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Chronic cough in preschool children

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ABSTRACT

Cough may be the first overt sign of disease of the airways or lungs when it represents more than a defense mechanism, and may by its persistence become a helpful pointer of potential disease for both patient and physician. On the other hand, impairment or absence of the coughing mechanism can be harmful and even fatal; this is why cough suppression is rarely indicated in childhood. Pediatricians are concerned more with the etiology of the cough and making the right diagnosis. Whereas chronic cough in adults has been universally defined as a cough that lasts more than 8 weeks, in childhood, different timing has been reported. Many reasons support defining a cough that lasts more than 4 weeks in preschool children as chronic, however; and this is particularly true when the cough is wet. During childhood, the respiratory tract and nervous system undergo a series of anatomical and physiological maturation processes that influence the cough reflex. In addition, immunological response undergoes developmental and memorial processes that make infection and congenital abnormalities the overwhelming causes of cough in preschool children. Cough in children should be treated on the basis of etiology, and there is no evidence in support of the use of medication for symptomatic cough relief or adopting empirical approaches. Most cases of chronic cough in preschool age are caused by protracted bacterial bronchitis, tracheobronchomalacia, foreign body aspiration, post-infectious cough or some combination of these. Other causes of chronic cough, such as bronchiectasis, asthma, gastroesophageal reflux, and upper respiratory syndrome appear to be less frequent in this age group. The prevalence of each depends on the population in consideration, the epidemiology of infectious diseases, socioeconomic aspects, and the local health system.

1. Introduction

Coughing is a reflex-evoked modification of normal breathing patterns [1]. Cough reflex is a multifaceted, precisely timed, neuromuscular phenomenon characterized by the precise concurrent and sequential coordination of the activation patterns of the diaphragm, various muscle groups of the chest wall, cervical muscles, abdominal muscles, laryngeal abductor and adductor muscles, and medullary and higher cortical regions of the brain [2–4].

Cough is a symptom that has been experienced by every human and is an essential protective and defensive act whose action secures the removal of mucus, noxious substances and infections from the larynx, trachea and larger bronchi. Coughing is the most efficient mechanism for clearing the upper airways, and can be considered to be an innate built-in defense mechanism [5].

Impairment or absence of the coughing mechanism can be harmful and even fatal in disease. On the other hand, cough may be the first overt sign of disease of the airways or lungs when it represents more than a defense mechanism, and by its persistence may become a helpful pointer of potential disease for both patient and physician. Nearly all conditions affecting the respiratory system and some extra-pulmonary conditions may cause cough, but the physician's main concern is ruling out the presence of more serious conditions that require prompt treatment [6].

The major aim of managing a patient presenting a cough is to identify and then treat its cause. Cough may indicate anything from the most trivial to very serious airway or lung pathology.

As cough is audible and can intensely interfere with the quality of life, it is not surprising that parents are often anxious about their children's cough and often seek medical advice and remedy. Parental concerns may differ significantly from physicians' concerns. Physicians are usually concerned with the etiology of cough and making the right diagnosis. Parental concerns, however, often regard their perceived effects of cough on their child (sleep, choking or permanent chest damage) [6].

Cough has three defining features: an initial deep breath, a brief powerful expiratory effort against a closed glottis, and the opening of

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the glottis with closure of the nasopharynx and vigorous expiration through the mouth. Within this definition there are several variants.

Cough is a complex motor act, and its different components, frequency, effort (intensity), and the balance between inspiratory and expiratory components reveal various regulatory processes that are often neglected [7–9]. Cough sound is due to the vibration of larger airways and laryngeal structures during turbulent flow in expiration. Airway structure, rheological properties of the mucus, and the shearing of the secretions from the airways influence cough sound. The sensitivity of the cough reflex varies with age and gender [10].

2. When is cough chronic? 4 is better than 8

Whereas chronic cough in adults has been universally defined as a cough that lasts more than 8 weeks, different timing has been reported for children. Both American [11] and Australia/New Zealand [12] guidelines classify chronic cough as lasting >4 weeks but the British Thoracic Society [13] uses a duration of >8 weeks. The durations used in other European countries vary. The Belgians, for example, define prolonged cough as a daily cough that lasts longer than three weeks [14].

