

Review

Eosinophilic Cationic Protein and Immunoglobulin E: Unraveling Biomarkers in Chronic Pediatric Cough

Snezhina Lazova ^{1,2,3,*} , Kremena Naydenova ⁴  and Tsvetelina Velikova ³ 

¹ Pediatric Clinic, University Hospital “N. I. Pirogov”, 21 “General Eduard I. Totleben” blvd, 1606 Sofia, Bulgaria

² Department of Healthcare, Faculty of Public Health “Prof. Tsekomir Vodenicharov, MD, DSc”, Medical University of Sofia, Bialo More 8 Str., 1527 Sofia, Bulgaria

³ Medical Faculty, Sofia University St. Kliment Ohridski, 1 Kozyak Str., 1407 Sofia, Bulgaria; tsvetikova@medfac.mu-sofia.bg

⁴ Clinical Center of Allergology, University Hospital Alexandrovska, Medical University of Sofia, Georgi Sofyiski 1 Str., 1431 Sofia, Bulgaria; kremenann@gmail.com

* Correspondence: snezhina@lazova.com

Abstract: Although the cough reflex is one of the essential protective mechanisms in the respiratory tract, it is considered a considerable health problem in adults and children when it becomes chronic and hypersensitive. However, the need for biomarkers for chronic cough in children and adults is critical. The problem with cough is also a severe symptom in hypersensitivity children. Respiratory infections are a considerable challenge for pediatricians, especially in allergic children. The term cough hypersensitivity syndrome, although introduced in adults, was questioned for children. Eosinophil cationic protein (ECP) is a promising marker for chronic cough but still needs to be validated and proved in clinical settings. In this review article, we aimed to discuss the possible role of ECP in connection to IgE for chronic cough in children.

Keywords: chronic cough; chronic cough in children; eosinophilic cation protein; ECP; immunoglobulin E; IgE



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1. Introduction

Although the cough reflex is one of the essential protective mechanisms in the respiratory tract, it is considered a considerable health problem in adults and children when it becomes chronic and hypersensitive [1]. The condition affects about 10% of adults in the general population [2] and between 5 and 10% of children in the general population [3].

Furthermore, the presence of chronic cough shows dysregulation and aberrant neurophysiology [4]. Therefore, a cough hypersensitivity syndrome was proposed for the intractable cough [5].

This concept is based on the paradigm for cough as a significant component of different conditions, such as rhinitis/rhinosinusitis, use of ACE inhibitors, cigarette smoke, asthma/eosinophilic bronchitis, other pulmonary diseases, gastroesophageal disease, etc. [6]. However, there is a need to change the paradigm of cough hypersensitivity while searching for numerous causes for chronic cough (i.e., immunologic, neurologic, genetic, comorbid, biological, and environmental factors).

Still, many challenges exist in diagnosing and managing chronic cough/ cough hypersensitivity syndrome. Despite the significant amount of healthcare expenditure for treatment, chronic cough is refractory in 12–42% of patients [7], and cough medications lost effectiveness in 36–57% [8]. However, recent randomized clinical trials demonstrated the promising efficacy of P2X3 receptor antagonists for managing chronic cough [9].

The problem with cough is also serious in hypersensitivity children. Respiratory infections are a considerable challenge for pediatricians, especially in allergic children [10].

Usually, respiratory infections take a protracted course in children with allergies or hypersensitivity, where chronic cough is usually the sole symptom, according to the British Thoracic Society [11]. In line with this, some authors recently discussed approaches to chronic cough in children, defined as longer than 8 weeks [12,13].

On the contrary, Chang et al. recently opposed using the term cough hypersensitivity syndrome in children. They considered it “inappropriate” because of the different nature and causes of chronic cough in children and adults [14].

However, the need for biomarkers for chronic cough in children and adults is critical. Some investigators proposed exhaled biomarkers with non-productive cough (i.e., NO, particles in exhaled air, etc.) or inflammatory biomarkers (i.e., complete blood count, inflammatory cell indexes, etc.) [15,16].

Eosinophil cationic protein (ECP) is one of the promising markers for chronic cough but still needs to be validated and proved in clinical settings. This comprehensive review article aims to elucidate the potential interplay between ECP and immunoglobulin E (IgE) in the context of chronic cough among pediatric populations. We systematically explore the intricate relationship between ECP and IgE, shedding light on their individual roles, interactions, and collective impact on the pathophysiology of chronic cough in children, and also compare the cough syndrome in adults. By synthesizing current knowledge and analyzing relevant studies, we aim to provide a nuanced understanding of the biomarker potential of ECP and IgE, offering insights that may guide future research endeavors and inform clinical approaches. Through this exploration, we aspire to contribute to the ongoing discourse surrounding biomarkers in pediatric cough, ultimately advancing the comprehension and management of this prevalent and complex respiratory condition in children.

