stages of the disease, and it is necessary to formulate a dynamically adjusted individualized combination plan based on the severity of the disease, the compliance of children and the risk of adverse reactions.

In the face of bottlenecks such as inconsistent efficacy evaluation criteria, insufficient follow-up data and lack of evidence-based support for individualized treatment, it is urgent to build a unified efficacy evaluation system covering clinical symptoms, histology and molecular indicators, establish a multi-center long-term follow-up database to systematically monitor the recurrence rate and drug safety, and carry out prospective verification of Th2 cell subsets and related biomarkers. At the same time, the standardized process and resource allocation of multidisciplinary collaboration platforms such as gastroenterology, pathology, endoscopy and molecular diagnosis should be improved. In the future, it is expected that through the closed-loop model of „mechanism-diagnosis-treatment-follow-up“, a standardized and systematic management path for children with EoG will be established, so as to improve the long-term prognosis, reduce the occurrence of complications, and finally achieve the goal of precision medical intervention for pediatric gastrointestinal eosinophilia.

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