Many reasons support defining a cough that lasts more than 4 weeks as chronic in preschool children, however; and this is particularly true when the cough is wet. During childhood, the respiratory tract and nervous system undergo a series of anatomical and physiological maturation processes that influence cough reflex. In addition, immunological response undergoes developmental and memorial processes that make infection the overwhelming cause of cough in preschool children. Moreover, children are more vulnerable to various environmental factors [15]. The thinking behind the decision to include an intermediate time zone defined as “prolonged acute cough” is to allow a period for cough resolution for the 10% of normal children who are still coughing due to a simple cold [16]. Delaying diagnosis and treatment in children may lead to damage, such as in the case of PBB or foreign bodies [17,18]. A “wait and watch” period may therefore delay necessary intervention. In favor of this is the recent study demonstrating that only 20% of cases of children classified as having a chronic cough >4 wks resolved spontaneously, whereas others had a specific cause [19,20]. The remaining 80% of children required further care, and this suggests that primary care pediatricians should consider starting investigations earlier. Further support for a 4-week definition of chronic cough includes the known natural history of cough in preschool children [21].

Physiologically, there are similarities and significant differences between adults and children [15]. Expectedly, the etiologies and management of cough in a child differ from those used for adults. Cough in children should be treated on the basis of etiology and no evidence supports the use of medication for symptomatic cough relief or an empirical approach based on the big three adult etiologies: GERD, asthma, and upper airway syndrome [22]. Regardless of setting and age, children with chronic cough should be evaluated carefully using children-specific protocols. Knowledge of the patho-physiology of the different conditions that cause chronic cough is vital to making a correct diagnosis and prescribing successful treatment. Table 1 shows the major causes of chronic cough during childhood. The prevalence of each depends on the population in consideration, the epidemiology of infectious diseases, age, and the local health system.

Chronic cough in preschool children may be a source of concern that requires extensive differential diagnosis, even if in most cases it is caused by protracted bacterial bronchitis, tracheobronchomalacia, foreign body aspiration, post-infectious cough or some combination of the above. As documented in many reviews or guidelines [11–14], other causes of chronic cough, such as bronchiectasis, asthma, gastroesophageal reflux, and upper respiratory syndrome appear to be less frequent in this age group.

Table 1
Age-related prevalence of causes of chronic cough. Abbreviations: (−) rarely occurs; (+/−) occasionally occurs; (+) occurs; (++) frequently occurs.

Causes	Preschool children	School children	Adults
Airway infection	++	+	+
Airway anomalies (predominantly tracheobronchomalacia)	++	+	+
Foreign body	++	+	+
PBB	++	+/−	−
Upper airway syndrome	+	+	++
GERD	+	+	++
Asthma	+	+	++
Eosinophilic inflammation	+	+	++
Vocal cord dysfunction	−	+	+
Psychological and tic cough	−	+	+

3. Protracted bacterial bronchitis

In recent years, increasing attention has been focused on PBB as the major cause of chronic wet cough in children [20,23–27]. These studies have shown its prevalence at preschool age to be nearly total. The microbial species responsible for the vast majority of cases are bacterial species *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae* (NTHi), and *Moraxella catarrhalis*. In healthy neonates, Bisgaard et al. reported a 21% to 71% increase in hypopharynx bacterial colonization with *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* during the first 12 months of life [28]. Several mechanisms could be involved in the later migration and colonization of these agents in the lower airways. Among such processes, anatomical and immunological immaturity [15,29–33], modifications at the laryngeal crossroad [33,34], airway malacia [26,35], and nutrition [36] may be reasonably postulated as playing key roles. Nasopharynx flora composition is influenced not only by age but also by socio-economic settings [37]. As with otitis media, these pathogens could to be co-associated as polymicrobial biofilm complexes in which combinations of pathogens enhance disease or predispose the host to colonization by co-infecting microbes [38]. Instead of considering infection as a defined host–pathogen relationship, it should rather be envisioned as a spectrum of host–microbe pathogenic mechanisms, microbe–microbe interactions, host immunity-mediated antimicrobial defenses, and environmental factors. Imbalances in any arm of this interdependent disease continuum may significantly affect disease outcomes [39]. Upper respiratory viral infections predispose the host to bacterial infection and enhance bacterial adherence to cell surfaces [40–43]. Moreover, pre-infection with various viruses changes the physiological properties of infected airways, and modulates innate and adaptive immune responses [44,45]. Alterations in immuno-response in children with PBB have been reported [46,47]. Impaired mucociliary clearance, especially after viral or bacterial infections [48–50], seems to be a significant risk factor for the establishment of bacterial colonization. Immunized children with PVC are highly unlikely to be infected with vaccine *S. pneumoniae* serotypes [51]. Based on recent knowledge, the term “persist” rather than “protracted” seems to be more descriptive of the disease [23,52]. Treatment of PBB is based on long-term use of antibiotics, and initial studies adopted a period of from 2 weeks to months [19,23,24]. In a recent, randomized controlled trial, however, Marchant et al. reported successful resolution in a significant number of children with PBB after a 2-week course of twice-daily oral amoxicillin clavulanate (22.5 mg/kg/dose) [53]. We routinely employ higher doses 80–90 mg/Kg/day divided q8hr for a period of 2–4 weeks. Table 2 reports the clinical profile of children with protracted bacterial bronchitis.