2. Search Strategy

We performed a search in the literature by using MeSH and free-text terms as follows: (“Eosinophil cationic protein” OR “ECP”) AND (“chronic cough” OR “cough syndrome”) AND (“Immunoglobulin E” OR “IgE”). Our search was confined to the bibliographic databases Medline (PubMed) and Scopus and complemented with a search through Google Scholar for the papers published before October 2023.

Additionally, older publications were also included due to the investigation of IgE and ECP dating from previous decades. All types of papers were examined: original articles, clinical trials, case reports, systematic reviews, and meta-analyses. Relevant data were also derived from preprints identified using search engines and information from the advisory committee. Finally, references of retrieved publications were further hand-searched for supplements. Our modified narrative review was designed and written according to the recent recommendations [17]. This systematic and thorough search strategy aimed to capture a comprehensive and up-to-date representation of the existing literature on the interplay between ECP, IgE, and chronic pediatric cough.

We tried to answer these questions:

1. Are there any connections between ECP and chronic cough?
2. What is the relationship between ECP and IgE?
3. Are there any clinical consequences and recommendations based on the relationship between chronic cough and laboratory markers, such as ECP and IgE?

Despite efforts to minimize bias, the search strategy’s inherent constraints emphasize the need for caution in generalizing findings and highlight the importance of considering alternative sources and ongoing research.

3. Eosinophil Cationic Protein—Current Understanding

ECP is a heterogenous molecule presented in the granules of activated eosinophilic granulocytes, along with major basic protein (MBP), eosinophil peroxidase, and eosinophil-derived neurotoxin/eosinophil protein X. ECP secretion by eosinophils is stimulated via antibody-dependent (IgG, IgA) or antibody-independent manner (C3, C5 complement

components) [18]. Additionally, it is encouraged by IL-3, IL-5, and granulocyte–monocyte colony-stimulating factor (GM-CSF). This molecule, ribonuclease 3 (RNase 3), is involved in the host immune response to parasites and some Gram-positive and Gram-negative bacteria and viruses [18].

Cytotoxic biologic activities of ECP could also be directed against the host. The most common damages of ECP are observed on neurons and respiratory epithelial cells. The latter is clinically associated with allergic asthma and allergic rhinitis, atopic eczema [19], inflammatory gastrointestinal and respiratory disorders, malignancies, and eosinophilia [20].

However, ECP exerts also non-toxic properties, such as immunomodulatory ones. ECP can inhibit T cell proliferation, activation, and histamine release by basophils and downregulating epithelial cells' receptors and adhesion molecules [21]. ECP also regulates tissue remodeling by stimulating the secretion of TGF β , which alters the fibroblasts' metabolism and inhibits proteoglycan degradation [22].

It was further demonstrated that ECP does not alter mediators and airway hypersensitivity but correlates positively with the eosinophils' activity in asthma pathophysiology. However, ECP failed to be a suitable asthma diagnostic marker and could only be applied to allergic asthma [18].

Although ECP was investigated mainly in eosinophilic conditions (i.e., asthma, rhinitis, atopic diseases, etc.), it was demonstrated that ECP could have a role in other conditions, such as bacterial sinusitis. ECP concentrations in the systemic bloodstream and locally usually correlate with disease activity. Also, increased ECP during asthma exacerbations could be used to monitor and assess a new therapeutic regimen or follow-up patients. Therefore, we were interested in gathering data on ECP and its possible role in chronic cough concerning IgE.

4. Immunological Mechanisms of ECP, IgE, and Chronic Cough

4.1. Immunological Mechanisms of ECP

The molecular mechanisms and genetic factors contributing to the suppression of innate antiviral immune responses by allergens have been the subject of recent research. Atopy-related allergen–virus interactions include intricate cellular and tissue processes. Potential treatment targets may be found in future investigations, elucidating the processes underlying these interactions. The information indicates that treatments designed to restore particular antiviral responses will probably enhance clinical results in allergic illnesses [23].

