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OPINION PAPER

Reflux related respiratory symptoms in children

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ABSTRACT

Gastro-esophageal reflux (GER) is one of the most common gastrointestinal conditions in childhood, affecting infants, toddlers, and school-age children alike. While regurgitation and vomiting are its most visible manifestations, a substantial proportion of children present with atypical or extra-esophageal symptoms that primarily involve the respiratory tract. The relationship between GER and conditions such as chronic cough, recurrent wheezing, recurrent pneumonia, laryngomalacia, brief resolved unexplained events, and even obstructive sleep apnea has been debated for decades. Two main mechanisms, vagal-mediated reflexes and direct microaspiration of gastric contents into the airways, are widely held to be responsible. Yet, establishing causality rather than coincidence remains a diagnostic challenge, particularly given the high prevalence of both GER and respiratory symptoms in young children. This opinion article critically examines the current evidence linking GER to respiratory manifestations, discusses the strengths and limitations of available diagnostic tools, and evaluates therapeutic strategies. We argue that a multidisciplinary approach, individualized clinical assessment, and cautious interpretation of pH-impedance findings are essential to avoid overdiagnosis and unnecessary pharmacotherapy. Clinicians must weigh the potential harms of empirical acid-suppressive therapy against the unproven benefit in respiratory endpoints.

INTRODUCTION

Gastro-esophageal reflux (GER) in children has been estimated to affect up to 2-8% of school-age children and approximately 50% of infants in the first three months of life, predominantly as physiological reflux (1). However, when reflux causes troublesome symptoms or complications, as defined by the joint ESPGHAN/NASPGHAN guidelines, it constitutes gastro-esophageal reflux disease (GERD) requiring clinical attention (2). Among the most challenging aspects of pediatric GERD is the heterogeneous spectrum of extra-esophageal manifestations, particularly those involving the respiratory tract. Otolaryngologists, pulmonologists, and gastroenterologists are frequently consulted for children presenting with chronic cough, recurrent wheezing, hoarseness or obstructive sleep apnea: symptoms that may or may not be causally linked to reflux.

The challenge lies in disentangling true reflux-driven respiratory disease from the high background prevalence of respiratory conditions in childhood. Both GERD and

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KEY WORDS
Gastro-esophageal reflux; respiratory symptoms; children; microaspiration.

conditions such as asthma, recurrent wheeze, chronic cough and laryngomalacia are common in the pediatric age group, making coincidence rather than causality a constant confounder (3). The purpose of this opinion article is to critically appraise the current literature, discuss the plausible pathophysiological mechanisms, evaluate diagnostic accuracy, and propose a pragmatic management framework for the clinician facing a child with suspected reflux-related respiratory symptoms.

In our view, one of the greatest contemporary challenges is the tendency to attribute otherwise unexplained respiratory symptoms to reflux in the absence of objective evidence. This practice risks overdiagnosis, unnecessary investigations, prolonged acid-suppressive therapy, and delayed identification of alternative respiratory, allergic, infectious, or functional disorders. Accordingly, clinicians should maintain a high threshold for assigning causality and should seek objective evidence whenever possible before initiating long-term therapy.

PATOPHYSIOLOGICAL MECHANISMS

Vagal-mediated reflex arch

The vagus nerve forms a bidirectional communication highway between the esophagus and the bronchopulmonary tree. Experimental models have demonstrated that acid instillation into the distal esophagus induces reflex bronchoconstriction without the acid reaching the airway, supporting a purely neurogenic pathway (4). Acid-sensitive chemoreceptors (primarily TRPV1 and ASICs) in the esophageal mucosa trigger afferent signals transmitted to the brainstem nucleus tractus solitarius, which subsequently activates vagal efferents to the airways, resulting in increased airway resistance, mucus secretion, and laryngeal adductor reflex activation (5). In infants, this laryngeal chemoreflex is particularly potent and may result in apnea and bradycardia, may contribute to a subset of brief resolved unexplained events (BRUE) formerly known as apparent life-threatening events (ALTE).

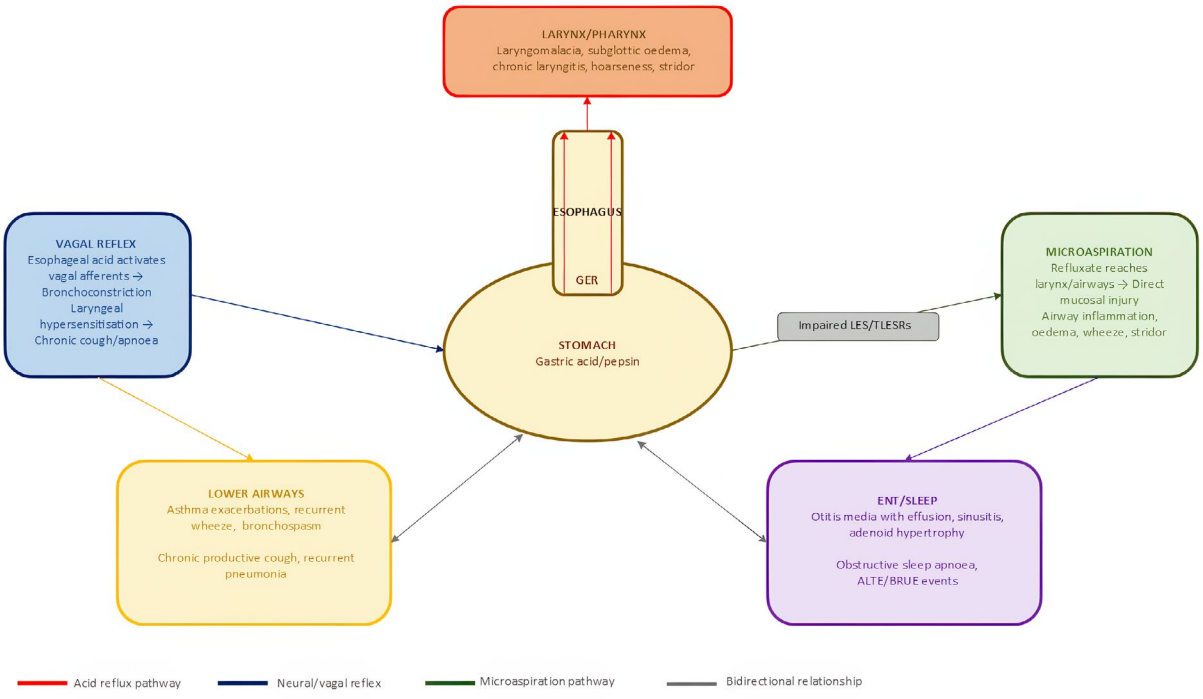

Figure 1. *Schematic overview of the main pathophysiological mechanisms linking gastro-esophageal reflux to respiratory symptoms in children.*

Two principal pathways are illustrated: 1) the vagal-mediated reflex arc, whereby acid-induced activation of esophageal chemoreceptors triggers afferent signals to the brainstem and subsequent efferent bronchoconstriction and laryngeal adductor responses; and 2) direct microaspiration of gastric refluxate beyond the upper esophageal sphincter, causing mucosal injury to the larynx, tracheobronchial tree, and lung parenchyma. Target organ manifestations are shown for the upper airway (larynx/pharynx), lower airways, ENT structures, and sleep-related respiratory control. Bidirectional arrows indicate the mutually exacerbating relationship between airway disease and reflux. LES: lower esophageal sphincter; TLESRs: transient lower esophageal sphincter relaxations; ALTE: apparent life-threatening event; BRUE: brief resolved unexplained event.

Direct microaspiration

When gastric contents escape beyond the upper esophageal sphincter and enter the hypopharynx or larynx, direct mucosal injury by acid, pepsin, and potentially bile acids may occur (6). Microaspiration, defined as the silent inhalation of small volumes of refluxate into the subglottis and tracheobronchial tree, can trigger a localized inflammatory response, epithelial damage, and, in the setting of repeated episodes, structural airway remodeling. Bronchoalveolar lavage (BAL) fluid analysis for pepsin has emerged as a biomarker of microaspiration, although its sensitivity and specificity in clinical practice remain debated (7). Similarly, the presence of lipid-laden macrophages (LLMs), typically quantified using the lipid-laden macrophage index (LLMI), has been investigated as a potential biomarker of aspiration. However, their diagnostic utility remains controversial owing to limited specificity, as elevated levels may occur in a range of pulmonary conditions unrelated to reflux (8). In our view, the clinical significance of isolated pepsin positivity or increased LLMs remains uncertain and should not be considered definitive evidence of reflux-mediated respiratory disease, though it could still offer helpful diagnostic guidance in a well-defined clinical context (9).

Figure 1 provides a schematic representation of both mechanisms and their target organs.

Table 1 summarizes the principal respiratory manifestations associated with GER across different anatomical levels of the airway, along with the proposed underlying mechanism for each.

DIAGNOSTIC CHALLENGES

Diagnosing reflux as the cause of respiratory symptoms requires more than demonstrating the presence of GER; it requires establishing a temporal relationship between reflux episodes and symptom occurrence. Combined multichannel intraluminal impedance and pH monitoring (MII-pH) represents the current gold standard, allowing detection of both acid and non-acid reflux events and calculation of the Symptom Association Probability (SAP) (10). A SAP > 95% is considered significant, yet its clinical applicability in young infants who cannot self-report symptoms is limited. In non-verbal children, caregiver-reported symptom diaries introduce observer bias.

Endoscopic findings such as posterior laryngitis or cobblestoning have been proposed as markers of laryngopharyngeal reflux (LPR), but studies demonstrate poor interobserver reliability and overlap with allergic or infectious laryngitis (11). The Reflux Finding Score (RFS) and Reflux Symptom Index (RSI) were validated in adults and their performance in children is uncertain. Furthermore, the high prevalence of physiological reflux in infancy means that detecting acid in the airway does not necessarily imply pathological disease. We believe that laryngoscopic findings have been overinterpreted in pediatric practice and should rarely be used as standalone evidence for anti-reflux treatment.

Flexible bronchoscopy with BAL pepsin assay or finding of LLMs may help confirm microaspiration in complex cases, particularly in neurologically impaired children with bulbar dysfunction (7, 9). High-resolution esopha-

***Table 1**. Respiratory and ENT manifestations associated with gastro-esophageal reflux in children, by anatomical region.*

Anatomical region	Symptom / Sign	Proposed mechanism
Upper airway	Chronic cough, hoarseness, throat clearing, globus sensation	Proximal reflux with direct laryngeal irritation; vagal-mediated reflex
Larynx	Laryngomalacia, subglottic oedema, recurrent croup, stridor	Mucosal oedema secondary to acid/pepsin injury; laryngeal chemoreceptor activation
Lower airway	Wheezing, asthma exacerbations, recurrent bronchitis	Microaspiration of gastric contents; vagal reflex bronchoconstriction
Lung parenchyma	Recurrent pneumonia, aspiration pneumonitis, bronchiectasis	Repeated microaspiration leading to chronic inflammation and structural damage
ENT / nasopharynx	Otitis media with effusion, sinusitis, adenoid hypertrophy	Eustachian tube dysfunction; refluxate reaching the nasopharynx
Sleep / autonomic	Obstructive sleep apnea, ALTE/BRUE events, apnea of prematurity	Laryngeal chemoreflex; vagally mediated cardio-respiratory inhibition

ALTE: apparent life-threatening event; BRUE: brief resolved unexplained event.

geal manometry and functional luminal imaging probe (FLIP) technology are advancing our understanding of esophageal motor disorders that predispose to reflux, though they are not yet routine pediatric tools.

SPECIFIC CLINICAL PRESENTATIONS

Chronic cough

Chronic cough, defined as cough persisting beyond four weeks, is one of the most common pediatric respiratory complaints. While GERD is frequently cited as a trigger, a landmark Cochrane review found no significant benefit of acid-suppressive therapy in children with chronic cough and suspected GER, casting doubt on the reflexive prescription of proton pump inhibitors (PPIs) for this indication (12). Emerging concepts in chronic cough propose the GERD may function as a modifiable “treatable trait” rather than a primary cause of cough in many children (13). Clinicians should first exclude alternative etiologies, including upper airway cough syndrome, eosinophilic airway inflammation, and habit cough, before attributing chronic cough to GER.

Recurrent wheezing and asthma

The relationship between GERD and asthma is complex and bidirectional: asthma and its treatments may worsen GER by reducing lower esophageal sphincter (LES) tone, while GERD may precipitate bronchoconstriction via vagal reflexes or microaspiration (3). Prospective trials of PPI therapy in asthmatic children with confirmed GERD have yielded inconsistent results, with some showing modest improvement in lung function or exacerbation rates and others demonstrating no significant benefit (3,9). Fundoplication in children with asthma refractory to medical management and documented severe GERD is supported by limited observational evidence.

Neonates, infants and ALTE/BRUE

Infants are particularly vulnerable to reflex-mediated apnea because of the potency of the laryngeal chemoreflex, immaturity of protective airway mechanisms, and the horizontal-body position favoring reflux (14). Although the temporal association between GER events and apnea in polysomnographic studies has been demonstrated, randomized controlled trials have not confirmed that acid suppression reduces ALTE or BRUE recurrence, and current guidelines do not support empirical PPI therapy in this context (15). Non-acid reflux, unaffected by PPIs, may account for a proportion of reflex apneas, underlining the need for pH-impedance rather than pH monitoring alone in this population.

Neurologically impaired children

Children with neurodevelopmental conditions such as cerebral palsy, chromosomal disorders, severe intellectual disability represent a high-risk subgroup in whom both GERD and aspiration are prevalent and may coexist (16). The impaired coordination of swallowing, reduced esophageal clearance, altered posture, and anti-epileptic drug-induced LES relaxation all conspire to increase reflux burden. In this group, multidisciplinary assessment encompassing gastroenterology, pulmonology, speech therapy, and nutrition is paramount. Surgical fundoplication is more frequently performed but carries higher perioperative risk, and gastro-jejunal feeding may be required in selected cases.

MANAGEMENT STRATEGIES

A stepped-care approach is recommended, starting with non-pharmacological measures and escalating only when clear clinical benefit is demonstrated, or when objective diagnostic data support a causal role for GER (2). The overuse of PPIs is well documented and has been associated with increased risk of respiratory infections, bone demineralization, and hypomagnesemia with long-term use (17). In children presenting with isolated respiratory or airway symptoms and no typical features of reflux, current guidelines do not support empirical acid suppression therapy, given the lack of robust evidence for benefit and the risk of overtreatment (2, 18). The widespread perception that PPIs are benign has likely contributed to their overuse in children with poorly defined extra-esophageal symptoms. Recent review emphasizes a shift away from symptom-based diagnosis toward objective testing and individualized treatment strategies in pediatric GERD (19). **Table 2** summarizes the principal diagnostic tools and therapeutic interventions, with key considerations for clinical practice.

Novel biomarker approaches under investigation include salivary pepsin point-of-care testing and exhaled breath condensate analysis for airway acidification, though neither has been validated for routine clinical use in children (20).

***Table 2**. Diagnostic tools and therapeutic strategies for reflux-related respiratory symptoms in children.*

Category	Tool / Intervention	Key considerations
Diagnostic - reflux detection	pH-impedance monitoring (MII-pH); pH-metry alone; esophageal manometry	MII-pH is preferred; detects non-acid reflux; correlates symptom index with respiratory events
Diagnostic - airway evaluation	Flexible laryngoscopy / bronchoscopy; BAL pepsin and LLMs assay; chest HRCT	Posterior laryngitis lacks specificity; BAL pepsin/ LLMs suggests microaspiration; HRCT identifies structural sequelae
Diagnostic - feeding assessment	Video fluoroscopic swallowing study (VFSS); fiberoptic endoscopic evaluation of swallowing (FEES)	Differentiates oropharyngeal dysphagia from GER-driven aspiration; guides feeding therapy
Non-pharmacological treatment	Positional therapy (prone caution in infants); dietary modifications; thickened feeds; smaller, more frequent meals	Evidence limited in infants; prone positioning contraindicated due to SIDS risk; avoid caffeine/ acidic foods in older children
Pharmacological treatment	Proton pump inhibitors (PPIs); H2-receptor antagonists (H2RAs); prokinetics	PPIs effective for acid-related symptoms; limited evidence for respiratory endpoints; avoid long-term use without clear indication
Surgical treatment	Laparoscopic Nissen fundoplication; Endoscopic anti-reflux procedures (investigational in pediatric populations)	Reserved for refractory cases with confirmed GER; neurologically impaired children at highest risk; may not resolve all respiratory symptoms

BAL: bronchoalveolar lavage; FEES: fiberoptic endoscopic evaluation of swallowing; HRCT: high-resolution computed tomography; MII-pH: multichannel intraluminal impedance and pH monitoring; LLMs: lipid-laden macrophages; PPIs: proton pump inhibitors; SIDS: sudden infant death syndrome; VFSS: video fluoroscopic swallowing study.

