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Treatment and Management of Chronic Cough in Children

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Background

Chronic cough (CC) in children is common and most often post-viral in nature. CC in children should be comprehensively evaluated and the underlying etiology treated to prevent irreversible lung damage. Refractory chronic cough (RCC) is proposed as a distinct clinical entity in children, which is defined by a persistent cough that does not resolve after comprehensive evaluation and adherence to systematic, guideline-based treatments. RCC may involve a heightened cough reflex sensitivity or altered neural regulation influenced by genetic, environmental, or immunologic factors. This review focuses on the definition, diagnostic approach, and evidence-based management of pediatric RCC, emphasizing the need for a multidisciplinary approach and highlighting research gaps for future targeted therapies.

Definition

Chronic cough (CC) in children is a distinct clinical entity that is defined by most expert panels as a daily cough that persists for more than 4 weeks in children 14 years or younger.[1-3] This 4-week cut-off aims to ensure that all children are universally and comprehensively assessed in a timely manner, minimizing the risk of progression to serious conditions while preventing respiratory morbidity.[4] *For the purposes of this review, chronic cough will be defined as a daily cough that lasts for longer than 4 weeks.*

CC is categorized into specific and non-specific types. Specific CC is cough accompanied by additional symptoms or signs indicative of an associated or underlying condition.[1] Non-specific CC describes a dry cough that occurs in children who otherwise appear well and do not seem to have a serious underlying disorder.[5] A non-specific CC is more likely to resolve without medications.[6]

Refractory chronic cough (RCC) is defined in adults as a persistent cough that does not resolve despite comprehensive evaluation and systematic, guideline-based trials of empiric treatments for causes of cough-associated conditions or traits.[2] In children, however, RCC has not been formally defined as a clinical entity. However, we propose that RCC in children is similarly defined as a persistent CC that does not resolve after a comprehensive evaluation and systematic, guideline-based trials of empiric treatment for cough-associated conditions or traits. RCC can be considered an overlapping entity with both specific CC and non-specific CC.

Epidemiology

The global prevalence of CC in children, particularly RCC, is not clearly defined. The estimated prevalence rates range from 1.1% to 21.9%. The methods of data collection, definition of chronic cough used, socio-economic status, culture and country of origin, under- and over- reporting age of the child, and the study setting are factors impacting the observed differences.[7] CC presents a significant burden not only to children but also to their families, causing significant distress to parents.[8] CC impacts children's daily activities, sleep, school performance, and social participation, and causes feelings of annoyance, discomfort, frustration, and embarrassment in children. CC imparts a high toll on health service utilization because of increased visits to primary care providers and specialist care providers. Furthermore, CC is associated with multiple clinic visits and inappropriate antibiotic use,[9] as well as overuse of over the counter (OTC) medications,[10] which can lead to toxicity.[11]

Etiology

Understanding the underlying causes of CC in children is essential for guiding appropriate management and treatment, especially because the causes of CC in children differ significantly from those in adults due to the unique respiratory physiology of prepubertal children compared to adults.[12] The child's age, country, and region must also be considered.[12] The etiology of CC also varies depending on whether the child is evaluated in a primary care setting, by a specialist, the type of specialist, or a team of specialists **(Table 1)**. In family practice and primary care settings in Westernized countries, the most common causes of CC include post-viral, respiratory tract infections, asthma, and pertussis.[13] These causes differ from those frequently identified in subspecialty clinics (e.g., pediatrics, pulmonology, allergy, and otolaryngology), where asthma or asthma-like conditions, protracted bacterial bronchitis (PBB), and natural resolution (no specific diagnosis) predominate.[12] In this setting, post-nasal drip and gastroesophageal reflux disease (GERD) are not commonly reported. This is in stark contrast to an exclusive pediatric otolaryngology setting where GERD is one of the common causes of CC in children. Children with CC presenting to a pediatric respirologist in a tertiary care centre will most likely have PBB.[14]

In children with refractory CC, the underlying cause may be more elusive and require comprehensive evaluation and targeted investigations to identify and address it effectively. This may include advanced imaging studies, specialized laboratory tests, or referrals to subspecialists for interdisciplinary assessment. Furthermore, there is data on the role of triple endoscopy in diagnosing the reason for CC in children.[15] Among 240 children (median age of 2 years), some of the diagnoses include laryngeal clefts, tracheoesophageal fistula (congenital or acquired), eosinophilic esophagitis, GERD, chronic aspiration in children with neuromuscular disorders, and congenital syndromes or genetic abnormalities (e.g., Trisomy 21, cystic fibrosis, immunodeficiencies).[15] It is also probable that a subset of children with chronic wet cough, including those with chronic suppurative lung disease of unknown etiology, remain unrecognized in the literature as having RCC, resulting in limited available data.