In line with this, it is well known that allergic inflammation in asthma patients is regulated by Th2 and Th1 cells and related cytokines (i.e., IL-4, IL-5, and GM-CSF, which exerted positive regulation, and IFN γ and IL-10, which are negative regulators, respectively). However, cytokines have little or no effect on eosinophils to produce ECP.

A recent study by Vega-Rioja et al. (2022) demonstrated that human neutrophils may directly regulate and inhibit ECP production. Although eosinophils are thought to be the source of ECP, the authors discovered that ECP can also be found in the neutrophils of allergic patients, where it produces IgE-dependently [24].

Moreover, the expression of IgE receptors was also shown in neutrophils [25]. Previously, the authors reported several neutrophil activities, such as generating inflammatory mediators, respiratory burst, and degranulation, in response to allergens through an IgE-dependent mechanism [26]. Additionally, encountering surface-bound IgE with anti-IgE antibodies or allergens leads to stimulation of neutrophils and secretion of ECP [27].

However, glucocorticoids could regulate histamine production by neutrophils in allergic patients in an IgE-dependent manner [28]. Thus, inhibition of ECP production could be exerted by corticosteroid treatment through neutrophil inhibition. Furthermore, Th2 inflammation alleviation by immunotherapy is also accompanied by IgE receptor downregulation, neutrophil transitory inflammatory phenotype reduction, and cellular responsiveness [29,30].

Furthermore, immunotherapy augments the secretion of immunosuppressive cytokines $\text{IFN}\gamma$ and IL-10. Thus, these cytokines may enhance the effect of allergen immunotherapy [31].

A very significant result reported by Vega-Rioja et al. is the correlation between ECP levels and airway obstruction and eosinophilic inflammation. Still, most importantly, FEV1 inversely correlates with the in vitro ECP secretion by peripheral neutrophils after an allergen challenge. The authors conclude that the in vitro production of neutrophil ECP could predict the severity of allergic asthma, and future strategies must consider the molecular pathways that offer potential therapeutic targets [24].

4.2. Connection of ECP with Chronic Cough

It is well established that the most common symptoms of childhood asthma are wheezing, dyspnea, and cough. However, a single sign could not adequately predict asthma [32].

One can speculate that cough alone could be the only sign of an ongoing lower respiratory tract problem. A population-based study by Skaaby et al. demonstrated that one in four children with asthma had a chronic cough for more than 3 months. Furthermore, they observed that 19.9% of children had a dry cough at night in the past 12 months. The authors found a connection between IgE sensitization to respiratory allergens and the risk of infection and disease, taking into account the T helper type 2 (Th2) lymphocytes skewed immune response and IgE antibody development. Almost 15,000 participants were included in the study, where IgE sensitization correlated with asthma, other chronic lower airway diseases, and pneumonia [33].

A similar study by De Amici et al. (2023) showed the significance of ECP in the clinical work-up of chronic cough. As mentioned above, chronic cough is a common symptom, sometimes challenging to diagnose. The authors investigated 194 patients with chronic cough, where ECP was a valuable marker for asthmatic patients, distinguishing them from other chronic disorders, especially in active disease [34].

Sadeghi et Morice (2017) hypothesized that chronic cough could be divided into eosinophilic and neutrophilic groups. Therefore, a more targeted and personalized therapy could be applied when assessing the type of inflammation [35].

Furthermore, they demonstrated that children who responded to the therapy had higher ECP levels, eosinophil blood counts, and IgE levels before treatment compared to non-respondent children. This aligns with the anti-inflammatory therapy for eosinophilic inflammation, which is usually prescribed based on clinical judgment instead of an evidence-based approach [35].

4.3. Connection between ECP and IgE

The role of ECP, total IgE, and eosinophilia in children with bronchial hyperresponsiveness is well established [36].

In the pediatric population, ECP is not only a non-invasive marker of bronchial hyperresponsiveness but may also predict asthma sensitivity and severity [37]. Moreover, total and specific IgE levels correlated with ECP levels in asthmatic children.

Dodig et al. assess the usefulness of ECP measurement in children with respiratory diseases ($n = 156$) and healthy controls ($n = 55$). Although the levels of ECP were higher in children with respiratory diseases than in healthy children, ECP could be used in assessing airway inflammation, allergic disease severity, treatment efficacy, and compliance [38].

However, Cetinkaya and Cakir found increased serum ECP and total IgE levels in children with acute laryngotracheobronchitis. Additionally, after treatment with nebulized budesonide, ECP and IgE levels dropped significantly, emphasizing that these two parameters are unsuitable for diagnosing and following up allergic conditions in children with recent acute laryngotracheitis [39].