CONTROVERSIES ANS AREAS OF UNCERTANITIES

The concept of LPR as a distinct entity from classic GERD remains contentious in pediatrics (11). Whether pediatric LPR represents a distinct disease entity or merely a descriptive label applied to non-specific upper airway findings remains unresolved. LPR implies proximal reflux reaching the laryngopharynx with predominantly upper airway manifestations and absent or minimal heartburn. However, the lack of validated pediatric diagnostic criteria, the non-specific nature of laryngoscopic findings, and the limited evidence for treatment efficacy question whether LPR is a robust diagnostic category or an overextension of GERD to explain symptoms that may have alternative etiologies.

Particular caution is warranted when interpreting laryngoscopic findings in children. Signs commonly attributed to reflux, including posterior laryngeal erythema, oedema, and interarytenoid thickening, may also occur in healthy children or in those with allergic, infectious, or irritant-related airway disease. Furthermore, many diagnostic scoring systems currently used in clinical practice were developed and validated in adults, limiting their applicability to pediatric populations. Consequently, laryngoscopic abnormalities should be regarded as supportive rather than diagnostic evidence of reflux-related disease.

The role of non-acid reflux in respiratory disease is an evolving area of research. Weakly acidic and weakly alkaline reflux events detected only by impedance monitoring have been implicated in symptom generation, particularly post-feed in formula-fed infants. Alginates and feed thickeners may attenuate these non-acid episodes, but high-quality pediatric trial data are sparse. Prokinetics such as domperidone are restricted in many jurisdictions due to cardiac safety concerns, further limiting therapeutic options.

AUTHORS' PERPECTIVE

The authors contend that reflux-related respiratory disease is both under-recognized in carefully selected high-risk populations and over-diagnosed in the broader pediatric population. Children with severe neurological impairment, recurrent aspiration, or objectively documented reflux-symptom association may derive substantial benefit from targeted intervention. In contrast, attributing chronic cough, wheeze, hoarseness, or sleep-related symptoms to reflux solely on the basis of symptom coexistence is unlikely to improve outcomes and may expose children to unnecessary treatment. Future research should focus on identifying reliable biomarkers of causality rather than merely documenting the presence of reflux.

CONCLUSIONS

Reflux-related respiratory symptoms in children represent a clinically important but diagnostically complex domain. While the biological plausibility of a GER-respiratory axis is well established through vagal reflex and microaspiration mechanisms, translating this into evidence-based management remains challenging. Clinicians should resist the temptation to attribute all respiratory symptoms in children with documented GER to reflux causality, particularly given the high background prevalence of both conditions. A systematic, multidisciplinary approach incorporating objective diagnostic assessment, careful interpretation of symptom-reflux associations, and judicious use of therapeutics is the cornerstone of good practice. Future research should prioritize randomized controlled trials in pediatric populations, development of validated pediatric-specific diagnostic criteria for LPR, and characterization of non-acid reflux biomarkers.

Ultimately, individualized management guided by objective evidence, rather than empirical assumptions regarding causality, is likely to provide the greatest benefit to children with suspected reflux-related respiratory disease. Until more definitive diagnostic tools become available, clinical restraint may be as important as clinical intervention.

COMPLIANCE WITH ETHICAL STANDARDS

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The authors declare no conflicts of interest.

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Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

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PERSPECTIVE

Italian Pediatric Respiratory Society position paper on physical activity recommendations in pediatric patients affected by chronic respiratory diseases: an expert group statement

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ABSTRACT

Physical activity (PA) is associated with numerous health benefits in healthy individuals; therefore, the World Health Organization (WHO) recommends specific levels of PA across all age groups. However, disease-specific guidelines, particularly for pediatric populations, are still lacking. This gap also applies to chronic respiratory diseases (CRDs). Several studies have identified PA and exercise as an important therapeutic strategy for individuals with CRDs, highlighting their value alongside pharmacological therapy as part of personalized disease management plans. However, practical guidance regarding exercise prescription for pediatric patients with CRDs remains limited. The Italian Pediatric Respiratory Society/Società Italiana per le Malattie Respiratorie Infantili (IPRS/SIMRI) aims to provide a comprehensive review of the available literature on the role of PA and E in CRDs management and, consequently, to develop pragmatic recommendations to support the safe and effective implementation of exercise prescriptions in this special population.

IMPACT STATEMENT

Physical activity should be considered a core component of the multidisciplinary management of pediatric chronic respiratory diseases. This position paper provides pragmatic evidence-based recommendations to support clinicians in prescribing individualized and safe exercise programs aimed at improving functional capacity, quality of life, and long-term respiratory outcomes in children and adolescents with chronic respiratory conditions.

INTRODUCTION

The latest World Health Organization (WHO) guidelines define physical activity (PA) as “any bodily movement produced by skeletal muscles that requires energy expenditure” (1). PA may occur at varying intensities and in various contexts (domestic, occupational and recreational), including exercise and sports. These recommendations apply to all age groups, from children aged 5 years to adults

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KEY WORDS

Physical activity; exercise; chronic diseases; respiratory diseases; children.

over 65 years, regardless of gender, culture, socioeconomic status or ability (1).

In children and adolescents, PA provides broad health benefits, including improved physical fitness, healthier body composition, better cardiometabolic and bone health, enhanced cognitive function, and improved mental well-being (1, 2).

Although international guidelines specify recommended PA levels for healthy youth (**Figure 1**), disease-specific guidelines for pediatric populations remain limited. As a result, clinicians often face uncertainty when prescribing the appropriate frequency, intensity, duration, and type of PA for children with chronic conditions.

Children with chronic respiratory diseases (CRDs) require individualized assessment of exercise tolerance, tailored to the severity of respiratory impairment (3). CRDs are characterized by structural and functional abnormalities that frequently result in exercise intolerance. Affected children commonly experience fatigue and breathlessness which restrict physical activity compared with healthy peers. Underlying mechanisms include: 1) ventilatory limitation; 2) impaired gas exchange; 3) central and peripheral hemodynamic limitations; 4) skeletal muscle dysfunction (3).

Physical inactivity may further aggravate respiratory mechanics and muscle dysfunction, leading over time to declining lung function, reduced oxidative type I muscle fibers, peripheral weakness, and diminished endurance during moderate-to-high intensity exercise (3).

To address this risk, the Italian Pediatric Respiratory Society/Società Italiana per le Malattie Respiratorie Infantili (IPRS/SIMRI) recommends integrating regular PA and structured exercise into CRDs management.

In the absence of national guidelines, an expert panel of pediatric pulmonologists developed pragmatic evidence-based recommendations to support safe and effective exercise prescriptions.

The panelists conducted a review of the literature on PA and specific respiratory conditions, aiming to address the following points: 1) the rationale for PA and exercise; 2) evidence on the health benefits of PA/exercise according to frequency, intensity, time, and type (FITT principles); 3) the impact of PA and exercise on specific chronic respiratory conditions and related extrapulmonary comorbidities. Based on the available evidence as well as the clinical experience of the working group, recommendations have been developed.

The resulting position paper serves as a practical guide.

Figure 1. *Levels of PA for healthy children and adolescents recommended by 2020 WHO guidelines.*

AI has been used for figure creation.

PA IN PEDIATRIC CRDs

Asthma

PA and structured exercise are increasingly recognized as core components of asthma management, supported by growing evidence of safety and multidimensional benefits across ages and disease severities (**Table 1**). Reduced habitual activity may contribute to rising asthma prevalence and severity, through deconditioning, increased breathlessness, and adverse airway biological effects (4, 5). Despite historical concerns about exercise-induced symptoms, substantial evidence shows that children and adults with asthma can exercise safely and achieve significant improvements in cardiovascular fitness, symptom burden, and quality of life without compromising asthma control (6).

Regular aerobic training appears to modulate airway inflammation and remodeling. Studies in adults and children report reductions in type 2 cytokines (IL-4, IL-5, IL-13), TNF-α, VEGF, fractional exhaled nitric oxide (FeNO), and circulating eosinophils, along with increases in anti-inflammatory mediators such as IL-10, IL-1ra, relaxin-3 (7). These biological effects, combined with consistent clinical improvements, have led guideline committees to endorse exercise as a key non-pharmacologic strategy in asthma care (4, 5, 8). Programs associated with the greatest benefits generally follow FITT (Frequency, Intensity, Time, Type) principles, most often three sessions per week, 30 to 60 minutes each, for 8 to 12 weeks (6, 7, 9). In adults, moderate-intensity aerobic training improves asthma control and quality of life while reducing airway inflammatory cells (9). Vigorous-intensity training (30 min, three times weekly) provides comparable, though slightly smaller benefits (9). In children, aerobic exercise prescribed at the ventilatory threshold or delivered progressively enhances VO_2peak and ventilatory efficiency (6). Modalities such as walking, cycling, running, and swimming improve aerobic capacity (VO_2peak), six-minute walk distance and selected spirometric indices (FVC%, FEF25%-75%) in pediatric meta-analyses (6). Combined aerobic and resistance programs (three times weekly, 60 minutes) add muscular strength with strong cardiovascular benefits, although quality-of-life changes are less consistent (6). High-intensity interval training (HIIT), often school-based (30 min, three times weekly, 10-30 second bouts >90% HRmax), improves maximal aerobic fitness and stabilizes BMI without worsening symptoms or lung function in adolescents (10). Breathing- and singing-based programs enhance respiratory and peripheral muscle strength, reduce dynamic hyperinflation, and improve dyspnea and quality of life in children (11, 12). Adding yoga to standard care further improves asthma control and reduces exacerbations compared with non-yoga exercise in adults (13).

Exercise also benefits key extrapulmonary comorbidities. In overweight and obese youth, structured programs reduce BMI and improve VO_2max and exercise capacity similarly to non-asthmatic peers (14). HIIT in adolescents improves LDL cholesterol and diastolic blood pressure, although effects on overall cardiometabolic risk are inconsistent (10). These findings align with broader evidence linking inactivity, symptom-related fear, and parental concern to overweight in pediatric asthma (4, 15). Aerobic training in obese asthmatic children lowers high-sensitivity CRP and IL-6 while enhancing cardiorespiratory fitness (15). In adults, exercise reduces airway and systemic cytokines and profibrotic markers, suggesting additional cardiometabolic benefits (7). Psy-

Table 1. *Typical exercise prescriptions and main asthma outcomes.*

Population & Type	Typical FITT	Main benefits	Citations
Adults, aerobic (moderate/vigorous)	3×/wk, 30–45 min, 12 wk, mod–vig intensity	↑AQLQ, ↑ACQ, ↓airway inflammation	(7-9)
Children, combined (aerobic+resistance)	3×/wk, 60 min, 12 wk	↑VO_2peak, ↑strength, no loss of control	(6)
Adolescents, HIIT	3×/wk, 30 min, 6 mo, >90% HRmax intervals	↑Fitness, BMI maintenance	(10)
Obese children, incremental aerobic	3×/wk, 8 wk, progressive	↓CRP/IL-6, ↑VO_2peak, ↑6MWT	(70)

FITT: Frequency, Intensity, Time, Type; wk: week; AQLA: asthma quality of life questionnaire; ACQ: asthma control questionnaire; min: minutes; VO_2peak: peak oxygen uptake; mo: months; HR: heart rate; BMI: body mass index; CRP: c-reactive protein; 6MWT: 6-minutes walking test.

chological health also improves: in fact, aerobic training reduces anxiety and depressive symptoms in adults with moderate to severe asthma (8), while pediatric studies associate regular activity with better quality of life particularly in those with more symptomatic disease (5).

Cystic fibrosis and Non-CF bronchiectasis

For individuals with chronic suppurative lung disease and bronchiectasis, regular airway clearance techniques (ACTs) reduce sputum burden, improve quality of life and may reduce exacerbations (16). Beyond its general health benefits, PA may complement ACTs by inducing mechanical airways stress and promoting mucus hydration, thereby facilitating expectoration (16).

Cystic fibrosis

Cystic fibrosis (CF) is characterized by thick secretions leading to multiorgan damage. Mucous stagnation drives inflammation, recurrent infections and progressive lung function decline, the leading cause of morbidity in CF patients (pwCF). Management includes CFTR-modulating therapies, multidisciplinary care, ACTs and structured exercise, all of which are integral to treatment. Annual cardiopulmonary exercise testing (CPET) is recommended for all pwCF (17) to establish functional capacity. PwCF are encouraged to follow general PA guidelines and remain active most days of the week, although adherence is often low (18).

Higher PA levels are associated with better respiratory outcomes, enhanced mucociliary clearance, bone mineral density improvement, better quality of life and prognosis in adolescents (19-21). Conversely, sedentary behavior and poor exercise capacity correlate with faster lung function decline and higher mortality (21).

Adults pwCF using exercise as an adjunct to ACT report slower lung function decline and reduced sputum production (22). A systematic review of 23 controlled trials found that pulmonary rehabilitation and exercise did not significantly improve FEV_1, FVC, FEV1/FVC, or RV/TLC, but increased VO_2max by 2.74 ml/kg/min, a key prognostic marker, and showed favorable trends in 6-minute walk distance. Effects on exacerbations and hospitalizations were not significant, though some studies reported improvements in vitality, emotions, well-being and physical functioning (23).

Establishing exercise efficacy as an ACT remains a research priority in CF (22).

A recent statement from European Cystic Fibrosis Society calls for large prospective studies evaluating mortality, morbidity, cost-effectiveness, and quality of life outcomes (24).

Telemedicine interventions, including web-based platforms, fitness trackers, and tailored exercise plans have shown limited additional benefits over standard care, with no consistent improvements in lung function or overall physical performance, aside from isolated gains in muscle strength in children and adolescents (25-27). With the advent of CFTR modulators, increasing attention is being directed toward promoting habitual moderate-to-vigorous PA and reducing sedentary time. However, optimal exercise type, intensity and duration remain undefined.

People with CF often perceive treatments such as aerosol therapy, ACTs, and the maintenance of respiratory equipment as time-consuming and burdensome. The advent of CFTR modulators has altered the natural history of the disease, with many patients becoming less prone to mucus hypersecretion and pulmonary exacerbations. For these reasons, many pwCF are independently modifying their treatment regimens based on personal preferences, replacing or supplementing conventional ACTs with exercise (ExACT) (28).

Although reducing treatment burden remains a key priority for pwCF, the current evidence supporting ExACT as a viable, lower-burden alternative to chest physiotherapy is limited.

Non-CF bronchiectasis

Bronchiectasis involves irreversible airway dilatation, chronic productive cough and recurrent exacerbations (29). ACTs and exercise are key management strategies (30), yet only about half of affected children meet PA recommendations, especially those older, and those with severe disease (31).

Interventions such as active video gaming and play-based therapeutic exercise programs have demonstrated improvements in aerobic fitness, muscular strength, fundamental movement skills, and quality of life (12, 32). Social engaging parent-supported activities also promote participation (33). Home-based respiratory programs performed twice daily for 8 weeks improved lung function, exercise capacity, and respiratory and peripheral muscle strength in children with bronchiectasis and CF (32).

Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is characterized by impaired mucociliary clearance due to defective cilia,

leading to bronchiectasis, airway obstruction and reduced exercise capacity (34, 35). In the absence of long-term RCTs, recommendations are extrapolated from other chronic lung diseases, with regular PA advised (36). However, the effect of physical exercise in this population remains understudied. Evidence remains limited, though inspiratory muscle training may improve maximal inspiratory pressure, and short PA may modestly increase oxygen saturation (37, 38).

Interstitial lung diseases

Interstitial lung disease in children (ChILD) comprises a heterogeneous group of rare disorders associated with high morbidity and mortality, posing significant challenges for pediatric pulmonologists. Exercise intolerance is a prominent symptom and results from three main mechanisms: 1) impaired gas exchange with hypoxemia; 2) ventilatory dysfunction due to reduced lung compliance and increased respiratory load; and 3) peripheral muscle dysfunction leading to deconditioning (39). All these factors promote a vicious cycle in which reduced exercise and daily activity further worsen functional capacity and quality of life. Pulmonary rehabilitation and structured exercise counteract deconditioning. Studies, mainly in adults, show improvements in exercise tolerance, 6-minute walk test (6MWTD), dyspnea scores, and quality of life (QoL) (40, 41). A 2020 review by the European Respiratory Society highlighted the role of pulmonary-function tests (PFT) in ChILD, including the use of the 6MWT or VO_2 peak and exercise limitation (42). Symptoms, such as dyspnea, fatigue and difficulty to run or to walk are common. Qualitative pediatric data indicate that fatigue significantly limits participation in PA and is influenced by physical, psychological, and social factors, underscoring that exercise capacity reflects more than physiological impairment alone (43). Most robust evidence derives from adult ILD. A meta-analysis of 16 RCTs including 899 adult patients found that exercise training improves 6MWTD, peak work rate, VO_2 peak measured with CPET, symptoms and QoL (44). Another review demonstrated that exercise capacity and PA levels predict important long-term clinical outcomes, supporting early intervention in adults (45). In children with ChILD, however, evidence is limited, with few trials and no standardized protocols regarding exercise type, intensity, duration, or safety threshold for desaturation. *Extrapolating adult data requires caution*. An older pediatric study showed that exercise-induced desaturation correlates with a lower FVC, indicating the need for careful monitoring (46). Exercise prescription in ChILD should therefore be individualized, considering disease severity and oxygenation. Aerobic activities such as walking, cycling, or swimming are generally preferred, performed several times per week in manageable sessions with gradual progression. Moderate intensity, possibly incorporating intervals, is advisable, with caution in more severe cases. A prospective, single-arm study in children aged 7-18 years with chronic lung diseases, demonstrated that a three-month home-based program (three sessions weekly) improved FEV_1, peak expiratory flow (PEF), respiratory muscle strength, 6MWTD, dyspnea and QoL with high adherence and no serious adverse events (47). Data on extrapulmonary comorbidities in ChILD are poor. A 2021 case-control study including children with bronchiectasis and ILD showed that nutritional intervention improved weight, body composition, lung function, respiratory symptoms, and hospitalizations, highlighting the importance of multidisciplinary rehabilitation approaches (48).

Lung transplantation

Lung transplantation is an established option for children with chronic lung diseases (CLDs) and severe respiratory failure unresponsive to other therapies. CF has historically represented the leading indication, but the introduction of CFTR modulators has markedly reduced transplants rates: in the USA, CF-related transplants declined from 49% in 2016 to 16% in 2021 (49).

Post-transplant survival has improved substantially, rising from a median of 5.7 years to 9.1 years beyond the first year. Children with CF show particularly favorable outcomes, with median survival of 9.7 years, compared with 7 years for idiopathic pulmonary arterial hypertension and 6 years for chronic obstructive pulmonary disease (50).

Transplantation leads to major improvements in QoL and respiratory function. However, exercise capacity remains reduced with VO_2max typically reaching only 40-60% of predicted values, partly due to sarcopenia and other multifactorial limitations (51).

Adult studies report that regular PA after transplantation offers important benefits, including increased

muscle mass and strength, improved cardiopulmonary performance, prevention of obesity and diabetes, and enhanced self-esteem and social participation (52). Resumption of activity should be gradual, beginning with physiotherapy and progressing gradually toward more demanding exercise programs. Contact sports and high-intensity aerobic activities are generally avoided during the first 6 months (53). Eligibility for competitive sports requires stable clinical status and close collaboration with the transplant center to ensure individualized risk assessment and safety.

TREATMENT STRATEGIES TO IMPROVE PA

CRDs can limit PA in children due to disease burden, symptom perceptions, and parental concern. Achieving good symptom control at rest and during exercise is essential to improve adherence to individualized programs. Four main strategies support PA participation: 1) optimizing pharmacological therapy; 2) providing oxygen when needed; 3) enhancing pulmonary rehabilitation; and 4) promoting behavioral change.

Pharmacological therapy

Optimizing medical treatment is the first step toward disease control. In asthma with exercise-induced bronchospasm (EIB), inhaled short-acting B2 agonist (SABA) at standard dose 200 µg taken 15 minutes before exercise or pre-exercise ICS/formoterol combination are first-line therapy (54). If symptoms persist or SABA is frequently required, daily inhaled corticosteroids (ICS) are recommended (54). In CF and non-CF bronchiectasis (NCFB), management may include aerosol therapies (*e.g.*, hypertonic saline, inhaled antibiotics when indicated) (30). CFTR modulators have further improved CF care (17). In childhood ILD, treatment may include systemic steroids, hydroxychloroquine, or azithromycin (55). After the lung transplantation management, immunosuppressive regimen, commonly methylprednisolone, tacrolimus and mycophenolate are essential to prevent rejection (55).

Oxygen therapy

Supplemental oxygen is indicated in cases of exercise-induced desaturation, enabling safe participation in PA. It is particularly important in ILD, where impaired gas exchange limits oxygenation (56).

Pulmonary rehabilitation

In CF and NCFB, pulmonary rehabilitation is a cornerstone treatment. Techniques include airway clearance methods (percussion, autogenic drainage, positive expiratory pressure [PEP], high-frequency chest wall oscillation) combined with exercises. Programs should be performed regularly and tailored to clinical status (30).

Behavior changes

Behavioral strategies are equally important. A structured warm-up exercise is recommended before exercise in all patients with CRD (54). Environmental factors, particularly air pollution and tobacco smoke, negatively affect respiratory health during PA (57). Avoiding smoke exposure is therefore a key preventive measure to support safe and sustained PA (58).

DIGITAL TOOLS FOR PROMOTING PA AND MANAGING CHRONIC RESPIRATORY DISEASE

Digital technologies are increasingly used to promote PA and support management of CRD, in children and adolescents (**Table 2**). In pediatric pulmonary hyper-

Table 2. *Summary of main digital tools and functions.*

Digital approach	Main role in PA/respiratory care	Citations
Wearables/accelerometers	Monitor daily PA, support home exercise, track PR outcomes	(58-61)
Apps, web platforms, SMS systems	Goal setting, feedback, adherence prompts, symptom/safety monitoring	(27, 58, 63, 64)
Active video games/exergames	Deliver engaging exercise, improve capacity and QoL	(61)
Telehealth/videoconferencing	Supervise remote exercise sessions, maintain access during constraints	(27, 61)
Smart inhalers, sensors, digital spirometers	Real-time lung function and treatment-use monitoring	(59, 61, 64)
AI/machine-learning on lung data	Advanced interpretation, pattern recognition, therapy evaluation	(59)

PR: patient reported; QoL: Quality of Life; AI: Artificial Intelligence.

tension, the iTONE trial demonstrates how a 16-week home-based exercise program can be "enhanced" by mobile health tools. The intervention combines individualized exercise prescriptions with wearable accelerometers for real-time activity monitoring, interval goal setting to build self-efficacy, and a digital platform for two-way communication and safety oversight (59). Automated text messages triggered by heart-rate thresholds, low device wear time, or symptoms alerts help maintain adherence and safety during unsupervised training, providing a model for future pediatric cardiorespiratory trials (59).

More broadly, innovation in respiratory monitoring include smart inhalers, wearable sensors and home spirometry devices that allow continuous assessment of lung function and treatment response in daily life. These data can be integrated with machine learning algorithms for advanced interpretation and personalized care (60). In pulmonary rehabilitation programs, wearable devices are increasingly embedded within behavior-change strategies to monitor PA and clinical outcomes (61).

In children with chronic suppurative lung diseases, especially CF, eHealth-delivered exercise interventions, such as video games, videoconferencing, and digital spirometers over 3-12 weeks, have shown measurable benefits. A meta-analysis reported a pooled improvement of approximately 37 meters in 6-minute walk distance compared with controls, along with gains in pulmonary function, exercise capacity, balance, muscle strength, and health-related quality of life, although many studies have short follow-up and risk of bias (62). Ongoing systematic reviews aim to clarify whether digital health tools improve adherence and clinical outcomes in CF (27).

Narrative reviews suggest that web/mobile apps, exergames, and web-based platform are generally feasible, acceptable, for increasing PA in healthy youth and those with CRD, including during periods of restricted mobility such as the COVID-19 pandemic (63). Emerging tools – including wearables, virtual reality, and location-based applications – offer scalable and engaging strategies to promote PA across home, school, and clinical settings, though they may also contribute to sedentary screen time if not thoughtfully designed (64).

In pediatric respiratory care, implementation requires attention to interoperability, data protection, equitable access, and standardized clinical validation. Professional guidance emphasizes careful governance to ensure that digital tools are safe, effective, and accessible within routine care pathways (65).

MEDICATIONS FOR CRD AND THE RELATIONSHIP TO DOPING

Medications for CRD include 1) bronchodilators to relieve airway obstruction; 2) anticholinergics to support bronchodilation; 3) anti-inflammatory drugs such as systemic and inhaled steroids and leukotriene receptor antagonists; and 4) mucolytics and expectorants to enhance mucus clearance. Some of these drugs may have performance-enhancing effects, improving muscle strength, endurance or recovery, and therefore raise concerns in competitive sports. The use of potentially doping agents is increasing among adolescents. Lifetime prevalence of nonprescribed anabolic steroid use ranges from 1% to 6%, with higher rates in boys (4.0%) than in girls (2.2%), and greater use among adolescent athletes compared with non-athletes (66, 67).

Doping in youth carries significant physical and psychological risk, including cardiovascular and liver damage, endocrine dysfunction, psychiatric disorders, low self-esteem, and anxiety (68). To protect athlete health and ensure fair competition, the World Anti-Doping Agency (WADA) and other regulatory bodies enforce strict rules on medication use in sport. Asthma therapies such as corticosteroids and long- and short-acting β2-agonists are regulated because of their potential performance effects. Nevertheless, as the health of athletes with asthma is always prioritized, inhaled beta-2 agonists (*e.g.*, salbutamol, formoterol) are permitted within specific dose limits, and therapeutic use exemptions (TUEs) are available when prohibited medications are medically necessary, provided that athletes can supply objective evidence of asthma.

PA IN PEDIATRIC CRDs: WHAT DOES IPRS/SIMRI SUGGEST?

PA provides substantial physical and mental health benefits across all ages. Nevertheless, about 80% of adolescents fail to meet the WHO recommendations (69), with even lower adherence among those with CRDs, despite strong evidence supporting PA as a key component of disease management.

Although acute exercise temporarily increases pro-inflammatory mediators, regular training exerts anti-inflammatory effects that may reduce disease progression (7). Experimental models show that aerobic exercise decreases airway inflammation, hyperreactivity, and remodeling by lowering T helper 2 (Th2) cytokines and increasing anti-inflammatory mediators such as interleukin (IL)-10 and IL-1 receptor antagonist (IL-1Ra) (7). In asthma, these effects correspond to reduced FeNO levels and sputum eosinophils (70).

Clinical studies demonstrate that structured programs, typically three weekly sessions of moderate-to-vigorous aerobic exercise lasting 30-60 minutes for at least eight weeks with or without resistance training – improve functional capacity in asthma and are safe adjuncts to pharmacologic therapy. Benefits extend beyond lung function, positively affecting obesity, anxiety, depression, sleep disturbances, gastroesophageal reflux disease, and bone fragility related to prolonged corticosteroid therapy in adults (71, 72). Exercise should therefore be considered foundational in asthma care.

In CF, PA improves FEV_1, FVC, and VO_2max; in NCFB it enhances endurance and six-minute walking test (32). While optimal training parameters remain unclear in CF and data are limited in NCFB, regular moderate-to-vigorous PA combined with reduced sedentary time is recommended. Nevertheless, based on the available evidence, it appears reasonable to recommend regular PA – particularly moderate-to-vigorous intensity exercise – within structured daily programs, alongside strategies aimed at reducing sedentary behavior, in both populations.

In ILD, mainly in adults, exercise training improves 6MWT performance, lung function, VO_2 peak, and may reduce pulmonary hypertension (44). Evidence in children with ChILD remains scarce. Exercise also benefits before and after lung transplantation, by improving exercise capacity and QoL (55).

Evaluating habitual PA levels and identifying barriers to participation are equally important.

As reported in some studies carried out in adult population, wearable devices can support individualized planning and monitoring (73, 74).

Exercise prescription should follow comprehensive baseline assessment, including medical history and, when feasible, spirometry with bronchodilator reversibility testing. Additional measures such as FeNO, blood eosinophil count, and diffusing capacity of the lung for carbon monoxide (DLCO) may be particularly useful for monitoring CRDs. CPET is considered the gold standard for evaluating exercise tolerance, as it provides an integrated assessment of the cardiovascular, respiratory, and musculoskeletal systems under physiological stress (75, 76). The 6MWT offers a practical functional assessment with heart rate and peripheral oxygen saturation (SpO_2). Digital tools, including telemedicine and mobile applications, show short-term promise in promoting adherence and reducing treatment burden. However, robust long-term trials and clear ethical, technical, and policy frameworks are still needed to ensure their safe and effective integration into routine care (27, 59, 65).

It must be taken into consideration that disease control is the "*conditio sine qua non"* for safe participation in most physical activities.

Although children and adolescents are usually encouraged to be physically active, some activities are less appropriate for people with CRDs, especially when their condition is not well controlled. For example, cold-weather endurance sports can worsen asthma because cold, dry air may trigger bronchospasm (77). High-altitude sports are not recommended for patients with impaired lung function and suboptimal gas exchange, as reduced oxygen availability can further stress compromised lungs (78). Swimming in poorly ventilated, chlorinated pools may exacerbate respiratory symptoms in individuals whose airways are sensitive to chlorine. Scuba diving is generally contraindicated in uncontrolled asthma because of the risk of air trapping and barotrauma.

Outdoor PA in areas with high air pollution or allergen exposure (*e.g.*, during pollen seasons) can worsen symptoms in patients with bronchial hyper-responsiveness and allergen sensitization. Contact sports are not recommended for patients with fragile health (*e.g.*, patients with CF or transplant recipients).

Finally, high-intensity continuous endurance sports (*e.g.*, running or cycling), which require sustained ventilation, can provoke symptoms when airway control is poor.

Given limited high-quality trials, disease-specific exercise guidelines remain underdeveloped.

A multidisciplinary approach is essential to tailor age, disease severity, fitness, and motivation, while ensuring safety through oxygen saturation monitoring and access to rescue medication.

