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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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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).

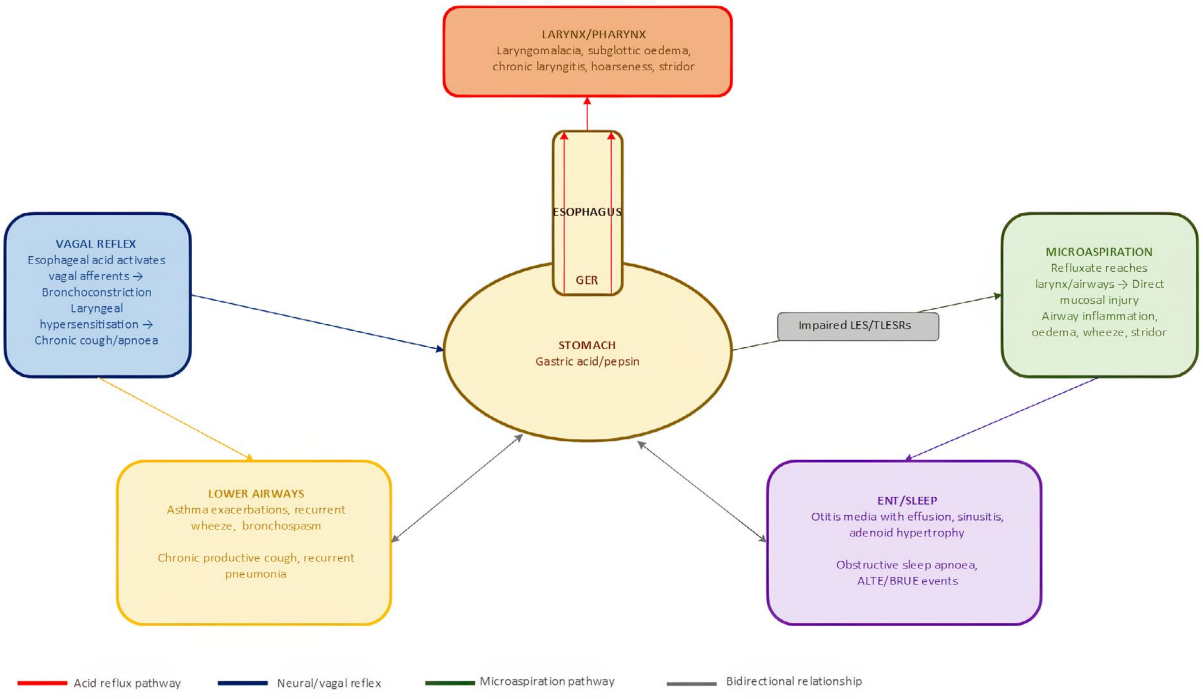

Figure 1. *Schematic overview of the main pathophysiological mechanisms linking gastro-esophageal reflux to respiratory symptoms in children.*

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

Conflicts of interest

The authors declare no conflicts of interest.

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Author contributions

IP: conceptualization. IP, IH: writing - original draft. AMP, BO: writing - review & editing. IP, IH, AMP, BO: validation.

Ethical approval

Human studies and subjects

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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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