Many studies demonstrated the positive effect of a leukotriene receptor antagonist (i.e., montelukast) on chronic cough. Kopriva et al. documented that children with chronic cough

with increased levels of serum ECP and absolute eosinophilic blood counts responded well to treatment with montelukast [40].

More recently, Wei et al. (2019) demonstrated the high clinical efficacy of montelukast sodium combined with budesonide or combined with loratadine in children with chronic cough. They found significantly lower IgE levels at the 4th and 12th week of treatment compared to the initial levels, along with the TNF α , IL-4, and eosinophil granulocyte count [41].

Similarly, Yi et al. (2022) confirmed the effects of treatment with montelukast alone, budesonide/formoterol alone, or a combination of both in children with cough variant asthma. Ninety-nine children, randomly assigned to different treatment regimens, showed improvement in the cough visual analog scale daytime and night-time cough symptom scores after 8 weeks in the three therapy regimens but not before this period. Moreover, the three therapeutic regimens effectively alleviated eosinophilic airway inflammation [42].

All cited studies focused on the connection between ECP and chronic cough. In some of them, this connection was confirmed empirically based on the effectiveness of the therapy.

5. Studies on ECP and Chronic Cough in Children

Our understanding of the connection between viral infections and asthma control has evolved in recent decades. Now we know more about how viruses interact with the host immune system, the impact of genetic background on the disease severity, the role of environmental factors for the onset and maintenance of chronic cough, the part of bacterial colonization of the respiratory mucosa, etc. [43].

Studies on ECP in children with cough are scarce, but we managed to summarize them [19,34,38–40,44–46] in Table 1.

Table 1. Studies investigating ECP levels in children with chronic cough.

Type of Study	Subjects	Treatment/Intervention	ECP, Laboratory Markers	Ref.
Meta-analysis protocol	Children with cough variant asthma	Of combined montelukast sodium and budesonide	Eosinophils, lymphocytes	Tang et al. (2021) [44]
Observational study	194 children with chronic cough	No anti-inflammatory treatment before	Higher ECP in asthma group of children	De Amici et al. (2021) [34]
Observational study	27 children with acute laryngotracheobronchitis	Before and after treatment with nebulized budesonide (on 3rd day and 3rd week)	ECP concentrations were 28.3 vs. 20.2 vs. 11.4 ng/mL before and after treatment; IgE 131.6 vs. 83.6 vs. 68.2 IU/mL; and significantly higher than in controls	Cetinkaya and Cakir (2005) [39]
Observational study	22 children with chronic cough	Treated with the leukotriene receptor antagonist montelukast	ECP in responders to treatment was 14.88 vs. 6.62 in non-respondents; ECP levels remained higher in non-respondents after treatment; high levels of eosinophils and IgE before treatment;	Kopriva et al. (2004) [40]
Observational study	25 children with Mycoplasma pneumonia, 25 children with asthma, and 11 healthy controls	N/A	ECP–18.7 M. pneumonia), 23.7 in asthma, and 6.5—healthy controls ($p < 0.001$); ECP correlated with the eosinophilia	Yamashita et al. (1994) [45]
Observational study	156 untreated and 55 untreated children with asthma, rhinitis, asthma+rhinitis	Standard therapy	ECP 35.1 in untreated vs. 11.3 in treated children; significantly higher during allergen exposure season 23.9 vs. out of season 8.3.	Dodig et al. (2011) [38]
Meta-analysis	Children with different respiratory and other pathologies	Various	ECP is elevated in children with classical asthma, cough variant asthma, occupational asthma, allergic rhinitis, preschool wheezing, etc.	Koh et al. (2007) [19]
Observational study	23 children with isolated unexplained chronic cough	Bronchoalveolar lavage	ECP was detected in 14% of children with chronic cough, 7% in healthy children, and 28% of atopic children	Fitch et al. (2000) [46]

Cetinkaya and Cakir, based on their results for the ECP and IgG levels during the acute phase of laryngotracheitis, suggested that because of their increase, these markers should not be used in diagnosing and follow-up of allergic children who experienced recent acute inflammation of the larynx for a few weeks [38]. Additionally, they pay attention to the limitations of clinical use of ECP based on the pre-analytical factors. Among them were using appropriate samples, gel and clot activator tubes, ensuring temperature and proper time of blood clotting tracking, etc. Therefore, since determining serum ECP concentration is a complex process that depends on numerous pre-analytical factors, this raises the question of external validity and generalizability. However, if all factors that could potentially limit the reliability of the determination are considered, the results could be useful for objectively assessing eosinophil degranulation in allergic inflammation and tracking the efficacy of anti-inflammatory treatment.