CONCLUSIONS

In line with current evidence, SIMRI supports regular physical activity as an essential component of the multidisciplinary management of pediatric chronic respiratory diseases (**Table 3**). Exercise should be considered a therapeutic intervention alongside pharmacological treatment because of its beneficial effects on functional capacity, exercise tolerance, psychological well-being, and quality of life.\n\nAlthough pediatric disease-specific exercise prescriptions remain incompletely defined, clinicians should promote individualized, safe, and enjoyable physical activity programs tailored to disease severity, patient preferences, and functional limitations. Future research should focus on standardized pediatric exercise protocols, long-term clinical outcomes, and the integration of digital health technologies into routine respiratory care.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

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Author contributions

FP, SLG: conceptualization. FP, CC, VF, EL, LM, GT, AT, SLG: writing – original draft, writing – review & editing. The members of SIMRI Advocacy Council and Executive Committee contributed to drafting the paper based on their expertise on the subject. All authors discussed and approved the final recommendations. All authors

Table 3. *SIMRI recommendations on physical activity (PA) in pediatric patients affected by CRDs.*

1. Physical activity, exercise and pulmonary rehabilitation provide numerous health benefits; therefore, they are to be considered as integral part of the treatment plan of CRD and lung transplanted patients, in addition to pharmacotherapy.
2. Before to suggest PA in patients affected by CRD, a respiratory function evaluation – including spirometry, cardiopulmonary exercise test, six-minutes walking test, diffusion lung capacity of carbon monoxide – should be made to ensure safety, efficacy and to personalize the exercise plan.
3. Comorbidities such as obesity, anxiety, depression, gastroesophageal reflux disease and cardiometabolic disease should be considered when PA is prescribed.
4. Aerobic activity is the suggested modality (walking, running, cycling, and swimming).
5. Warm up exercise should be considered at the beginning of the activity.
6. PA frequency should be about 3-5 days per week.
7. Daily session of moderate-to-vigorous aerobic exercise should last about 30-40 minutes.
8. Intensity should be gradually adjusted according to patient resistance.
9. Administration of SABA before PA or O2 delivering during PA could facilitate adherence to the exercise program.
10. Avoidance of exercise following acute exacerbation is recommended until symptoms and lung function have improved.
11. For lung transplanted patients sports contact and those with high aerobic impact should be avoided for at least the first 6 months.
12. Periodical evaluation of patients is useful to assess disease and redraw the exercise plan according to patient's condition and disease evolution.
13. Telehealth and remote monitoring can be used for managing CRD patients, assessing respiratory function periodically and empower adherence to PA.
14. Despites the benefits of regular exercise outweigh the health risks associated with air pollution in the general population, it should be useful to consider that some factors (chemical components, air pollutants, airborne allergens and the atmospheric temperature) can trigger or worsen respiratory symptoms in CRD patients.
15. Because, overuse or misuse can lead to positive doping tests, even if the drug was medically indicated, physicians must balance therapeutic needs with regulatory compliance, especially in pediatric or competitive sports contexts.

read, critically reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical approval

Human studies and subjects

N/A.

Data sharing and data accessibility

Data are available along with the paper.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All data reported are accurate and authentic. AI used for Figure 1.

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NARRATIVE REVIEW

Biologics in severe pediatric asthma: advances and unmet needs

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ABSTRACT

Severe pediatric asthma is defined as asthma that remains uncontrolled despite confirmed adherence to optimized high-dose inhaled corticosteroid therapy combined with long-acting β_2-agonists, appropriate inhaler technique, and systematic management of modifiable risk factors, or that deteriorates when treatment is stepped down. Affecting approximately 3% of children in Europe, severe asthma imposes a substantial clinical and socioeconomic burden because of frequent exacerbations, persistent symptoms, impaired lung function, and increased healthcare utilization, including emergency department visits and hospitalizations.

Advances in the understanding of asthma immunopathology have led to the development of targeted biologic therapies, including omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab, which have significantly improved disease control while reducing the need for systemic corticosteroids. These agents decrease exacerbation frequency, improve lung function, and support a personalized treatment approach based on inflammatory phenotype and endotype. Treatment selection is guided by clinical characteristics together with biomarkers such as blood eosinophil count, fractional exhaled nitric oxide, and serum IgE levels.

Despite these therapeutic advances, several challenges remain, including high treatment costs, unequal access to biologic therapies, immunogenicity, and the limited availability of pediatric evidence regarding treatment duration, discontinuation strategies, and standardized definitions of remission. Multidisciplinary, phenotype-driven management combined with long-term monitoring remains essential to optimize clinical outcomes. Future research should focus on refining predictive biomarkers, broadening the representation of pediatric populations in clinical trials, and establishing standardized definitions of treatment response and remission to facilitate earlier and more effective precision-based interventions in children with severe asthma.

IMPACT STATEMENT

Biologic therapies have transformed the management of severe pediatric asthma by enabling precision medicine approaches based on inflammatory endotypes. Nevertheless, validated predictive biomarkers, standardized remission criteria, and evidence-based strategies for treatment duration and discontinuation remain major unmet clinical needs.

KEY WORDS
Severe pediatric asthma; biologics; precision medicine.

INTRODUCTION

According to the 2025 Global Initiative for Asthma (GINA), severe asthma is defined as asthma that remains uncontrolled despite verified adherence to optimized high-dose inhaled corticosteroids (ICS) in combination with long-acting β2-agonists (LABA), appropriate inhaler technique, and management of modifiable risk factors, or that worsens when high-dose therapy is reduced (1). According to recent epidemiological data from a systematic review and meta-analysis, approximately 3% of the pediatric population in Europe is affected by severe asthma (2).

Severe asthma in children is associated with elevated morbidity and increased healthcare demands, including frequent hospitalizations, emergency department visits, and prolonged pharmacotherapy, leading to considerable socioeconomic burdens. Despite optimized therapy, many children with severe asthma continue to experience persistent symptoms, recurrent exacerbations, and impaired lung function (3, 4).

Advances in the understanding of asthma immunopathology have led to the development of targeted biologic therapies.

Monoclonal antibodies directed against specific inflammatory pathways, such as immunoglobulin E (IgE; omalizumab), interleukin-5 (IL-5; mepolizumab), IL-5 receptor alpha (IL-5Rα; benralizumab), and the interleukin-4/interleukin-13 (IL-4/IL-13) axis (dupilumab), have demonstrated clinical efficacy in reducing exacerbations, improving lung function, and decreasing dependence on systemic corticosteroids (5, 6).

Emerging evidence also highlights the role of airway epithelium as a key initiator of inflammatory responses in asthma pathophysiology. Biologics targeting epithelial cytokines (alarmins), such as thymic stromal lymphopoietin (TSLP; tezepelumab), have shown substantial efficacy in improving symptom control in severe asthma. However, further studies are needed to fully elucidate their mechanisms of action and long-term clinical impact (7).

The selection of biologic therapy is primarily guided by the patient's clinical phenotype and underlying endotype, in conjunction with a comprehensive evaluation of factors contributing to poor disease control. In this context, validated biomarkers, including blood eosinophil count (BEC), fractional exhaled nitric oxide (FeNO), markers of allergic sensitization, and serum IgE levels, play a central role in identifying patients most likely to benefit from specific biologic agents (8). The implementation of biomarker-driven biologic therapies has substantially transformed the management of severe asthma, leading to significant improvements in disease control and meaningful reductions in exacerbation frequency. Despite these advances, important knowledge gaps remain.

A comprehensive literature search was conducted to evaluate the current evidence on biologic therapies for severe pediatric asthma. The PubMed database was searched using predefined combinations of Medical Subject Headings terms and keywords, including "severe pediatric asthma", "biologic therapy" and "monoclonal antibodies" as well as the names of individual agents (*e.g.*, omalizumab, mepolizumab, benralizumab, dupilumab, tezepelumab). Additional search terms addressed key domains of interest, including mechanisms of action, clinical efficacy, safety, and criteria for patient selection. Publications from 2000 to 2026 were eligible for inclusion and encompassed original research articles, randomized controlled trials (RCTs), observational studies, systematic reviews, meta-analyses, international clinical practice guidelines, and reviews. Relevant articles were further identified through manual screening of reference lists. Given the substantial heterogeneity across studies with respect to design, patient populations, biologic agents evaluated, and outcome measures, quantitative synthesis through meta-analysis was not considered appropriate. Consequently, a narrative synthesis was performed, enabling an integrated and critical appraisal of the available evidence and providing a structured overview of the current and emerging role of biologic therapies in the management of severe pediatric asthma.

FROM ASTHMA PATHOPHYSIOLOGY TO SEVERE DISEASE ENDOTYPES

Although severe asthma does not represent a distinct pathophysiological entity, it reflects the most complex end of the asthma spectrum, characterized by persistent inflammation, greater biological heterogeneity, and reduced responsiveness to conventional therapy. Understanding the immunopathogenesis of asthma is therefore essential to explain the mechanisms underlying severe disease and the rationale for biologic therapies (1).

A variety of factors, including allergens, infections, obesity, hormonal influences, tobacco smoke exposure, exercise, cold air, and genetic mutations (*e.g.*, ADAM33, PHF11, DPP10, GPRA), have been shown to contribute to chronic airway inflammation, ultimately leading to airway obstruction, remodeling and hyperresponsiveness (9).

The immune dysregulation underlying asthma, and driving the different inflammatory endotypes observed in severe disease, results from activation of both the innate and adaptive immune systems, resulting in two broad inflammatory classifications: type 2 (T2)-high and T2-low inflammatory pathways (10).

In children, T2-high inflammation represents the predominant endotype. Upon exposure to inhaled allergens, naïve T cells differentiate into Th2 cells, which subsequently release cytokines such as IL-4, IL-5, IL-9, and IL-13. IL-4, IL-9, and IL-13 promote B-cell activation and IgE production, which in turn triggers mast cell degranulation with the release of histamine and leukotrienes, leading to bronchoconstriction. IL-5 plays a central role in eosinophil maturation, while IL-9 and IL-13 further contribute to mucus hypersecretion (9).

Recent studies have underscored the critical role of the epithelial barrier in asthma pathophysiology. Indeed, dysregulation of this barrier facilitates allergen penetration and promotes the release of alarmins, including TSLP, IL-25, and IL-33. TSLP activates dendritic cells, which drive the differentiation of naïve T cells into Th2 cells. The alarmins IL-25 and IL-33 further amplify T2 inflammation by activating group 2 innate lymphoid cells (ILC2s), as well as mast cells, eosinophils, and basophils (11, 12).

Although less prevalent, T2-low asthma endotypes are observed in both adults and children and are increasingly recognized as clinically significant. T2-low asthma is primarily driven by the activation of T helper (Th)1 and Th17 cells, leading to the release of proinflammatory cytokines such as IL-17, IL-6, and tumor necrosis factor-α (TNF-α). This inflammatory pattern is typically associated with neutrophilic or paucigranulocytic airway inflammation, reduced responsiveness to corticosteroids, and a more challenging clinical course (13, 14).

Advances in asthma immunology have enabled a more precise characterization of severe asthma endotypes, allowing biomarker-guided selection of biologic therapies.

Biomarkers play a central role in differentiating endotypes and guiding targeted treatment. In clinical practice, BEC, FeNO, and serum total IgE are the most widely used markers for identifying both T2-high and T2-low asthma. Notably, however, 30-50% of patients demonstrate variability in T2 status over time (14).

BEC ≥ 150 cells/μL indicates T2 inflammation and is associated with asthma exacerbations. Alone or in combination with elevated FeNO (≥ 20 ppb in children), it predicts high airway inflammation, poor asthma control, increased risk of severe exacerbation, and favorable responsiveness to biologics targeting the IL-5 and IL-4/IL-13 pathways (15).

Serum total IgE levels are critical for determining the appropriate therapeutic dose of omalizumab and are currently under investigation for treatment monitoring. Allergen-specific IgE levels, however, are more closely associated with asthma severity. Emerging biomarkers, including periostin, TSLP, natural killer cells, urinary eicosanoids, and specific microRNAs, are being evaluated for their potential to further refine pediatric asthma endotyping (8).

Systemic IL-6 has also been proposed as a biomarker for non-T2 asthma phenotypes; however, its clinical utility is limited by lack of disease specificity, as elevated IL-6 levels may occur in other inflammatory conditions (16).

BIOLOGIC THERAPIES APPROVED FOR SEVERE PEDIATRIC ASTHMA

Omalizumab

Omalizumab represents the first humanized monoclonal antibody introduced into clinical practice within the field of allergology (17). It was initially authorized in 2003 by the U.S. Food and Drug Administration (FDA) for the management of moderate-to-severe persistent allergic asthma in patients aged 12 years and older who had a positive skin prick test (SPT) or *in vitro* reactivity to a perennial aeroallergen, and whose symptoms remain uncontrolled despite high-dose inhaled ICS plus additional controller therapy (18). The therapeutic indication was subsequently expanded in 2009 to include children aged ≥ 6 years in European countries, and this extension was later adopted in the United States as well (19-21).

According to the National Institute for Health and Care Excellence (NICE), omalizumab is recommended as an add-on therapy for patients ≥ 6 years old with severe

persistent allergic (IgE-mediated) asthma who have a positive SPT or serum-specific IgE, a total serum IgE level between 30-1500 IU/mL, and require frequent oral corticosteroids (OCS) courses (≥ 4 in the previous 12 months) despite optimized treatment (22).

Omalizumab is administered subcutaneously every 2-4 weeks depending on the patient's total serum IgE levels and body weight (23).

Omalizumab binds to the Cε3 domain of circulating IgE, forming inactive immune complexes that do not trigger complement activation. This interaction markedly reduces free serum IgE levels and prevents IgE from binding to high- (FcεRI) and low-affinity (FcεRII/CD23) receptors on effector cells such as mast cells, basophils, and dendritic cells. Consequently, receptor expression and mediator release are downregulated.

Omalizumab also targets membrane-bound IgE on B cells, disrupting IgE-CD21 and soluble CD23 signaling, thereby inhibiting IgE synthesis and inducing apoptosis of IgE-producing B cells. Beyond modulating allergic inflammation, omalizumab enhances antiviral immunity by restoring Toll-like receptor function and interferon (IFN)-α production in plasmacytoid dendritic cells, which are often impaired in allergic asthma with high IgE levels. Additionally, omalizumab reduces IL-33 concentrations, leading to decreased expression of proinflammatory cytokines such as IL-6, IL-1β, and TNF-α, ultimately contributing to airway inflammation control (24).

The efficacy of omalizumab in severe pediatric asthma has been established through both RCTs and real-world studies.

A Cochrane systematic review of 25 RCTs published up to 2013 – including studies involving children aged 5-12 years and adolescents aged 12-17 years – demonstrated a significant reduction in asthma exacerbation rates among patients receiving omalizumab compared with placebo. Omalizumab-treated patients experienced fewer exacerbations requiring OCS, lower hospitalization rates, and a reduced need for ICS. The therapy also increased the likelihood of discontinuing or tapering ICS doses (25).

Several individual RCTs have further confirmed these findings. Milgrom *et al*. reported in 334 children with moderate-to-severe allergic asthma that omalizumab led to a complete discontinuation of ICS in many cases and markedly reduced the frequency of acute exacerbations (26). In the IA-05 trial, which included 627 pediatric patients, omalizumab reduced the annual exacerbation rate by approximately 40%-50% compared with placebo, particularly in those receiving high-dose ICS plus LABA (27). Similarly, the Inner-City Anti-IgE Therapy for Asthma (ICATA) study demonstrated reductions in symptom days, exacerbations, and treatment intensity over a 60-week period. Importantly, post hoc analyses indicated that omalizumab mitigated seasonal peaks in exacerbations often associated with viral infections (28).

Real-world evidence supports the durability of these benefits. In a French multicenter cohort of 104 children, one year of omalizumab therapy reduced severe exacerbations by more than two-thirds and hospitalizations by nearly 90%, while improving lung function and allowing ICS dose reduction. These improvements persisted in over 80% of patients after two years (29). Comparable outcomes were observed in an Italian multicenter study involving 47 children, which reported substantial declines in exacerbations and hospitalizations, complete cessation of maintenance OCS, and improved FEV_1 values (30).

Biomarker analyses suggest that omalizumab achieves its greatest efficacy in patients with elevated T2 inflammation. Patients with higher FeNO and BEC values consistently derive the greatest clinical benefit, whereas baseline total IgE has shown limited predictive value (31).