While not usually life threatening in the short term, colonization of the airways is responsible for considerable and often unrecognized morbidity, such as bronchiectasis [17,54–56]. Research in the past decade has produced exciting new observations on the important role of bacterial infections in chronic obstructive pulmonary disease (COPD)

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Table 2
Clinical profile of protracted bacterial bronchitis from reference [19].

Clinical profile of protracted bacterial bronchitis
Young children <5 yrs
Chronic wet cough
Minimal or non-specific systemic effects (attributed to disturbed sleep and infection). Systemic symptoms usually improve before the cough resolves when appropriate treatment is commenced.
Misdiagnosis of asthma (night time cough)/may co-exist with asthma and therefore does not respond to bronchodilators.
Significant morbidity and multiple medical visits
Resolves after a prolonged course of appropriate antibiotics
After a typical course of antibiotics (5–7 days), cough either relapses within 2–3 days or slightly subsides but does not resolve completely.
Slow recovery

[57]. Although the associations between lower respiratory tract infection during the major period of postnatal growth and impaired lung function in adulthood are now well established, there is ongoing debate whether this association reflects a cause–effect relationship. An alternative explanation for the observed association is that an impaired lung growth antedates the respiratory tract infection, with the infectious episode as a result of the vulnerability of smaller lungs to infection [57]. Further studies are warranted to investigate whether protracted bacterial bronchitis is a risk factor for developing COPD.

4. Tracheobronchomalacia

Tracheobronchomalacia (TBM) is a condition characterized by excessive airway collapsibility caused by weakness of the airway walls and supporting cartilage, as well as by the increased flaccidity of the membranous portion of the central airways [58,59]. This disease may either arise congenitally (from disorders associated with impaired cartilage maturation or in combination with other anomalies like tracheoesophageal fistula) or it may be acquired from prior intubation, trauma, infection, long-standing extrinsic compression, or chronic inflammation [60]. Carden et al. have reported numerous diseases associated with congenital (primary) and acquired (secondary) TBM [61]. TBM is the most common congenital anomaly of the central airways. In addition, flaccidity and abnormal compliance of the airway can be focal or diffuse. Most pediatric TBM is localized [62]. Most cases of TBM are intrathoracic and are therefore present during expiratory maneuvers. In comparison, extrathoracic or cervical TBM is less common and is present during inspiration. The incidence of TBM disorders is thought to range between 1:1500 and 1:2500 children [61]. Despite this relatively low incidence, these lesions are encountered commonly in pediatric bronchoscopic practice, particularly when investigating wheezing, chronic cough and "rattly" conditions, especially in association with congenital heart disease and syndromic conditions [62–64]. TBM has been reported in up to 15% of infants and 30% of children younger than 3 years old who had undergone bronchoscopic evaluation for respiratory distress [65–69]. With the emergence of sophisticated neonatal pediatric respiratory care in the last 10 years, a growing number of premature infants with TBM are surviving.