Based on their study, Kopriva et al. recommended that children with chronic cough with increased levels of ECP and absolute eosinophil count might benefit from montelukast treatment [40].

Managing chronic cough in children is also challenging. Tang et al. created their protocol for meta-analysis on using montelukast combined with budesonide in children with cough variant asthma based on the recommendations of The American College of Clinical Pharmacy, British Thoracic Society, and Chinese guidelines. The study would assess the efficacy and safety of combining leukotriene receptor antagonists with inhaled corticosteroids [44].

The meta-analysis by Koh et al. (2006) investigated the clinical usefulness of ECP in children with different respiratory disorders [19]. The authors confirmed that ECP could be useful in assessing airway inflammation independently of the causing agent or type of virus but does not correlate well with airway hyperresponsiveness. Additionally, ECP could not be useful as a diagnostic tool in children with asthma (including cough variant asthma) because there are too many other atopic diseases associated with elevated ECP. ECP could be an assessment and management tool—ECP is more sensitive than eosinophil counts in evaluating asthma severity, with sputum ECP overweighting serum ECP. Furthermore, ECP is great for compliance assessment because it decreased during treatment with inhaled and oral corticosteroids, mast cell stabilizers, leukotriene receptor antagonists, tacrolimus, and immunotherapy [19].

The study conducted by Fitch did not confirm the use of ECP in diagnosing children with chronic unexplained cough [46].

6. ECP and Chronic Cough in Adults

The differential diagnosis of chronic cough is a long-standing clinical–diagnostic problem. It is still a challenge for clinical specialists due to the diverse etiology, various factors, and the increased cough reflex. Several diagnostic algorithms have been developed, but they still lack prognostic markers. However, chronic cough's most common etiological causes, such as obstructive airway diseases and other pulmonary and extrapulmonary conditions, are known. Speaking of the most common causes of chronic cough in non-smoking adult patients with a normal chest radiograph, they are bronchial asthma and its subtypes (such as cough variant asthma, non-asthmatic eosinophilic bronchitis, rhinitis and rhinosinusitis (considered a cough syndrome by upper respiratory tract), and gastroesophageal reflux disease [47].

In contrast, respiratory infections, asthma, and environmental factors are the predominant triggers for chronic cough in children. Additionally, variations in the immune response, airway anatomy, and environmental exposures contribute to age-specific differences in chronic cough. Therefore, a comprehensive understanding of these shared and distinct features is essential for tailored diagnostic and therapeutic approaches. Still, inhaled corticosteroids are the leading therapeutic approach for adult patients with chronic cough due to asthma or non-asthmatic eosinophilic bronchitis.

The presence of biomarkers for eosinophilic airway inflammation observed in 30% to 50% of patients with a chronic cough could facilitate the diagnosis. It is often found in asthma and cough syndrome by the upper respiratory tract and is essential in diagnosing non-asthmatic eosinophilic bronchitis [48]. ECP is a known marker studied for many years for distinguishing bronchial asthma from other diseases [49]. However, eosinophilia is not a diagnostic criterion for asthma but can be found in patients with early allergic and late nonallergic asthma. Moreover, blood eosinophils are prognostic criteria for asthma and markers for initiating biological therapy [50]. However, the underlying causes of respiratory tract inflammation may vary. In children, allergic conditions and respiratory infections often contribute to elevated ECP, while in adults, chronic conditions such as asthma, eosinophilic bronchitis, and environmental exposures may be predominant. Understanding these distinctions is crucial for tailoring diagnostic and therapeutic strategies, emphasizing the importance of age-specific considerations in evaluating and managing chronic cough related to ECP.

Additionally, eosinophilic inflammation can be assessed in peripheral blood and the airways by sputum induction or bronchoscopy. As a mediator in eosinophilic granules, ECP can be used as an additional biomarker in diagnosing chronic cough with eosinophilic involvement. The involvement of eosinophils and ECP in patients with classical bronchial asthma and cough variant asthma is known, and there is a correlation with the severity of their course [51]. High levels of ECP have been measured in the blood and sputum of patients with severe asthma (predominantly atopic) compared to milder asthma [52]. It is assumed that ECP can be used as a marker for administering and dosing corticosteroids, but further studies are needed in this direction [53].