Omalizumab has also been shown to improve lung function, particularly in adolescents and in patients with elevated T2 biomarkers. Positive predictors of therapeutic response include polysensitization to multiple allergens and higher total IgE levels, while weaker responses have been associated with older age, recent exacerbations, lower baseline FEV_1, and comorbidities such as obesity or gastroesophageal reflux (32, 33).

Discontinuation studies indicate that clinical benefits may persist after treatment withdrawal in selected patients. In a large real-world analysis including over 19,000 patients, most children maintained asthma control for up to three years after omalizumab discontinuation, with stable hospitalization and corticosteroid use (34). Smaller prospective and retrospective pediatric studies further confirmed sustained improvements in lung function, exacerbation rates, and quality of life (QoL) for at least one year following therapy discontinuation (35, 36).

Overall, omalizumab remains the reference biologic for severe allergic asthma in children, with robust evidence supporting its efficacy, long-term safety, and corticosteroid-sparing effect. The most common adverse events are mild injection-site reactions, while serious events are rare (37).

Ongoing studies will clarify whether earlier intervention may also modify the natural history of the disease. Trials, including the Preventing Asthma in high Risk Kids (PARK) study, are exploring whether early omalizumab intervention in high-risk toddlers may prevent or modify asthma development, potentially expanding the therapeutic scope of anti-IgE therapy in pediatric populations (38).

Mepolizumab

Mepolizumab is a humanized IgG1κ monoclonal antibody approved by both the FDA and the European Medicines Agency (EMA) as an add-on maintenance therapy for children aged six years and older with severe eosinophilic asthma (39, 40). Eligibility criteria typically include BEC ≥ 300 cells/μL with frequent systemic corticosteroid-requiring exacerbations (≥ 4 in the past year) or prolonged daily corticosteroid use (equivalent to ≥ 5 mg/day of prednisolone for six months) or, alternatively, frequent exacerbations or chronic corticosteroid use, or BEC ≥ 400 cells/μL with at least three corticosteroid-treated exacerbations in the preceding year (41). The recommended dosing regimen consists of 40 mg subcutaneously every four weeks for children aged 6-11 years and 100 mg for those aged 12 years and above, administered via prefilled syringe (23).

Mepolizumab binds IL-5, preventing its interaction with the IL-5 receptor α-subunit (IL-5Rα) on eosinophils. By neutralizing IL-5 activity, mepolizumab reduces eosinophil maturation, recruitment, and survival, thereby attenuating eosinophilic airway inflammation. Furthermore, beyond reducing eosinophil counts, mepolizumab may modulate antiviral immunity. Indeed, eosinophils contribute to antiviral defense by releasing ribonucleases such as eosinophil-derived neurotoxin and eosinophil cationic protein, which degrade viral RNA, limiting viral replication and spread. However, excessive eosinophilic inflammation can impair immune balance and exacerbate respiratory viral infections. By restoring the ratio of IFN-γ to IL-5 expression, mepolizumab may enhance antiviral responses while suppressing tissue-damaging inflammation (24).

An open-label pharmacokinetic study involving children aged 6-11 years demonstrated that 12 weeks of subcutaneous treatment achieved substantial reductions in BEC – approximately 85% to 90% – comparable to reductions seen in adolescents and adults, confirming consistent pharmacological activity across age groups (42).

The pivotal Mechanisms Underlying Asthma Exacerbations Prevented and Persistent with Immune-Based Therapy: A Systems Approach-Phase 2 (MUPPITS-2) trial, a multicenter RCT involving 290 urban children aged 6-17 years, provided strong evidence of mepolizumab's clinical efficacy. Treatment led to a 27% reduction in the annualized rate of asthma exacerbations compared with placebo. Transcriptomic profiling of nasal samples revealed downregulation of eosinophil-associated and T2 inflammatory gene modules, while pathways linked to epithelial activation (including IL-33 signaling) remained active in a subset of non-responders. These findings indicate that persistent, non-eosinophilic inflammation may underlie residual disease activity despite IL-5 blockade (43).

Further analyses from Fricker *et al*. and Vultaggio *et al*. showed that mepolizumab selectively depletes inflammatory eosinophils expressing low CD62L, while sparing subsets involved in tissue homeostasis, suggesting immune rebalancing rather than complete eosinophil depletion (44, 45).

The Sputum CyTOF Substudy (SCOUT), nested within MUPPITS-2, used high-dimensional cytometry to characterize eosinophil diversity in induced sputum. Three eosinophil subpopulations – CD62L low, intermediate, and high – were identified. Children who experienced exacerbations despite mepolizumab exhibited higher proportions of CD62L-intermediate and -high eosinophils, expressing increased activation markers (CD69, CCR3) and secreting IL-5, IL-13, and TNF-α. These data suggest that airway-resident, activated eosinophil subsets may drive breakthrough exacerbations even when circulating eosinophils are suppressed (46).

A subsequent systems-level analysis of MUPPITS-2 participants confirmed that, under mepolizumab, residual exacerbations were primarily associated with non-T2 inflammatory signatures, including macrophage acti-

vation, epithelial stress responses, and mucus hypersecretion. Distinct molecular exacerbation patterns were also identified based on the presence or absence of viral infection, underscoring the complexity of asthma endotypes in children (47).

Long-term extension studies demonstrate that mepolizumab maintains a favorable safety and tolerability profile in pediatric patients with severe eosinophilic asthma. Reported adverse events are generally mild and transient, most commonly upper respiratory infections and headaches. Serious adverse reactions are rare, and no cases of anaphylaxis or systemic hypersensitivity have been documented (48).

Benralizumab

It is an IL-5Rα-directed cytolytic monoclonal antibody (IgG1κ) approved by the FDA as an add-on maintenance treatment for patients aged 6 years and older with severe eosinophilic asthma. In contrast, the EMA and the NICE guidelines currently approve its use only in adults (≥ 18 years) who meet at least one of the following criteria: BEC ≥ 0.3 × 10^9/L with ≥ 4 exacerbations requiring OCS in the previous 12 months or maintenance OCS therapy equivalent to ≥ 5 mg/day of prednisolone over the past 6 months; or BEC ≥ 0.4 × 10^9/L with ≥ 3 exacerbations in the preceding year (49-51).

According to the FDA-approved dosing regimen, children aged 6-11 years weighing ≥ 35 kg should receive 30 mg subcutaneously, while those weighing < 35 kg should receive 10 mg. Treatment begins with an induction phase of three doses administered every four weeks, followed by maintenance dosing every eight weeks (23).

Benralizumab exerts its therapeutic effect by binding to the IL-5Rα on eosinophils and basophils, triggering antibody-dependent cell-mediated cytotoxicity that leads to rapid and sustained eosinophil depletion (24).

The FDA approval for pediatric use was supported by data from the TATE study, a 48-week open-label trial that assessed the pharmacokinetic and pharmacodynamic properties of benralizumab in 28 children with severe eosinophilic asthma. The study demonstrated a 50% reduction in asthma exacerbations and notable improvements in symptom control. Benralizumab exhibited a favorable safety profile, with the most frequently reported adverse events being mild upper respiratory tract infections and localized injection-site reactions (52).

Dupilumab

Dupilumab is a fully human IgG4 monoclonal antibody approved by both the FDA and the EMA as an add-on maintenance therapy for moderate-to-severe asthma in patients aged 6 years and older with an eosinophilic phenotype or OCS-dependent asthma (53, 54). According to the NICE guidelines, eligibility criteria include a history of ≥ 4 OCS-treated asthma exacerbations in the previous year, failure or ineligibility for anti-IL-5 therapy, BEC ≥ 0.15 × 10^9/L, and FeNO ≥ 25 ppb (55). The dosing is based on body weight, age, and OCS use (23).

Dupilumab is a fully human IgG4 monoclonal antibody that inhibits the IL-4 receptor α-subunit (IL-4Rα), thereby inhibiting signaling through both IL-4 and IL-13 pathways. This dual inhibition downregulates the molecular cascade responsible for T2 inflammation, leading to reductions in eosinophilic inflammation, mucus hypersecretion, IgE class switching, bronchial hyperresponsiveness, and airway remodeling. By suppressing IL-4Rα signaling, dupilumab decreases biomarkers of T2 inflammation, including blood eosinophil levels and FeNO. In addition to its anti-inflammatory effects, dupilumab may exert immunomodulatory and antiviral benefits by shifting the immune balance from a Th2-dominant to a Th1-skewed profile, thereby enhancing IFN-γ production and improving antiviral defenses (24).

The Phase III VOYAGE trial, a pivotal study in children aged 6-11 years with uncontrolled moderate-to-severe asthma, demonstrated that dupilumab significantly reduced the annualized rate of severe asthma exacerbations. After 52 weeks, 78% of patients receiving dupilumab remained exacerbation-free, compared with 60% in the placebo group. Improvements in percent predicted FEV_1 were observed as early as week 2 and were maintained throughout the treatment period. The benefits were most pronounced in children with T2-high asthma, particularly those with baseline eosinophils ≥ 300 cells/μL or FeNO ≥ 20 ppb, underscoring the predictive value of these biomarkers for dupilumab responsiveness (56).

A post hoc analysis further confirmed that dupilumab combined with medium-dose ICS achieved significant reductions in FeNO and serum total IgE levels compared with placebo plus high-dose ICS. Median BEC decreased steadily from week 12 and remained stable through week 52 (-130 cells/μL in the dupilumab group *vs* -70 cells/μL with placebo). Over one year, the addition of

dupilumab to medium-dose ICS led to a 74% reduction in severe exacerbations and superior improvements in lung function and asthma control compared with high-dose ICS alone. These findings suggest that dupilumab may enable effective asthma control with lower corticosteroid exposure, potentially reducing steroid-related adverse effects (57).

Transient blood eosinophilia, observed in 4-14% of dupilumab-treated patients compared with < 1% in placebo, is thought to result from inhibited eosinophil migration into tissues rather than increased production or release from the bone marrow (23).

Further analysis by Bacharier *et al.* confirmed that blood eosinophils and FeNO are both valuable predictive and prognostic biomarkers for dupilumab response. The most substantial improvements in exacerbation rates and lung function occurred in patients with elevated levels of both markers, whereas minimal benefit was seen in those with eosinophils < 150 cells/μL and FeNO < 20 ppb (58).

Long-term outcomes from the EXCURSION extension study demonstrated that dupilumab maintains durable efficacy and safety over two years. Children who continued therapy showed sustained improvements in lung function and reduced exacerbation frequency, while those transitioning from placebo experienced rapid clinical benefits after initiation. The safety profile remained favorable, with mild upper respiratory tract infections and injection-site reactions as the most common adverse events, and no new safety signals emerging over extended follow-up (59).

Tezepelumab

Tezepelumab is a fully human IgG2λ monoclonal antibody that targets thymic stromal lymphopoietin (TSLP), an epithelial-derived cytokine that plays a pivotal role in initiating airway inflammation. Unlike currently available biologics that selectively inhibit downstream type 2 inflammatory mediators, tezepelumab acts upstream in the inflammatory cascade and therefore has the potential to modulate both T2-high and T2-low asthma endotypes. It has been approved by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as add-on maintenance therapy for adolescents (≥12 years) and adults with severe asthma inadequately controlled despite high-dose inhaled corticosteroids and additional controller therapy, irrespective of baseline blood eosinophil count (60-62).

The recommended dose is 210 mg administered subcutaneously every four weeks (23).

By neutralizing TSLP, tezepelumab suppresses the activation of multiple downstream inflammatory pathways, including those involving dendritic cells, group 2 innate lymphoid cells (ILC2s), eosinophils, mast cells, and T-helper lymphocytes. This upstream mechanism distinguishes tezepelumab from other biologics by providing broader immunomodulatory activity and extending potential therapeutic benefit to patients with low type 2 biomarker expression who are often less responsive to currently available targeted therapies (24).

Mechanistic studies have further clarified the biological effects of TSLP inhibition.

Sverrild *et al.* demonstrated that tezepelumab significantly reduced epithelial IL-33 expression and attenuated the production of pro-inflammatory cytokines following viral stimulation without impairing antiviral interferon responses or increasing viral replication. These findings suggest that TSLP blockade effectively dampens airway inflammation while preserving antiviral immune competence, an important consideration in children who experience recurrent virus-induced asthma exacerbations (63).

The pivotal Phase III NAVIGATOR trial established the clinical efficacy of tezepelumab in adolescents and adults with severe uncontrolled asthma. Treatment significantly reduced annual exacerbation rates, improved lung function, enhanced asthma control, and increased health-related quality of life. Importantly, clinical benefits were observed across a broad range of inflammatory phenotypes, including patients with low blood eosinophil counts (<150 cells/μL) and low FeNO values, populations for whom therapeutic options have traditionally been limited (64, 65).

Although pediatric experience remains limited, an ongoing Phase III clinical trial is currently evaluating the pharmacokinetics, efficacy, and safety of tezepelumab in children aged 6 to <12 years with severe uncontrolled asthma. The results of this study are expected to provide the evidence required to extend regulatory approval and further define the role of TSLP inhibition in younger pediatric population (66).

Table 1 summarizes the main characteristics of biologics approved in children and adolescents with severe asthma.

Table 1. *Main characteristics of biologics currently approved for severe pediatric asthma.*

Biologic	Target	Mechanism and key immunologic effects	Dosing and mode of administration	FDA authorization	EMA authorization
Omalizumab	IgE (Cε3 domain)	Binds free IgE; ↓ FcεRI/FcεRII engagement; ↓ FcεRI expression; ↓ mast cell/basophil activation; ↓ IgE synthesis; ↑ pDCs TLR function and IFN-α; ↓ IL-33, IL-6, IL-1β, TNF-α	Administered subcutaneously every 2–4 weeks; dose determined by baseline total serum IgE levels and body weight according to validated dosing tables	≥ 6 years	≥ 6 years
Mepolizumab	IL-5	Neutralizes IL-5; ↓ eosinophil maturation, recruitment, survival, activation; ↓ eosinophilic airway inflammation; restores IFN-γ/IL-5 balance; potential antiviral immunomodulation	40 mg subcutaneously every 4 weeks in children aged 6–11 years; 100 mg subcutaneously every 4 weeks in patients ≥12 years	≥ 6 years	≥ 6 years
Benralizumab	IL-5Rα	Binds IL-5Rα; ADCC; near-complete eosinophil and basophil depletion; ↓ eosinophilic inflammation	Subcutaneous administration; in children aged 6–11 years, 30 mg if body weight ≥35 kg and 10 mg if <35 kg (FDA-approved regimen)	≥ 6 years	≥ 18 years
Dupilumab	IL-4Rα	Blocks IL-4Rα; inhibits IL-4/IL-13 signaling; ↓ T2 inflammation; ↓ IgE class switching; ↓ eosinophilic inflammation; ↓ mucus hypersecretion; ↓ bronchial hyperresponsiveness; ↓ airway remodeling; ↓ FeNO; Th2→Th1 immune shift; ↑ IFN-γ	Subcutaneous administration; dosing based on age, body weight, and concomitant OCS use	≥ 6 years	≥ 6 years
Tezepelumab	TSLP	Neutralizes TSLP; blocks upstream alarmin signaling; ↓ T2 and non-T2 inflammation; ↓ IL-33, IL-4, IL-13, IL-17A; preserves IFN-β/IFN-λ antiviral responses; efficacy across biomarker-defined endotypes	210 mg administered subcutaneously every 4 weeks	≥ 12 years	≥ 12 years

ADCC: antibody-dependent cellular cytotoxicity; EMA: European Medicines Agency; FDA: Food and Drug Administration; FeNO: fractional exhaled nitric oxide; IFN: interferon; IgE: immunoglobulin E; IL: interleukin; IL-4Rα: IL-4 receptor α-subunit; IL-5Rα: IL-5 receptor α-subunit; OCS: oral corticosteroid; pDCs: plasmacytoid dendritic cells; T2: type 2; Th: T helper; TLR: toll-like receptor; TNF-α: tumor necrosis factor-α; TSLP: thymic stromal lymphopoietin

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

Emerging biologic therapies are expanding the horizons of precision medicine in severe pediatric asthma. Anti-IL-33 monoclonal antibodies, including itepekimab and etokimab, target the IL-33/ST2 signaling pathway, which is critical for activation of ILC2s and eosinophilic inflammation. Early trials in adults have demonstrated reductions in exacerbation frequency and symptom severity, highlighting the potential of IL-33 blockade for children with severe asthma. Depemokimab, a long-acting anti-IL-5 monoclonal antibody with an extended dosing interval, has recently demonstrated promising efficacy in reducing exacerbations in eosinophilic asthma

and may further expand future treatment options, pending pediatric evaluation. Similarly, tralokinumab, an IL-13-specific antibody, has shown clinical efficacy in atopic dermatitis and is under investigation for asthma phenotypes predominantly driven by IL-13. Additional investigational agents are focusing on pathways involving IL-1 family cytokines, TSLP receptors, IL-4/IL-13, and IL-17, reflecting the complex interplay of Th2 and non-Th2 inflammatory responses in severe asthma (67-69). The clinical integration of these therapies will depend on the results of ongoing pediatric trials, validation of epithelial and immunologic biomarkers, and development of individualized treatment strategies informed by molecular and cellular profiling.