Pathophysiology

Cough is typically triggered by an irritant stimulus in the airway leading to activation of the airway mucosal sensory fibres. A signal is then transmitted to the brainstem circuitry, which modifies the normal breathing cycle into a cough specific pattern.[7] The maturation of the neuronal circuits is demonstrated as age-related alterations in the sensitivity of the cough reflex in infants and young children, as well as sex-related differences that become apparent in adolescence.[17] In essence, children may have a more sensitive cough reflex that is more easily activated due to ongoing neural development and heightened activity of neuromodulators such as substance P and neuropeptides, resulting in an exaggerated response.[17]

Different stimuli such as viral infections or inflammatory mediators can increase the physiologic cough reflex, possibly inducing plasticity in the neural pathways associated with coughing, leading to the persistence of cough even after the pathogenic trigger has been resolved.[18] However, there is limited data on the pathophysiology or natural history of post-viral cough, which is the most common cause of CC in children in the community beyond 25 days.[19] Possibly, children with RCC represent a subset of individuals with heightened cough reflex sensitivity or altered neural pathway regulation, making them more prone to persistent cough even after the resolution of the initial trigger. Understanding these mechanisms may help identify children at risk for recurrent or CC and guide targeted therapeutic approaches to improve outcomes. Further research is needed to elucidate the pathophysiology and natural history of post-viral and recurrent CC in children, especially to differentiate those with self-limiting conditions from those requiring medical intervention.

Diagnostic Approach

The evaluation of CC in children begins with a thorough history and physical exam with the goal of characterizing the cough as either specific or non-specific.[1] Initial investigations include a chest radiograph and spirometry (where age-appropriate).[4] Although both investigations lack sensitivity, their specificity is high, as abnormal findings strongly indicate underlying pathology.[20] Advanced diagnostic techniques such as CT imaging or bronchoscopy

Specialist/Clinical Setting	Etiology of Chronic Cough	Comments
Family practice and primary care[13]	Respiratory tract infections Asthma Pertussis	Systematic review; low methodological quality of individual articles
Pediatrics, Pulmonology, Allergy, Otolaryngology[12]	Asthma/Asthma-like conditions Protracted bacterial bronchitis Natural resolution without specific cause	Systematic review; significant difference in quality of studies used (e.g., rural vs urban)
Otolaryngology[16]	Upper respiratory infection Airway hyperreactivity GERD	Retrospective study; small sample size; limited to otolaryngology settings
Pediatric Pulmonology[14]	Post-acute respiratory illness Protracted bacterial bronchitis	Prospective; focused on post-acute illness; limited generalizability to non-acute settings

Table 1. Etiology of Chronic Cough is dependent on the clinical care setting; *courtesy of Tristan Henry, MBBS and Anya McLaren, MD, MSc, FRCPC*
Abbreviations: GERD: gastroesophageal reflux disease

are reserved for cases where initial evaluations are incomplete.[4] Triple endoscopy performed by an aerodigestive team can identify structural or functional abnormalities in RCC cases, reducing the need for multiple sedations. Routine tests such as the skin prick test, Mantoux test, Bordetella pertussis testing, or GERD studies should only be performed if clinically indicated.[4] The use of CC management protocols/algorithms improves outcomes in children under 15 years of age and is recommended despite the severity of the cough.[4] As the CHEST guideline provides the highest level of evidence for the optimal pathway, it is the approach discussed here.[1] Furthermore, the protocol algorithm can eliminate the inappropriate use of OTC medications, antibiotics, proton pump inhibitors, corticosteroid metered-dose inhalers, and unnecessary investigations for children with chronic non-specific cough.[4]

Management

General principles

For all CC cases, environmental factors that could exacerbate cough, such as tobacco smoke exposure, should be taken into consideration. Testing such as the skin prick test, Mantoux test, Bordetella pertussis testing, bronchoscopy, and chest CT should not be routinely performed. Instead, testing should be individualized based on the clinical setting.[4] An empiric approach to treating post-nasal drip, GERD, and/or asthma is not recommended unless other features consistent with these conditions are present.