Because TBM symptoms are nonspecific and overlap with other pulmonary disorders, clinical diagnosis is difficult. Clinical signs of TBM are reported in Table 3. The characteristic cough is a seal-like bark, presumably the result of expiratory collapse and vibration of the floppy membranous wall against the anterior airway wall [70]. During the explosive expiratory phase of cough, high intra-pleural pressure causes the dynamic compression of the central airways and results in increased linear velocity that aids the proximal clearance of airway secretions and debris. The cross sectional area of the trachea may be reduced by up to 80% [71,72]. In subjects with tracheomalacia, the instability of the tracheal wall is such that the more marked dynamic compression of the trachea during coughing that ensues may impair rather than enhance the cough's efficiency to clear mucus, and this produces the characteristic brassy sound of the cough. Chang et al. have shown that an unusual quality of cough, such as a vibratory or brassy cough, has high levels of association with bronchoscopically-proven malacia [73]. In addition, several studies have demonstrated that a high percentage of children with PBB also have TBM as well [19,23–27].

This diagnosis should be considered in children who have persistent or protracted recurrent airway symptoms (persistent or recurrent "wet" cough, unusual cough, expiratory stridor, wheeze, rattling or rattly respiration, dyspnea/respiratory distress), recurrent protracted bacterial bronchitis, pneumonia (particularly with atypical radiographic features such as persistent or recurrent collapse), localized gas trapping, and unusual radiographic densities [35,74]. Suspicion of this diagnosis should also be increased in children who have syndromes involving cardiac disorders, tracheoesophageal fistula, bronchopulmonary dysplasia, persistent wheezing including "happy wheezers", and all those who have undergone prolonged intubation or tracheotomy [61,74,75]. All children in whom the diagnosis is suspected should have simple radiographic assessments, even if some may require bronchoscopic assessment and more invasive and detailed radiographic assessment, such as a contrast swallow, CT scanning or MRI [61,76].

The management of TBM disorders is essentially based on expert opinion derived from anecdotal experience. The treatment of TBM is tailored to the child's age, the severity and distribution of malacia, symptom severity, and the presence of extrinsic airway compression [65]. Management details are reported in several reviews [61,72,74].

5. Foreign body aspiration

Retained inhaled foreign body (FB) is most commonly seen in young children between 0 and 3 years of age [77]. Food, particularly nuts and seeds, may be the cause of obstruction in children who have incomplete dentition (lack of cuspid molars) or those who simply do not chew their food well because of immature swallowing coordination or the tendency to be easily distracted when eating (e.g. playing, running or laughing) [77–79]. Data gathered from scientific literature on FB injuries in high-income countries indicated that among organic FB, nuts seem to be the cause of the injury in 40% of the cases and seeds in 20%. Among inorganic FB instead, the greatest pooled proportion (34%) has been recorded for magnets, followed by toys (12%) and batteries (12%) [79]. This diagnosis should be suspected if there is a history of choking followed by prolonged cough and non-resolving pneumonia. The yield from physical examination and radiological studies in the diagnosis of FB aspiration is relatively low but is increased when the presentation

Table 3
Clinical signs of tracheobronchomalacia, modified from reference [61].

Clinical signs of pediatric tracheobronchomalacia
Stridor
Seal-like bark or unusual cough (parents are able to identify their child by solely hearing the cough)
Respiratory distress
Wheeze (usually central and localized, low-pitched, homophonous, modifies in the prone position and unchanged or worsen after beta-agonists)
Anoxic spells
Cyanosis
Bradycardia
Tachyarrhythmias
Spontaneous hyperextension of the neck
Feeding difficulties (dysphagia, regurgitation, intermittent respiratory obstruction, arterial desaturation or cyanosis during feeding)
Prolonged expiratory phase
Breath-holding spells
Failure to thrive
Increased work of breathing
Sternal, substernal, and intercostal retractions
Recurrent pulmonary infections (increased initial severity and slower recovery)
Reflex apnea
Respiratory or cardiac arrest