Ongoing monitoring remains a cornerstone of biologic therapy. Follow-up should include symptom assessment, lung function testing, QoL questionnaires, and periodic biomarker reassessment to evaluate treatment efficacy and guide long-term decisions. The optimal duration of therapy and criteria for tapering or discontinuation are not yet clearly established in pediatric populations (70).

Real-world evidence provides valuable insights. The Severe Pediatric Asthma Collaborative in Europe (SPACE) study, which followed 250 European children with severe asthma treated with biologics, demonstrated that most achieved good disease control, though approximately one-third maintained partial or poor control. The SPACE network aims to refine recommendations regarding biologic continuation, switching, or discontinuation, promoting a more personalized therapeutic approach (71).

Despite their clinical benefits, biologic therapies pose economic and practical challenges. High treatment costs and variability in insurance coverage may limit access, necessitating careful cost-benefit considerations that weigh reductions in exacerbations, hospitalizations, and corticosteroid exposure against overall healthcare expenditure (72).

Another critical challenge involves immunogenicity, as biologic agents can elicit anti-drug antibodies (ADAs) that may compromise therapeutic outcomes. Among these, neutralizing antibodies represent a clinically significant subset that directly interferes with the biologic's mechanism of action by preventing its binding to the target antigen (73).

The immunogenicity of biologics is determined by a complex interplay of patient-specific and drug-specific factors. Patient-related factors include genetic susceptibility, co-treatments and disease state. Drug-related factors encompass dose, route and frequency of administration, formulation components, post-translational modifications, molecular origin, and the specific target of the monoclonal antibody. ADAs may be generated via T cell-dependent or T cell-independent pathways. In the T cell-dependent pathway, biologics are internalized by antigen-presenting cells, processed, and presented to T cells via major histocompatibility complex (MHC) class II molecules. Depending on the local cytokine milieu, Th cells differentiate into distinct subsets – primarily Th1 or Th2 – which, through interaction with B cells, promote the proliferation of plasma cells (PCs) that secrete ADAs. Th2 responses have been associated with increased production of IgG4 isotype ADAs, whereas Th1 responses may favor the generation of IgG1 and IgG2 subclasses. Conversely, in the T cell-independent pathway, biologics presenting multiple epitopes can crosslink B cell receptors (BCRs), directly stimulating B cell activation and differentiation into PCs. Aggregates or impurities in biologic formulations can enhance epitope clustering, thereby favoring BCR crosslinking and T cell-independent ADAs production (74).

This immunogenic response can interfere with treatment through several mechanisms. ADAs may neutralize the biologic by binding to its active site, thereby preventing interaction with its target. They can also accelerate drug clearance by promoting Fc-mediated uptake through the reticuloendothelial system. Additionally, the formation of immune complexes between the biologic and ADAs can provoke hypersensitivity reactions, including infusion-related responses, serum sickness, or anaphylaxis (75).

Given the increasing use of biologics in the management of severe pediatric asthma, there is a critical need to elucidate the mechanisms, prevalence, and clinical implications of ADAs development. Improved knowledge in this area will facilitate the identification of predictive biomarkers for early ADAs detection, support the implementation of personalized treatment strategies, and ultimately enhance long-term therapeutic efficacy and safety.

CONCLUSIONS

When children with severe asthma remain symptomatic despite optimal therapy, treatment with biologics should be considered. These targeted agents require precise identification of the patient's inflammatory endotype to ensure appropriate selection. Choice of therapy depends on age, biomarker profile, comorbidities, and psychosocial context. Although recent trials have advanced biomarker-based stratification, greater inclusion of diverse pediatric phenotypes is needed. A standardized definition of remission in childhood asthma is still lacking, and prospective evidence confirming biologic-induced remission is absent. Establishing remission as a therapeutic goal could promote earlier, individualized interventions and long-term disease modification. Key priorities include defining optimal treatment duration, discontinuation criteria, and long-term safety. Global inequities in access persist due to variable regulatory and reimbursement frameworks. Multidisciplinary management and updated guidelines integrating precision tools, shared decision-making, and real-world monitoring are essential to optimize biologic therapy and ensure equitable, evidence-based care for all children with severe asthma.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

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Author contributions

AL: conceptualization, project administration. SFR: methodology. LEMA, FC, CC, MVM, MS: investigation, literature review, writing - original draft. GLM: data curation. SFR, AL: writing - review & editing. SFR, LEMA, FC, CC, MVM, MS, GLM, AL: visualization. GLM, AL: supervision.

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N/A.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All data reported are accurate and authentic.

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NARRATIVE REVIEW

Respiratory involvement in inflammatory bowel disease in children: a case-based narrative review

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ABSTRACT

Pediatric inflammatory bowel disease (IBD) is increasingly recognized as a systemic inflammatory disorder, although its respiratory manifestations remain frequently overlooked. While clinically apparent pulmonary involvement occurs in fewer than 1% of patients, subclinical abnormalities may affect up to 40% of children and adolescents with IBD. We present the case of a 15-year-old boy with Crohn's disease (CD) who developed chronic tracheobronchitis, highlighting the diagnostic challenges involved in distinguishing primary extraintestinal manifestations (EIMs) from treatment-related pulmonary toxicity and opportunistic infections. We also review the spectrum of respiratory involvement in pediatric IBD, in which airway disease and interstitial lung disease (ILD) may evolve independently of intestinal disease activity. Current evidence suggests that impulse oscillometry (IOS) and measurement of the diffusing capacity of the lung for carbon monoxide (DLCO) are more sensitive than conventional spirometry for the early detection of pulmonary abnormalities. A multidisciplinary approach combined with structured longitudinal follow-up is essential to ensure early diagnosis, individualized management, and prevention of long-term respiratory sequelae.

IMPACT STATEMENT

Pulmonary involvement in pediatric IBD is uncommon but probably underrecognized, with subclinical abnormalities occurring far more frequently than clinically overt disease. This narrative review highlights the central role of the gut-lung axis in the pathogenesis of respiratory involvement and emphasizes the value of sensitive functional assessments, including DLCO and IOS, for the early detection of pulmonary abnormalities. Greater clinical awareness and a multidisciplinary approach are essential to improve the timely diagnosis and management of these potentially irreversible EIMs in children and adolescents.

INTRODUCTION

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U), is a chronic immune-mediated inflammatory disorder with well-recognized systemic manifestations (1-3). The global incidence of pediatric IBD has increased steadily over recent decades, particularly in Europe and North America, and approximately one-quarter of all patients are diagnosed before 18 years of age (2, 4). Compared with adult-onset disease,

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KEY WORDS
Pediatric inflammatory bowel disease; pulmonary manifestations; extraintestinal manifestations; gut-lung axis; pulmonary function tests.

pediatric IBD presents unique clinical challenges, including impaired growth, delayed puberty (5), and a greater burden of extraintestinal manifestations (EIMs) (3, 4). Although EIMs affecting the skin, joints, eyes, and hepatobiliary system are well recognized, pulmonary manifestations (PMs) remain considerably underdiagnosed (6). Increasing evidence indicates that the gastrointestinal and respiratory tracts constitute a functionally integrated mucosal immune system linked through the gut-lung axis (4). Nevertheless, it remains uncertain whether pulmonary involvement represents a primary extraintestinal manifestation of IBD or results from immunosuppressive therapies or opportunistic infections (7). Distinguishing between these mechanisms is of major clinical importance because an incorrect diagnosis of drug-induced lung toxicity may lead to the unnecessary discontinuation of highly effective IBD treatments.

In this narrative review, we use a representative clinical case to discuss the spectrum of pulmonary involvement in pediatric IBD, focusing on current pathogenetic concepts, diagnostic challenges, and implications for clinical practice.

METHODS

A comprehensive literature search was performed using PubMed to identify relevant publications from January 1982 through April 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords, including “inflammatory bowel disease”, “Crohn’s disease”, “ulcerative colitis”, “pulmonary manifestations”, “extraintestinal manifestations”, and “gut-lung axis”, together with pediatric age-related filters.

Eligible studies included original research articles, systematic reviews, narrative reviews, and clinically relevant case series involving pediatric patients (<18 years of age). Only articles published in English were considered. Studies exclusively involving adult populations and conference abstracts without full-text availability were excluded.

CASE PRESENTATION

A 15-year-old boy with a one-year history of CD was followed at our institution for severe ileocolonic disease. Owing to persistent disease activity despite conventional therapy, he sequentially received mesalamine, azathioprine combined with systemic corticosteroids, methotrexate, and subsequently the anti-tumor necrosis factor (TNF) agent infliximab. Despite intensive medical treatment, his intestinal disease continued to progress, ultimately requiring surgical resection of the terminal ileum, cecum, and ascending colon. The postoperative course was initially uneventful.

Shortly after hospital discharge, the patient developed fever, sore throat, and symptoms consistent with acute bronchitis. Empirical treatment with azithromycin was prescribed by his primary care physician. Although the fever resolved promptly, a persistent productive cough prompted referral to our pediatric pulmonology clinic.

At presentation, the patient was afebrile, in no respiratory distress, and maintained an oxygen saturation of 98% while breathing room air. Chest auscultation revealed diffuse bilateral rhonchi with occasional wheezing. Laboratory investigations showed mildly elevated inflammatory markers. Spirometry demonstrated a mild obstructive ventilatory defect with significant bronchodilator responsiveness. Sputum culture yielded *Staphylococcus aureus*, while chest radiography showed bilateral hilar prominence with increased perihilar bronchovascular markings. Treatment with inhaled bronchodilators, airway clearance therapy, and targeted antibiotic therapy with amoxicillin-clavulanate resulted in partial clinical improvement; however, the productive cough persisted.

Given the persistence of respiratory symptoms, a comprehensive diagnostic workup was undertaken. Repeat pulmonary function testing demonstrated a mild restrictive ventilatory pattern, whereas bronchodilator responsiveness, fractional exhaled nitric oxide (FeNO), diffusing capacity of the lung for carbon monoxide (DLCO), and methacholine challenge testing were all within normal limits. Extensive investigations excluded alternative causes of chronic cough, including allergic disease, gastroesophageal reflux, primary immunodeficiency, cystic fibrosis, tuberculosis, and atypical respiratory infections.

High-resolution computed tomography (HRCT) of the chest demonstrated diffuse bronchial wall thickening with intraluminal mucus plugging but no evidence of bronchial stenosis, bronchiectasis, or parenchymal lung disease. Flexible bronchoscopy revealed diffusely inflamed tracheobronchial mucosa characterized by marked vascular congestion and abundant thick whitish secretions. Cytological analysis of bronchoalveolar lavage (BAL) fluid demonstrated a predominance of granulo-

cytes. Based on the combination of persistent respiratory symptoms, exclusion of infectious and alternative systemic causes, and characteristic bronchoscopic and radiological findings, chronic tracheobronchitis was diagnosed as an extraintestinal manifestation of CD. Treatment with inhaled corticosteroids resulted in complete resolution of respiratory symptoms and normalization of pulmonary function at follow-up.

A major diagnostic challenge was distinguishing persistent infection, drug-induced pulmonary toxicity, and a primary pulmonary extraintestinal manifestation of CD. The initial isolation of *Staphylococcus aureus* together with partial improvement following antibiotic therapy initially suggested prolonged bacterial tracheobronchitis. However, the persistence of symptoms despite appropriate antimicrobial treatment, the absence of radiological evidence of pneumonia or bronchiectasis, and the lack of sustained systemic inflammatory activity argued strongly against ongoing infection.

Drug-induced pulmonary toxicity was also carefully considered. Methotrexate-associated lung disease typically manifests as diffuse interstitial involvement with restrictive impairment accompanied by radiological infiltrates, none of which were observed in our patient. Likewise, pulmonary complications associated with anti-TNF therapy, including opportunistic infections, granulomatous disease, and hypersensitivity pneumonitis, were systematically excluded through microbiological, radiological, and bronchoscopic investigations. No imaging findings suggestive of interstitial lung disease (ILD) or pulmonary granulomatosis were identified.

The diagnosis of chronic tracheobronchitis as a pulmonary manifestation of IBD was ultimately supported by several converging findings: persistent productive cough despite adequate anti-infective therapy, bronchoscopic evidence of diffuse tracheobronchial inflammation with excessive airway secretions, exclusion of alternative etiologies, and rapid clinical response to inhaled corticosteroid therapy. Furthermore, the predominance of granulocytes in BAL fluid supported ongoing neutrophilic airway inflammation rather than persistent infection. Notably, respiratory symptoms developed during a period of severe, refractory intestinal disease requiring surgical intervention, consistent with previous observations that pulmonary EIMs may occur during periods of heightened systemic inflammatory activity.

Although chronic tracheobronchitis is a recognized pulmonary manifestation of IBD, pediatric cases remain exceedingly rare, particularly among patients receiving multiple immunomodulatory and biologic therapies. The principal strength of this case lies in the detailed diagnostic approach adopted to distinguish inflammatory airway disease from infectious and treatment-related pulmonary complications in an immunosuppressed adolescent. It also emphasizes the complementary role of bronchoscopy and HRCT in evaluating persistent respiratory symptoms, even in the absence of significant parenchymal abnormalities.

Overall, this case underscores the importance of considering pulmonary involvement in any child or adolescent with IBD who presents with persistent respiratory symptoms and illustrates the multidisciplinary diagnostic approach required to establish this uncommon but clinically significant extraintestinal manifestation.

Written informed consent for publication was obtained from the patient's parents before submission of this manuscript.

Pathophysiology: the gut-lung axis

The pathogenesis of PMs in IBD is complex and remains incompletely understood. Current evidence suggests that respiratory involvement results from the bidirectional immunological communication between the gastrointestinal and respiratory tracts, commonly referred to as the gut-lung axis (3, 8, 9). Although both organs originate from the primitive foregut during embryonic development, their relationship appears to be driven primarily by shared immune mechanisms rather than by their common embryological origin alone (10, 11).

Genetic susceptibility plays a pivotal role in this process. Variants in genes such as *NOD2*, *ATG16L1*, and *IL23R* predispose individuals to an exaggerated mucosal immune response and may increase susceptibility to EIMs (8, 12). Environmental factors, including intestinal dysbiosis, smoking, medications, and microbial exposures, may subsequently trigger immune activation in genetically susceptible individuals (3).

Disruption of the intestinal epithelial barrier facilitates the translocation of microbial products and inflammatory mediators into the systemic circulation, thereby influencing the pulmonary microenvironment (9). This mechanism may explain why subclinical pulmonary abnormali-

ties are frequently detected even during periods of gastrointestinal remission (9, 11).