Oftentimes, the primary concern of families may not be the cough itself, but rather the associated consequences, such as sleep disturbances, daytime drowsiness, and the impact on school, work, and overall quality of life. Adopting a shared decision-making approach and collaboratively defining goals can enhance the patient-caregiver relationship and improve outcomes.[4]

In children who present with a wet or productive CC in the absence of an underlying disease and without any cough specific pointers, a 2-week course of antibiotics targeting common respiratory bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) should be trialled. If there is resolution with the antibiotic course, a diagnosis of PBB is appropriate.[4] Treatment of CC in children should be targeted to the underlying etiology. As most non-specific CC is post-viral, a watchful waiting period with re-evaluation in a few weeks is acceptable.[12] Beyond a period of 2-4 weeks, the child should be re-evaluated for the emergence of specific etiological pointers.[4] If asthma is suspected, an assessment of airway hyper-responsiveness should be undertaken. If there are risk factors for asthma in a child with CC, a

short (2-4 weeks) trial of inhaled corticosteroid may be considered. A defined trial of therapy is often attempted for non-specific CC such as a 2–4-week period with the plan to evaluate for the emergence of specific pointers to an underlying cause.[4]

Empirically treating conditions such as upper airway syndrome, GERD, and/or asthma without the presence of signs and symptoms consistent with these conditions is not recommended.[4] Antihistamines have not shown significant benefit, and while cetirizine showed benefit over placebo in a relatively small randomized controlled trial, this benefit was only observed in patients with seasonal allergies.[21] Honey has been shown to be of more benefit in relieving symptoms of cough compared to no intervention, diphenhydramine, or placebo, making it a better alternative than antihistamines that do not include dextromethorphan.[21] Further research is needed to understand if there is a role for dextromethorphan and other neuromodulators in the treatment of CC.

A detailed review of the treatment of specific CC based on underlying etiology is outlined in the CHEST guidelines.[4] For the other specific cough syndromes, their investigation and management should be tailored to the specific etiologies which are beyond the scope of this review.

Refractory Chronic Cough (RCC)

Mukerji et al recommend triple endoscopy conducted by an aerodigestive team for patients with problematic and persistent CC after the appropriate management.[15] This triple endoscopy includes direct laryngoscopy conducted by ENT, flexible bronchoscopy conducted by a pulmonologist, and upper gastrointestinal endoscopy conducted by a gastroenterologist, all completed at one sitting, which may lead to an earlier diagnosis without the need for multiple sedations for different procedures and a possible cost-saving benefit. In one study that employed triple endoscopy for RCC, 83.5% of the cohort had at least one abnormal finding, while 42% had abnormalities that involved at least 2 of the 3 subspecialities of the aerodigestive team.[15]

Invariably, there remains a subset of patients with CC who, after a thorough history and appropriate extensive investigations, remain symptomatic with an undefined etiology. These patients are classified as having unexplained CC. These patients will require having pointed conversations with specialist providers that consider how the cough is affecting their quality of life. If there is no significant impact on quality of life, a watch and wait approach may be appropriate. Two European-wide studies conducted in adults reported unsatisfactory or limited satisfaction with the care of RCC, with rates of 57% and 32% respectively.[22] This has led to several studies in adults to assess interventions including cough-directed physiotherapy and speech and language interventions, the use of neuromodulators, older drugs such as opioids and gabapentin/pregabalin,[2] as well as newer drugs including P2X3 and P2X2/3 receptor antagonists (e.g., gefapixant, eliapixant, among others).[22] While these interventions have shown promise in adults, their external validity is limited, and there are no trials involving children for any of these interventions. These, along with other applicable interventions, will form the basis for further inquiry and evaluation for managing RCC in children.

Emerging Therapies and Future Directions

While long-term azithromycin is commonly used for chronic wet cough owing to its anti-inflammatory properties, the role of this therapy in other types of RCC is unclear.[23] Neuromodulators and targeted therapies such as P2X3 inhibitors (e.g., gefapixant) are promising but lack pediatric-specific data.[24] Research into biomarkers, genetic predispositions, and neural plasticity could refine diagnostic criteria and guide personalized treatments. Global or multicenter studies are needed to establish standardized definitions and management strategies for RCC in children.

Summary

Pediatric CC is a common condition that affects both the child and their family. Extensive research on this subject has resulted in expert panel guidelines for its management. The population of children with RCC is less well-defined, and there remains much to be understood about its underlying mechanisms and optimal management strategies. In most cases, the etiology of CC in children can be identified through thorough investigations and appropriate treatments. A comprehensive understanding of the diverse etiologies of CC in children, tailored to their unique physiology, age, clinical setting, and regional context, is essential for guiding effective diagnoses and management strategies. The above

review may assist community MDs to investigate and treat pediatric CC to minimize morbidity and improve quality of life for child and family. Further research is needed to define the population of children with RCC and to develop approaches to care, to optimize outcomes and improve care for this complex and heterogeneous population.

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