In the simultaneous course of diseases with eosinophilic inflammation and accompanying chronic cough, eosinophilic infiltrates in the tissues and eosinophilia in the blood can be characteristics of several processes that would increase the values of serum ECP, but the result of which would not help distinguish the origin of the disease. In this regard, the ECP measurement alone would not be sufficient for diagnosing cough.

A study by Ryttila et al. [54] found eosinophilic airway inflammation as a common cause of persistent cough and higher ECP and EPO (eosinophilic peroxidase) concentrations even in patients without asthma, chronic obstructive pulmonary disease, or cough of unknown origin.

Amici et al. [34] present the role of serum ECP as a useful biomarker in the clinical diagnosis of chronic cough, supporting the differentiation of asthma from other chronic diseases. It is also important to emphasize that eosinophilic inflammation in chronic cough can occur with or without allergy and may be due to other extrinsic factors [48].

In conclusion, at this stage, there are no recommendations for routine ECP testing in clinical practice as an independent marker for determining eosinophilic inflammation in adult patients with chronic cough.

7. Limitations and Future Perspectives

Despite its comprehensive nature, our review of ECP and IgE as potential biomarkers in chronic pediatric cough has certain limitations. Firstly, the available literature may exhibit publication bias, favoring studies with positive results, potentially influencing the overall conclusions. Additionally, the heterogeneity in study designs, methodologies, and patient populations across the selected articles could introduce variability in the interpretation of findings. The review's reliance on existing studies may also be constrained by the quality and depth of available evidence, limiting the ability to draw definitive conclusions. Furthermore, the evolving nature of medical research could lead to gaps in recent developments, impacting the review's currency. While every effort has been made to present a comprehensive synthesis, acknowledging these limitations is essential for a nuanced understanding. It underscores the need for ongoing research to address these constraints.

Future research in the domain of ECP and IgE as biomarkers in chronic pediatric cough could explore several promising avenues. Firstly, there is a need for well-designed prospective studies to establish the relationship between changes in ECP and IgE levels and the onset and resolution of chronic cough in children. Investigating the specificity and sensitivity of these biomarkers in distinguishing various etiologies of pediatric cough, such as infectious, allergic, or environmental triggers, could further refine diagnostic approaches.

Additionally, exploring the impact of age, gender, and geographical variations on ECP and IgE levels in pediatric populations may enhance our understanding of the contextual factors influencing biomarker expression. Longitudinal studies tracking the trajectory of ECP and IgE levels from childhood into adolescence and adulthood could provide insights into the continuity or evolution of these biomarkers over time.

Furthermore, interventional studies assessing the effectiveness of targeted treatments based on ECP and IgE levels in managing chronic pediatric cough could pave the way for personalized and more efficient therapeutic strategies. Finally, integrating advanced technologies, such as omics approaches, could offer a comprehensive molecular understanding of the intricate mechanisms involving ECP and IgE in the pathophysiology of chronic pediatric cough.

8. Conclusions

In conclusion, this review highlights chronic cough's dual nature as a respiratory safeguard and a potential health challenge, notably in children. The critical requirement for precise biomarkers in diagnosing chronic cough, especially among children, is evident.

Complexities tied to chronic cough in sensitive children and infections and allergies underscore the necessity for individualized diagnostics and treatments. While "cough hypersensitivity syndrome" originated in adults, its relevance to children remains uncertain, prompting tailored approaches.

ECP emerges as a promising chronic cough biomarker, though further pediatric validation is essential. Examining ECP-IgE interplay deepens insight into a chronic cough, laying the groundwork for future pediatric respiratory studies. Well-designed prospective studies are required to better understand the relationship between changes in ECP and IgE levels and the onset and resolution of chronic cough in children. Additionally, investigations into the effects of age, gender, and geographic variations on ECP and IgE levels in pediatric populations are necessary. Longitudinal studies that track the trajectory of ECP and IgE levels from childhood into adolescence and adulthood may shed light on the continuity or evolution of these biomarkers over time. Interventional studies that evaluate the efficaciousness of targeted treatments based on ECP and IgE levels in managing chronic pediatric cough could also be helpful. Nevertheless, integrating cutting-edge technology, such as omics methods, may provide a thorough molecular knowledge of the complex pathways linking IgE and ECP in the pathophysiology of persistent childhood cough.

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