The recruitment of inflammatory cells is believed to represent a key pathogenic mechanism. Neutrophils activated within the inflamed intestinal mucosa migrate into the bloodstream and accumulate within the pulmonary microvasculature, where they contribute to local tissue injury (3, 13). Likewise, gut-primed memory T lymphocytes may aberrantly home to the bronchus-associated lymphoid tissue (BALT) through chemokine-mediated trafficking involving receptors such as CCR4 and CCR6 (11). This process is amplified by a pro-inflammatory cytokine network dominated by tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, and the Th17/IL-17 pathway (3, 4).

Collectively, these mechanisms support the concept that the lung functions as an immunological extension of the intestine rather than as an independent target organ, providing the biological basis for pulmonary involvement in pediatric IBD (**Figure 1**).

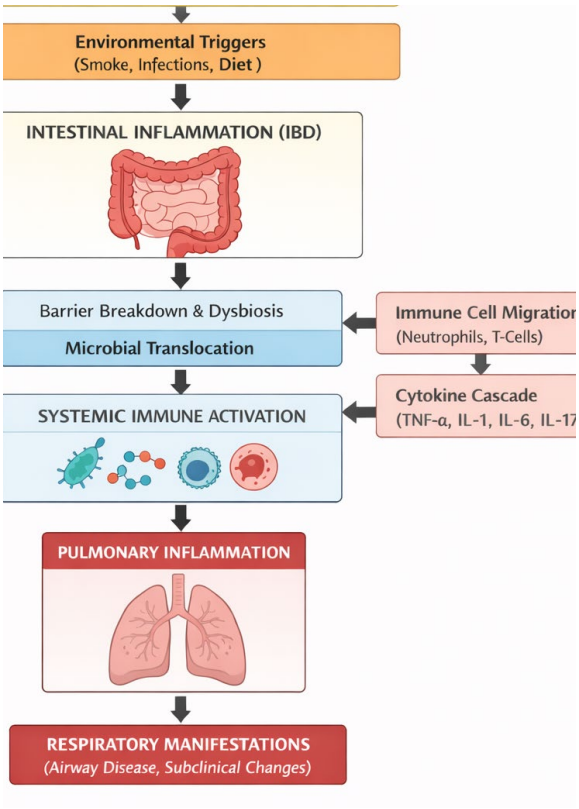

Figure 1. *Simplified model of gut-lung axis-mediated pulmonary involvement in pediatric IBD.*

Epidemiology

The reported prevalence of PMs in IBD varies considerably according to study design and diagnostic methodology. Clinically overt respiratory disease has traditionally been estimated to occur in fewer than 1% of patients. However, systematic screening using pulmonary function tests (PFTs) and high-resolution imaging has revealed subclinical pulmonary abnormalities in up to 40% of pediatric patients (4), indicating that respiratory involvement is substantially more common than previously recognized.

Importantly, prevalence estimates approaching 75% reported in some studies refer to the overall frequency of EIMs rather than to pulmonary disease specifically (14), and should therefore not be interpreted as reflecting respiratory involvement alone.

Children with pediatric-onset IBD appear to have a greater burden of EIMs than adults, possibly owing to longer cumulative disease duration, earlier immune dysregulation, and differences in disease phenotype (15). Although airway disease predominates in adults, particularly among patients with UC, available pediatric evidence suggests that CD is more frequently associated with interstitial pulmonary involvement (4, 15). Nevertheless, the rarity of pediatric cases and the predominance of retrospective studies continue to limit accurate estimates of disease prevalence and risk factors.

Spectrum of pulmonary manifestations and clinical presentation

Pulmonary involvement in pediatric IBD may affect virtually every anatomical component of the respiratory tract, including the upper airways, lower airways, lung parenchyma, pleura, and pulmonary vasculature (3, 5). Clinical presentation is highly heterogeneous, ranging from completely asymptomatic disease detected only through functional testing to severe, life-threatening respiratory failure (7).

The most common respiratory symptoms include chronic cough, dyspnea, wheezing, reduced exercise tolerance, sputum production, and, less frequently, chest pain or stridor (16). Importantly, respiratory manifestations often show little or no correlation with intestinal disease activity. Pulmonary involvement may precede the diagnosis of IBD, occur simultaneously with gastrointestinal symptoms, or develop years later despite complete intestinal

remission (7, 8). Consequently, clinicians should maintain a high index of suspicion whenever persistent respiratory symptoms occur in patients with established IBD. A substantial proportion of pediatric patients remain asymptomatic despite demonstrable abnormalities on pulmonary function testing or thoracic imaging (20). This silent clinical course contributes significantly to delayed diagnosis and probably explains why pulmonary involvement remains underrecognized in routine clinical practice. An additional diagnostic challenge is differentiating primary PMs of IBD from secondary pulmonary disorders related to immunosuppressive therapy, including opportunistic infections and drug-induced lung toxicity (16). This distinction has major therapeutic implications because inappropriate discontinuation of effective biologic therapy may adversely affect intestinal disease control.

Large-airway involvement includes chronic tracheobronchitis, chronic bronchitis, suppurative bronchitis, and glottic or subglottic stenosis (8). Bronchiectasis represents the most frequently reported structural airway abnormality, accounting for up to two-thirds of confirmed airway cases (21). Patients commonly present with productive cough, dyspnea, wheezing, excessive sputum production, or stridor. Because these symptoms frequently resemble asthma or recurrent respiratory infections, diagnosis may be delayed.

Persistent inflammation of the tracheobronchial tree may eventually result in irreversible structural remodeling, including fibrotic stenosis, airway webs, and fixed airflow obstruction. Early recognition is therefore essential to prevent permanent respiratory impairment.

Small-airway disease, including bronchiolitis obliterans and granulomatous bronchiolitis, usually follows a more insidious course. Patients often report only chronic dry cough or progressive exercise intolerance, while PFTs may reveal subtle abnormalities before overt symptoms become evident (8).

Parenchymal lung disease represents another important category of pulmonary involvement. Organizing pneumonia is the most frequently reported interstitial pattern, whereas nonspecific interstitial pneumonia, necrobiotic pulmonary nodules, eosinophilic pneumonia, pulmonary vasculitis, and diffuse alveolar damage occur less commonly (8, 22). Clinical presentation may include fever, progressive dyspnea, non-productive cough, pleuritic chest pain, hypoxemia, and, in severe cases, acute respiratory failure requiring hospitalization.

Less frequently, clinicians should also consider pleural disease, pulmonary thromboembolism, and the rare occurrence of enteropulmonary fistulas (19, 23). Although uncommon, these complications are poten-

Table 1. *Respiratory manifestations in pediatric inflammatory bowel disease.*

Respiratory site	Typical manifestations	Clinical presentation / symptoms	Subclinical findings	Notes / frequency
Large airways	Tracheobronchitis, chronic or suppurative bronchitis, glottic/ subglottic stenosis	Dyspnea, wheezing, productive cough, stridor, hoarseness	Airway narrowing detectable on imaging or bronchoscopy before symptoms	Bronchiectasis is common (up to 66% of cases); irreversible if untreated
Small airways	Bronchiolitis obliterans, granulomatous bronchiolitis	Non-specific dry cough, mild dyspnea, exercise intolerance	Reduced FEV1 or DLCO, subtle imaging changes	Often insidious; may remain asymptomatic for years
Lung parenchyma	Organizing pneumonia (OP), non-specific interstitial pneumonia (NSIP), necrobiotic nodules, pulmonary vasculitis	Fever, dyspnea, dry cough, chest pain, acute respiratory failure	Abnormal HRCT patterns, mild PFT changes	OP most common in children; other patterns rarer
Pleura	Pleural effusion	Chest pain, dyspnea	Often asymptomatic if small	Rare
Rare / severe complications	Thromboembolic events, enteric–pulmonary fistulas	Acute respiratory compromise, hypoxemia	N/A	Life-threatening; requires high clinical suspicion

DLCO: Diffusing capacity of the lung for carbon monoxide; FEV1: Forced expiratory volume in 1 second; HRCT: High-resolution computed tomography; NSIP: Non-specific interstitial pneumonia; OP: Organizing pneumonia; PFT: Pulmonary function tests.

tially life-threatening and require prompt recognition and multidisciplinary management.

A comprehensive overview of PMs associated with pediatric IBD is summarized in **Table 1**.

Management and prognosis

Management of PMs in pediatric IBD remains particularly challenging because of the absence of randomized controlled trials (RCTs). Consequently, current therapeutic strategies are largely extrapolated from adult studies or based on retrospective case series and expert opinion, resulting in a relatively low level of evidence (35). Corticosteroids remain the cornerstone of treatment and are effective in approximately two-thirds of reported cases (35). The choice between inhaled and systemic corticosteroids should be guided by the anatomical distribution and severity of pulmonary involvement (7). Inhaled corticosteroids are generally recommended for isolated airway disease, whereas systemic therapy is reserved for diffuse parenchymal or interstitial lung involvement (5). However, important pediatric-specific issues remain unresolved, particularly regarding the optimal duration of treatment and the minimum effective dosage required to prevent irreversible pulmonary damage while minimizing corticosteroid-related adverse effects in growing children. In patients with severe or refractory disease, biologic agents, particularly anti-TNF therapies such as infliximab, have expanded the available therapeutic options (5). Although infliximab has shown encouraging results in patients unresponsive to conventional treatment, evidence supporting its efficacy for PM remains limited to isolated pediatric case reports and small case series, as these agents are generally introduced to control intestinal disease rather than PMs (35, 36). A major therapeutic challenge arises from the dual role of anti-TNF agents: while they may successfully treat severe pulmonary inflammation, they have also been implicated in drug-induced ILD (37). Distinguishing between primary pulmonary involvement requiring treatment escalation and drug-related toxicity requiring treatment withdrawal therefore represents a critical step in clinical decision-making.

Macrolide antibiotics are frequently prescribed in patients with bronchiectasis complicated by chronic bacterial colonization (7). In addition to their antimicrobial activity, macrolides exert well-recognized immunomodulatory effects on neutrophilic airway inflammation, contributing to a reduction in exacerbation frequency and improvement in respiratory symptoms (38). Supportive interventions, including pulmonary rehabilitation and airway clearance techniques, should also be considered in symptomatic patients (39), although their long-term impact on disease progression has not yet been systematically evaluated in pediatric IBD.

One of the most debated aspects of management concerns the high prevalence of subclinical pulmonary involvement in children. Because respiratory abnormalities frequently remain asymptomatic, it is still unclear whether isolated functional alterations, such as a reduced diffusing capacity for carbon monoxide (DLCO), should prompt early pharmacological intervention to prevent irreversible pulmonary sequelae later in life (20, 24). This represents one of the major unresolved questions in pediatric clinical practice. Until stronger evidence becomes available, structured multidisciplinary follow-up combined with longitudinal assessment of pulmonary function should be regarded as an essential component of patient care to detect disease progression and preserve long-term respiratory health during the transition to adulthood (6, 40).

Future directions

Despite increasing recognition of PMs in pediatric IBD, substantial gaps remain in their early detection, pathophysiological understanding, and clinical management. Future research should prioritize the development of standardized screening strategies for children at increased risk, particularly those with persistent respiratory symptoms, severe intestinal inflammation, or prolonged disease duration.

The identification of reliable non-invasive biomarkers, including advanced pulmonary function parameters such as DLCO and impulse oscillometry (IOS), together with circulating inflammatory biomarkers, may facilitate the early detection of subclinical pulmonary involvement. Furthermore, additional prospective studies are required to better define the role of emerging imaging techniques, including lung magnetic resonance imaging (MRI) and low-dose HRCT, in longitudinal disease monitoring while minimizing cumulative radiation exposure.

A more comprehensive understanding of the immunological crosstalk between the gastrointestinal tract and the respiratory system may ultimately lead to novel therapeutic strategies. Targeted biologic therapies and pre-

cision medicine approaches directed at specific inflammatory pathways represent particularly promising areas for future investigation.

Finally, large prospective multicenter pediatric studies are urgently needed to clarify the natural history of PMs, identify predictors of disease progression, evaluate treatment efficacy, and define long-term respiratory outcomes in children with IBD.

CONCLUSIONS

PMs represent an uncommon but clinically significant extraintestinal complication of pediatric IBD and remain substantially underrecognized in routine clinical practice. As illustrated by the present case, respiratory involvement may evolve independently of intestinal disease activity and frequently presents with subtle or nonspecific symptoms, such as persistent cough, leading to delayed diagnosis.

From a clinical perspective, pediatricians should increasingly consider the lung as an immunologically integrated component of the gut-lung axis rather than an isolated organ. Persistent respiratory symptoms, even during periods of gastrointestinal remission, should prompt consideration of pulmonary involvement as an extraintestinal manifestation and warrant a structured diagnostic evaluation based on sensitive pulmonary function testing, particularly DLCO, complemented by targeted imaging and bronchoscopy whenever clinically indicated. Equally important is the careful differentiation between primary PMs and drug-induced pulmonary toxicity, as this distinction has major therapeutic implications and may prevent the unnecessary discontinuation of highly effective IBD therapies.

Ultimately, greater awareness among pediatric gastroenterologists, pulmonologists, and general pediatricians, together with a multidisciplinary approach and structured longitudinal follow-up, will be essential to optimize individualized patient management, facilitate early diagnosis, and reduce the risk of irreversible long-term pulmonary sequelae.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

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Author contributions

CC, IP: conceptualization, formal analysis, data curation, writing – original draft. AA, IP: methodology, supervision. AA, IP, ZM: validation, writing – review & editing. CC, IP, AA, ZM: investigation. IP, ZM: visualization. AA: project administration.

Ethical approval

Human studies and subjects

Specific ethical approval was not required for this case report in accordance with institutional guidelines.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All data reported are accurate and authentic.

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CASE REPORT

Pulmonary involvement with immunodeficiency: the role of CTLA-4 in the pathogenesis of granulomatous lymphocytic interstitial lung disease (GLILD) - an Italian case report

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ABSTRACT

We present the case of a 14-year-old female patient who was referred to us in 2024 due to coughing, widespread dermatitis and frequent episodes of diarrhea. Her medical history included atopic dermatitis in childhood. Initial blood tests and diagnostic tests revealed autoimmune hemolytic anemia, widespread lymphadenopathy and splenomegaly. Further diagnostic investigations revealed rounded pulmonary opacities on chest X-ray, so second-level diagnostic tests were performed, which revealed the presence of a mutation in the CTLA-4 gene on genetic analysis, suggesting a form of primary immunodeficiency, leading to a diagnosis of GLILD. Treatment initially involved corticosteroid therapy and the administration of intravenous immunoglobulins. The therapeutic breakthrough came with the introduction of biological therapy with abatacept, a CTLA-4 signal modulator, which led to remission of the disease.

IMPACT STATEMENT

This case highlights the importance of differential diagnosis and multidisciplinary collaboration in the management of GLILD, offering a superior strategy compared to traditional corticosteroid-based management. Early adoption of targeted biological interventions is essential to halt disease progression, preventing the development of irreversible pulmonary fibrosis and reducing treatment-related morbidity, thereby improving long-term survival and quality of life for patients with CVID or CVID-like disorders.

INTRODUCTION

GLILD is defined as a clinical-radiological-pathological entity characterized by the presence of granulomatous inflammation and/or lymphocytic infiltrates in the lung parenchyma (1). Histologically, it presents a spectrum of extremely heterogeneous lymphoproliferative patterns, including follicular bronchiolitis and lymphoid interstitial pneumonia (LIP), which are often associated with multisystem involvement such as splenomegaly and lymphadenopathy (2). The precise pathogenic mechanisms driving this pulmonary lymphoproliferation remain only partially understood. Recent advances in genetic screening have identified a subgroup of CVID or CVID-like disorder phenotypes caused by specific monogenic defects, including

KEY WORDS
Case report; GLILD; immunodeficiency.

alterations in the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene. CTLA-4 acts as a key negative immune regulator that maintains self-tolerance by competing with the costimulatory receptor CD28 for ligands on antigen-presenting cells. By removing these ligands via transendocytosis, CTLA-4 effectively suppresses excessive T cell activation and proliferation (3)

Heterozygous germline mutations leading to CTLA-4 haploinsufficiency result in a complex syndrome of immune dysregulation where T-cell homeostasis is severely disrupted (3). In these patients, the lack of effective T-cell checkpoint control facilitates the accumulation of activated lymphocytes in various organs, with the lungs being a primary target. Consequently, GLILD has become one of the signature clinical features of CTLA-4 deficiency, representing the pulmonary manifestation of a broader, systemic lymphoproliferative process driven by uncontrolled T-cell signaling (2).