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is delayed and when history is doubtful [79]. Delayed diagnosis may be related to an unobserved aspiration event or lack of physician awareness and has serious consequences, such as chronic cough, recurrent pneumonias and eventually localized areas of bronchiectasis. The immediate management is endoscopic removal of the foreign body, and this should be performed wherever there is parental or clinical suspicion [16,80]. The key clinical diagnostic feature is the penetration syndrome corresponding to respiratory defense reflexes (expulsive cough and laryngeal spasm) in response to penetration by a foreign body. Although the penetration syndrome consists of elements of asphyxia with cyanosis associated with coughing fits, it can also be clinically silent in 12 to 25% of cases [81–83]. Symptoms may vary considerably according to the site of the FB in the airways. When the FB is trapped in the larynx or trachea, this diagnosis is immediately suggested by respiratory distress or stridor. In the vast majority of cases (75 to 94% of cases) however, the FB migrates to the bronchi, and clinical signs are much less constant [81,84–86]. The positive diagnosis of bronchial FB can therefore be difficult in the presence of few or no symptoms.

The relative sensitivity, specificity, positive predictive value, and negative predictive values of children with aspirated FB who typically present symptoms of coughing, dyspnea, wheezing, cyanosis, or stridor, were recently reported in a literature review [87].

A suggestive history is important in diagnosing an aspirated object because it is often difficult to make a definitive diagnosis on the basis of an abnormal physical examination or radiological studies alone. The work-up of the stable patient should include a chest radiograph to assess other potential causes of symptoms, identify a radio-opaque FB, or detect the position of the FB on the basis of localized emphysema and air-trapping, atelectasis, infiltrate, or mediastinal shift.

Thoracic computed tomography (CT) and virtual bronchoscopy—a reformatted 3-dimensional CT image that generates intra-luminal views of the airway to the sixth and seventh generation bronchi—are emerging as new ways to diagnose tracheobronchial FB in children [87,88].

6. Post-infectious cough

While the pathogenesis of the post-infectious cough is still unknown, it has been thought to be due to the extensive disruption of epithelial integrity and widespread airway inflammation of the upper and/or lower airways [89]. The specific infection causing post-infectious cough in children remains unidentified in most cases. Respiratory viruses (particularly respiratory syncytial virus, influenza, parainfluenza, and adenovirus), *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Bordetella pertussis* have all been implicated. Transient inflammation of the lower airways is likely to be important in pathogenesis in some patients with post-infectious cough. This speculation is based on the fact that cough may be induced by the enhanced responsiveness of the cough receptors [90], alterations in mucociliary clearance, and prolonged ciliary repair or increased mucus secretion [91]. Post-infectious cough is self-limited, usually resolves in time [92], and appears to be a tail end of infection.

In children, co-infection with more than one organism can occur, and this can increase the period of paroxysmal coughing [93]. Prolonged cough after *Chlamydophila* and *Mycoplasma* infections may also be quite common. A duration of cough of >21 days in young children following pneumonia with these organisms has been found in 57% and 28% of patients, respectively [89,93].

Wang et al. recently demonstrated that cough duration in children with positive *M. pneumoniae* serology (median: 39 days, 95% CI: 24–54) was significantly shorter than in children with positive pertussis serology (median: 118 days, 95% CI: 82–154, $P < 0.001$) [94]. *M. pneumoniae* and/or *C. pneumoniae* play a significant role in community-acquired LRTIs in children of all ages, even in preschool age, and may have different clinical presentation compared to older children [95–97].

At least one third of children who initially have a treated empyema are still coughing by 4 weeks, whereas one quarter are still coughing at 6 months, and around 3% at 12 months. Some of these patients have prolonged cough due to residual disease and as a result benefit from a prolonged course of antibiotics of 1–4 weeks from discharge or longer [16,98,99].

Respiratory viral infection is an important cause of morbidity and mortality in early life. The disease observed in children is composed of both a virus- and an immune-mediated component. The relative contributions of these two factors vary among individuals and are influenced by infecting virus host genetics and age [100]. Viral infections are very frequent in preschool children currently attending day care or exposed to environmental irritants, such as tobacco smoke [101–103]. Some viruses induce a prolonged coughing phase; Ryan et al. reported chronic cough following H1N1 infection in 43% of patients. These subjects displayed increased cough reflex sensitivity up to 220 days after confirmed infection [104].