The granulomatous-lymphocytic interstitial lung disease (GLILD) is a particularly severe manifestation, occurring in approximately 8% to 30% of CVID patients. Common variable immunodeficiency (CVID) is the most frequent clinically significant primary immunodeficiency in adults, historically characterized by hypogammaglobulinemia and an increased susceptibility to recurrent infections (2).

The clinical characteristics of the disease are extremely variable and include a range of symptoms starting with asthenia and possibly associated with pulmonary symptoms such as coughing and dyspnea, although in some cases the disease may be asymptomatic.

The aim of this clinical case is to highlight how varied and subtle the symptoms of this condition can be and how a multidisciplinary approach is essential to reach a diagnosis.

The objective of the discussion of this case is to highlight how immune dysregulation can be closely associated with pulmonary diseases and should therefore always be taken into consideration in order to increase awareness of the existence of the disease and improve its clinical recognition, thereby optimizing diagnostic and therapeutic strategies for affected patients.

CASE PRESENTATION

We present the case of a 14-year-old female patient. Born at term following a normal pregnancy. Neuropsychomotor development was adequate. Atopic dermatitis reported in childhood. No previous surgery, no hospital admissions, no significant infectious episodes reported.

In October 2023, a gastroenterological evaluation was performed for diarrhea lasting about a year and dermatitis. Blood tests were performed and the results were normal. Stool culture and parasitological tests were negative, while a slight increase in fecal calprotectin was found (59 µg, normal value < 50) and the fecal occult blood test was positive in 3 samples.

To rule out chronic inflammatory bowel disease, an abdominal ultrasound with loop study was performed in November 2023, revealing the following findings: Spleen 12 cm at upper limits (vn < 12cm), liver and bile ducts normal, no thickening of the last ileal loop.

In May 2024, the patient underwent a hematological assessment at our center to follow up on blood tests relating to autoimmune hemolytic anemia, which had been detected 20 days earlier but not subsequently confirmed. The examination revealed widespread lymphadenopathy, splenomegaly (stable compared to previous check); no weight loss.

Blood tests showed:

- Complete blood count: GB 7,700/mmc, Hb 8.8 g/dl, MCV 106.2 fl, PLT 295,000/mmc.
- Immunological tests: Coombs test: indirect/direct positive, presence of warm IgG antibodies, IgG 594 mg (slightly below normal), IgA 49 mg/dl, IgM 28 mg/dl. Blood group 0 Rh positive with anti-A and anti-B isohemagglutinins present; Tetanus antibodies doubtful.
- Various tests: Total bilirubin 2.15 mg/dl (indirect 1.44 mg/dl) LDH 669 U/L.
- Urine test normal and fecal occult blood negative; Calprotectin negative.

In October 2024, the patient was referred to us due to a dry, persistent cough, widespread dermatitis and frequent bouts of diarrhea. Respiratory function tests, such as spirometry and FeNo, were performed, with normal results.

To identify the cause of the cough more accurately, a chest X-ray was taken around 15 days later, revealing round opacities with a maximum projected diameter of approximately:

- 12 mm in the upper right field.
- 11 mm in the right basal area.
- 15 mm in the left basal area.

No pleural effusion. Cardio-mediastinal image within normal limits.

Suspecting a lymphoproliferative or metastatic process, advanced imaging tests were performed.

Second-level blood tests revealed hypogammaglobulinemia, with selective IgG2 deficiency: IgG2 38 (vn 106-610). Lymphocyte typing revealed humoral immune dysregulation.

To rule out an infectious cause, a number of serological tests were carried out on blood and stool samples, screening for the main potential infectious agents responsible for the condition, including EBV, CMV and parvovirus; all results were consistent with a previous infection.

In November 2024, due to persistent dermatitis, several skin biopsies were performed, which revealed spongiotic-eczematous dermatitis on histological examination.

From a hematological perspective, a bone marrow biopsy was also performed in November 2024, which revealed signs of macrocytosis and dyserythropoiesis, consistent with the hemolysis reported in the patient's medical history. Mild hyperplasia of megakaryocytes, of variable size, without significant atypia.

The lymphoid series consisted of cells with both T (CD3+) and B (CD20+) phenotypes, accounting for a total of approximately 15-20%, scattered throughout the interstitium and focally in centrilacunar follicular-type aggregates, likely reactive, to be correlated with the phenotypic data from flow cytometry. The bone marrow smear, on the other hand, revealed a hypercellular marrow with hyperplasia of the erythroid and megakaryocytic series, in the absence of morphological changes suggestive of MDS.

In December 2024, in order to investigate the radiological findings seen on chest X-ray, we performed a CT scan of the chest and mediastinum, which revealed lymphadenopathy in the hilo-mediastinal region, the largest and confluent in the subcarinal region – right hilar and para-aortic. Enlarged lymph nodes were also found in the lateral cervical region, the largest on the left measuring approximately 2 × 1.3 cm. Multiple lymphadenopathy was found in the axillary region bilaterally, some rounded, with a maximum short axis of approximately 1.3 cm and smaller in the pectoral region.

Multiple bilateral central and peripheral parenchymal thickening, the most numerous and largest in the lower lobes (1.5 cm - 2 cm), in the basal segments of the LID tending to converge, but still widely recognizable, and some with a rounded morphology, these more evident in the LSD and LM.

It was not possible to perform a diagnostic bronchoscopy with bronchoalveolar lavage as the patient's parents refused the procedure due to its invasive nature.

To complete the diagnosis, the same month an MRI scan of the brain was also performed, which was normal, and a CT scan of the abdomen confirmed splenomegaly (bipolar diameter of approximately 15 cm), with minute parenchymal hypodensities, and lymphadenopathy of approximately 1 cm was reported in the perihilar hepatic region – interportal-caval region, also recognizable in the para-aorto-caval retroperitoneal region, in the mesenteric region and in the bilateral inguinal region.

In January 2025, as part of the diagnostic tests, a PET scan was also carried out, which described a hypermetabolic state in several mediastinal and extra-thoracic lymphnode districts and also highlighted numerous hypermetabolic areas with a nodular pattern in the lungs, with a prevalence in the lower lobes bilaterally. Areas of altered hyperperception were also described in other body regions such as the spleen, caecum, ascending colon, rectum, and last portion of the sigmoid colon.

In February 2025, we finally received the results of the genetic test, which revealed the presence of the NM_005214.5c.439A>G mutation in the CTLA-4 gene, suggesting a form of primary immunodeficiency, leading to a diagnosis of GLILD.

The patient's treatment initially involved the use of immunoglobulins due to her hypoglobulinemia, but this proved to be of little benefit. Oral steroid therapy was therefore initiated, resulting in partial clinical and radiological remission. The therapy we used was Prednisone at 1 mg/kg. Steroid therapy induced partial remission of the disease, with subsequent relapse, so we switched to a biological drug, abatacept.

We opted to administer abatacept subcutaneously, at a dose of 125 mg per week, for a period determined by the patient's clinical response.

Its main role is as a targeted therapy for patients with specific genetic defects, particularly CTLA-4 or LRBA deficiency. The use of abatacept allowed for a gradual reduction in oral steroid therapy, leading to a marked reduction in pulmonary thickening, until almost complete regression.

DISCUSSION

We present a clinical case of GLILD in a 14-year-old female patient with no suggestive clinical history of infections, significant respiratory symptoms and a negative family history of immunodeficiency.

The variant identified in our patient, who is responsible for the condition GLILD), is the CTLA-4 c.439A>G (NM_005214.5) variant is a recurrent pathogenic missense mutation that causes CTLA-4 haploinsufficiency, an autosomal dominant immune dysregulation syndrome with incomplete penetrance. Even within the same family carrying identical mutations, clinical manifestations vary dramatically from asymptomatic carriers to severe disease This mutation results in decreased CTLA-4 protein expression in regulatory T cells (Tregs), impaired transendocytosis of CD80/CD86 molecules, a key functional mechanism of CTLA-4. CTLA-4 haploinsufficiency causes a complex immune dysregulation syndrome characterized by both immunodeficiency and autoimmunity, which determines Hypogammaglobulinemia, Lymphoproliferation, autoimmune cytopenias, respiratory manifestations, such as recurrent infections, interstitial lung disease, lymphocytic infiltration. This condition can also lead to gastrointestinal and neurological involvement (9).

The diagnosis, clinical management and treatment of granulomatous lymphocytic interstitial lung disease (GLILD) represent one of the most significant challenges in the care of patients with common variable immunodeficiency (CVID) and non-CVID (4).

The management of infectious complications currently involves replacement therapy with immunoglobulins (IgRT) as a therapeutic strategy. The clinical manifestations that currently emerge as the primary causes of morbidity and reduced life expectancy are non-infectious manifestations caused by immune dysregulation (1-5).

A critical aspect of GLILD is its often insidious and asymptomatic onset (1). Symptoms, when present, are often non-specific, frequently manifesting as coughing and exertional dyspnea, and are not always correlated with the severity of lung parenchyma involvement, making the condition very difficult to diagnose (6).

The above is confirmed in the case of our patient, whose respiratory symptoms were very mild, manifesting only as a dry cough, with respiratory function tests, such as spirometry and FeNo, remaining consistently negative.

Diagnostically, High-Resolution Computed Tomography (HRCT) is the gold standard for detection, typically revealing a lower-lobe predominant pattern of nodules, ground-glass opacities, and interlobular septal thickening (2).

Respiratory function tests, on the other hand, could show a restrictive pattern with reduced DLCO in the presence of pulmonary manifestations.

Furthermore, GLILD should not be considered an isolated lung disease, but rather a component of a multisystemic lymphoproliferative process. The clinical manifestations of our patient are consistent with the literature, which suggests a strong correlation between GLILD and extrapulmonary features such as splenomegaly, generalized lymphadenopathy, and autoimmune cytopenia (7).

Perhaps the most interesting aspect of the clinical management of this disease is the recent possibility of introducing biological drugs. Initial treatment with immunoglobulins and oral corticosteroids may represent a first therapeutic approach, but it is often associated with relapses. The use of biological therapy with abatacept (CTLA-4-Ig) has become an innovative and fundamental strategy for patients with specific monogenic defects that overlap with the CVID phenotype, particularly CTLA-4 haploinsufficiency and LRBA deficiency (1). Abatacept acts as a soluble CTLA-4 mimic, binding these ligands and effectively suppressing excessive T-cell activation and proliferation.

In our case, the introduction of abatacept therapy enabled us to discontinue oral steroid treatment, resulting in a subjective clinical and radiological improvement.

CONCLUSIONS

In conclusion, the management of granulomatous-lymphocytic interstitial lung disease (GLILD) represents one of the most difficult clinical challenges, especially in the context of common variable immunodeficiency. As current evidence shows, this condition can no longer be considered an entity limited exclusively to the lung, but must be interpreted as the visible manifestation of a lymphoproliferative and multisystemic process driven by profound immune dysregulation. The wide clinical and radiological variability underscores the need for a multidisciplinary approach that integrates clinical, immunological and genetic data.

The future of treatment is moving away from the exclusive use of steroid therapy, which, although effective in induc-

ing initial remission, is associated with frequent relapses. The introduction of biological therapies marks a decisive shift towards precision medicine. The use of rituximab in combination with antimetabolites has already demonstrated a superior ability to ensure lasting remissions and improve lung function compared to standard therapies. Even more promising is the use of targeted agents such as abatacept, which acts as a selective modulator of T cell co-stimulation, providing a great therapeutic alternative. Early identification of genetic and immunological biomarkers will be key to personalizing treatment. Personalized therapeutic management will therefore be useful in preventing irreversible parenchymal damage and fibrosis, significantly improving the survival and quality of life of patients affected by this disease.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

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Author contributions

The authors contributed equally to the work.

Ethical approval

Human studies and subjects

This case report was determined to not require Ethics Committee review.

Data sharing and data accessibility

The respiratory sound database is not available for researchers.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All data reported are accurate and authentic.

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OBITUARY

In memory of Professor Roberto Ronchetti

Professor Roberto Ronchetti was a true master of Pediatrics and Pediatric Pulmonology.

He was our mentor, as well as the mentor of many colleagues who trained in the Fourth Chair of Pediatric Medicine at Sapienza University of Rome, which he directed for many years.

His scientific interests in pediatric pulmonology were remarkably broad, encompassing nuclear medicine with ventilation-perfusion lung scintigraphy, respiratory physiology, respiratory physiotherapy, sleep medicine and long-term ventilation, rare respiratory diseases, congenital malformations of the respiratory tract, and infectious respiratory diseases, foremost among them bronchiolitis caused by Respiratory Syncytial Virus (RSV). Bronchial asthma and recurrent wheezing were also major areas of research within his school, leading to numerous influential publications, including pioneering work on asthma self-management.

In the later years of his professional career, he turned his attention to one of the greatest emerging challenges to children's health: the impact of environmental pollution and environmental change.

Professor Ronchetti was one of the founders of the European Pediatric Respiratory Society (EPRS), which later became part of the European Respiratory Society (ERS). He encouraged nearly all of his trainees to spend time in leading research centers in the United States, Canada, the United Kingdom, and France. He also established long-standing collaborative projects with Poland, particularly with the Mother and Child Health Center in Rabka. He founded the Pediatric Bronchopneumology Study Group within the Italian Society of Pediatrics, bringing together the country's leading experts in the field. The group developed some of the first national consensus statements in pediatric pulmonology, addressing topics such as oxygen therapy, aerosol therapy, and the treatment of childhood asthma. This initiative played a fundamental role in establishing modern pediatric pulmonology and promoting its development throughout Italy.

When we trained in his department, inhaled salbutamol – now universally recommended by international guidelines – was still rarely used. His determination to promote its use by inhalation was instrumental in changing clinical practice.

His intellectual curiosity constantly drove him to explore new frontiers. He recognized the potential of lung ultrasound at a time when its application was still considered pioneering. He promoted pulmonary function testing in infants, advanced the use of cardiopulmonary exercise testing, and fostered the development of pediatric bronchoscopy and bronchoalveolar lavage analysis, techniques that are now standard practice but were then available in only a few specialized centers. As early as the late 1980s, he also encouraged the application of molecular biology techniques to pediatric respiratory medicine.

The results of his research were published in more than 300 international scientific papers.

On a personal level, much of what we have been able to achieve in our own institutions stems directly from his visionary ideas. We particularly remember his articles describing the pediatric wards of the future: units designed to care for children with acute and chronic respiratory failure, equipped with dedicated respiratory technology, non-invasive monitoring, long-term ventilation facilities, and, above all, highly trained physicians and nurses. Today, these concepts have become reality in Pediatric Intermediate Respiratory Care Units. Likewise, his early vision in sleep medicine ultimately led to the development of specialized services for pediatric sleep disorders and long-term ventilation.

Many of his former trainees have gone on to hold leading academic and clinical positions in Italy and abroad. Regardless of where their careers have taken them – in universities, hospitals, or community practice – they all bear witness to the remarkable medical school that Professor Roberto Ronchetti created.

Yet, beyond all his scientific achievements, the greatest lesson he taught us was a way of thinking. He encouraged us always to ask *why*; never to stop at appearances or accept unquestioningly what everyone else considered established truth; always to look beyond the obvious.

In one of his autobiographical works, published by the Italian Society of Pediatrics, Professor Ronchetti imagined a dialogue with Albert Einstein about life.
It is therefore fitting that we remember our mentor with one of Einstein's most celebrated reflections:

"*Everybody knows that something is impossible. Then someone comes along who doesn't know that…and does it.*"

Thank you, Professor.

All your pupils from Italy and abroad

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