Viruses are also responsible for the recruitment of a number of inflammatory cells to the airway and the production of a series of inflammatory cytokines. These inflammatory mediators and/or alterations in airway pH may activate certain receptors on afferent sensory nerves such as transient receptor potential vanilloid (TRPV-1) receptors and acid-sensing ion channel receptors [105]. Recent discoveries in signaling pathways mediating cough provide the basis to further our mechanistic understanding of how viral infection increases cough sensitivity. Experimental studies in animal models have shown that infection of guinea pigs with Sendai virus increased afferent neurons from the trachea and that this resolves in convalescence [106]. Total increase in tachykinin levels in the lung and expression of NK-1 receptor further amplify virus induced neuro-stimulatory signals [107]. This effect was shown in young rats to be dependent on Nerve Growth Factors (NGF). Piedimonte et al. demonstrated that RSV causes a persistent increase in the susceptibility of the respiratory tract to the pro-inflammatory effects of sensory nerves, which is still present after the acute phase [108]. These authors demonstrated that sensory innervation in the airways undergoes remodeling after an acute RSV infection, probably due to the up-regulation of NGF. NGF is a key regulatory element that controls the expression of genes encoding the precursors of SP and other peptide neurotransmitters in sensory neurons. Using plethysmography, Ye et al. demonstrated an increase in cough reflex sensitivity in guinea pigs caused by para-influenza virus type 3 infection [109].

Several members of the Transient Receptor Potential (TRP) superfamily of ion channels are expressed on sensory neurons [110]. Recently, ion channels of the TRP class, TRPA1 and TRPV1, have been implicated in the afferent sensory loop of the cough reflex and in the heightened cough sensitivity seen in disease [111]. Bradykinin plays a role in the initiation of cough during *B. pertussis* infection. Many effects triggered by these gram-negative bacteria are likely to drive increased bradykinin production [112]. Bradykinin has been shown to induce coughing in humans and animals and to sensitize the cough reflex to activation by other tussive irritants via activation of their associated G-protein coupled receptors [110]. TRPV1 channel involvement in the bradykinin-induced increase in the excitability of these sensory neurons has been reported in several recent studies [113]. Understanding the mechanisms provoking virus-induced cough hypersensitivity will likely offer significant opportunities for improved management.

In many respiratory infections, cough is often the last symptom to disappear. Children aged 2 to 5 may have 4 to 10 episodes of respiratory infection, especially if they attend day care. Persistent coughing after each bout may thus blend seamlessly into the next infection and this may be reported erroneously as chronic cough. A careful history and inquiry on the timing of coughing bouts are helpful in differential diagnosis. Observation of cough waning after the child's withdrawal from day care confirms the diagnosis.

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7. Conclusion

Chronic cough in children is a complex problem because differential diagnosis is broader than for acute cough. One of the primary goals in the management of chronic cough in children is to make an accurate underlying diagnosis and then to start targeted treatment. Chronic cough in preschool children may be representative of a specific serious disorder. The initial assessment should focus on identifying pointers that suggest specific disorders. Pediatric Guidelines and clinical algorithms have identified pointers or "red flags" to suggest and conduct investigations for a specific diagnosis. Early diagnosis of serious underlying disease imposes a 4-week cut-off over any longer period in defining chronic cough in preschool age. One alarming possibility is that a considerable percentage of children with chronic cough is not diagnosed and appropriately treated in time by their primary care physicians and may therefore develop serious complications, such as bronchiectasis. Children of preschool age have frequent respiratory infections—especially if they attend day care—manifested by bouts of coughing associated with bronchitis. These infections may occur "back to back" and give the impression of a chronic cough [102]. The progressive decrease in prescribing antibiotics for viral respiratory infections in early childhood over the past decade has been appropriate. This may have the consequence of inadvertently increasing the incidence of PBB and possibly bronchiectasis in coming years, however [23,52]. The benefits to the child of making an accurate diagnosis and prescribing adequate treatment therefore extend well beyond merely eliminating cough. In preschool children, the major causes of chronic cough appear to be persistent infection denoted by PBB, the post-infectious and structural alterations in airways known as TBM, and foreign body aspiration. Other causes of chronic cough seem to be less common at this age.

Author's contributions

All of the authors contributed for the concept, design and writing of the manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to the subject of this article

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