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REVIEW

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Acute cough in children and adolescents: A systematic review and a practical algorithm by the Italian Society of Pediatric Allergy and Immunology

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Abstract
The current systematic review presented and discussed the most recent studies on acute cough in pediatric age. After that, the Italian Society of Pediatric Allergy and Immunology elaborated a comprehensive algorithm to guide the primary care approach to pediatric patients, such as infants, children, and adolescents, with acute cough. An acute cough is usually consequent to upper respiratory tract infections and is self-resolving within a few weeks. However, an acute cough may be bothersome, and therefore remedies are requested, mainly by the parents. An acute cough may significantly affect the quality of life of patients and their family.

Several algorithms for the management of acute cough have been adopted and validated in clinical practice; however, unlike the latter, we developed an algorithm focused on pediatric

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age, and, also, in accordance to the Italian National Health System, which regularly follows the child from birth to all lifelong. Based on our findings, infants from 6 months, children, and adolescents with acute cough without cough pointers can be safely managed using well-known medications, preferably non-sedative agents, such as levodropropizine and/or natural compounds, including honey, glycerol, and herb-derived components.

Introduction

Cough is a vital neuromediated reflex that evolved to enhance airway clearance, protect the upper airways from obstruction, and expel chemical and mechanical irritants.[1] The cough reflex is evoked by noxious stimuli, which, detected by receptors and ion channels primarily distributed throughout the larynx, pharynx, esophagus, trachea, and pulmonary parenchyma, stimulate polymodal vagal nerves afferent (C-fibers and A-δ fibers) to the somatosensory cortex devoted to cough. Following the transmission of afferent signals, the cerebral cortex elaborates a specific response resulting, first, in the urge to cough and, successively, in cough reflex.[1]

Based on its duration, cough is classified into acute if it lasts less than 4 weeks and chronic if it lasts longer than 4 weeks.[2]

Upper respiratory tract infections (URTIs), mainly sustained by viruses, account for acute cough in up to 90% of cases. Exposure to irritants (such as aerosols, pollutants, and tobacco smoke), allergens, cold, and/or dry air may also cause acute cough.[3] An acute cough is a symptom that is usually benign and self-limiting, with an average duration of 14 days; it can resolve in 50% of cases within 10 days and in 90% of children within 25 days.[4,5] Epidemiological data show that acute cough affects approximately 35% of preschool children at any given time, resulting in significant morbidity and representing a widespread health problem in childhood.[6] In older children and adolescents, acute cough episodes tend to be rarer and short-lived, consistently with the lower impact of respiratory infection over time.

Acute cough is responsible for more than 50% of new patient attendance in primary care and hospitalization, with significant implications for the patient's family and the pediatrician. Acute cough also has a relevant burden from a pharma-economic point of view.[7] As symptomatic treatment is the mainstay of therapeutic management of this usually benign and self-limiting complaint, a "do-it-yourself" approach and the use of over-the-counter (OTC) antitussive drugs are surprisingly widespread. However, there is a stark contrast among the evidence of efficacy/safety and extensive clinical use of drugs for acute cough. Many of the available therapies are currently recommended based on custom and traditional practice or supported by randomized clinical studies of insufficient quality. Consumers spend billions of dollars on OTC antitussive drugs per year, suggesting the degree of suffering experienced by patients, and overall by their parents, with acute cough as well as a "personalized approach" to the disease with a "personal" conceptualization of the cause, diagnosis, and treatment of their illness.[8]

To clarify the management, the Italian Society of Pediatric Allergy and Immunology (SIAIP) provided a pragmatic update of the current and new treatment for the acute cough to promote evidence-based therapy for pediatric patients in primary care. A diagnostic algorithm for acute cough has also been developed to offer a practical guide for all healthcare professionals.

Treatment of Acute Cough

Historic drugs for the treatment of acute cough

Based on their site of action, antitussive drugs are commonly classified into peripheral and central agents. Peripheral antitussive drugs act outside the central nervous system (CNS) via the suppression of one or more vagal sensory receptors. Central antitussive drugs, entering the CNS, exert their effects directly on central reflex pathways for cough. However, this classification does not imply that peripheral drugs cannot have a central activity and vice versa.[9] A summary of randomized clinical trials (RCTs) focusing on acute cough treatment in pediatric patients is presented in Table 1.

Peripheral antitussive drugs

H1-receptor antagonists

As suggested by *in vivo* models, H1-antihistamines or histamine H1-receptor antagonists appear as effective antitussive drugs mainly due to their properties, including modulation of histamine H1-receptor, anticholinergic mechanisms, reduction of histamine release, and inhibition of transient receptor vanilloid-1 (TRPV1) receptor activation. However, in contrast with these findings, there is currently no firm evidence of clinical efficacy on acute cough suppression in the pediatric population. In a systematic review collecting three randomized controlled trials (RCTs) focused on antihistamines and evaluating their efficacy in the treatment of acute cough, Smith et al.[10] showed that antihistamines were no more effective than placebo in reducing cough frequency and sleep-related outcomes. A significant risk of adverse effects was also recorded in children receiving antihistamine compared to those receiving placebo.

Taking advantage of the effects of α-adrenoceptor agonist, which causes vasoconstriction of mucosal blood vessels, the antihistamine-decongestant combination has also been proposed as a treatment of acute cough in children. In this regard, two RCTs, involving 155 children, compared antihistamine-decongestant combinations with placebo and revealed that brompheniramine/phenylpropanolamine administration was no more effective than placebo in reducing the number of children coughing. Moreover, a higher proportion of children experiencing adverse effects

Table 1 Randomized clinical trials (RCTs) on antitussive drugs for pediatric population with acute cough.

Investigated drug	Authors	N. pts	Age of pts	Diagnosis	Primary Outcome Measures	Interventions	Results	Safety
Antihistamines	Bhattacharya et al. 2012	120	1 to 22 years	URTIs*	Cough frequency score Child's sleep score Parental sleep score Post-tussive vomiting score Composite score of the above and adverse effects	Promethazine (0.5 mg/kg 8-hourly for 3 days) Dextromethorphan (5 mg 6- to 8-hourly for 3 days) Placebo	No superior benefit was noted among promethazine, dextromethorphan, and placebo.	Adverse effects were more frequent in the dextromethorphan and promethazine groups: Abdominal pain Nausea Vomiting Drowsiness Irritability
	Paul et al. 2004	100	6 to 11 years	URTIs	Cough frequency Sleep disturbance in children and their parents Composite score of the above and adverse effects	Diphenhydramine (1.25 mg/kg, single dose) Dextromethorphan (a single dose based on age) Placebo	No superior benefit was noted among diphenhydramine, dextromethorphan, and placebo.	No differences between treatment arms, including placebo
	Sakchainanon et al. 1990	143	<5 years	Common cold	Parent assessment	Clemastine (0.05 mg/kg/d twice daily for 3 days) Chlorpheniramine (0.35 mg/kg/d 3 times daily for 3 days)	Not stated	No differences between treatment arms: Drowsiness Sleepiness
Antihistamines decongestants combination	Clemens et al. 1997	59	6 months to 5 years	URTIs	Parent questionnaire	Brompheniramine maleate (2 mg/5 ml as needed every 4 hours) Phenylpropanolamine-hydrochloride (12.5 mg/5 ml as needed every 4 hours) Placebo	No superior benefit was noted among treatment group and placebo group	Adverse effects were more common in treatment group: Sleepiness
	Hutton et al. 1991	96	6 months to 5 years	URTIs	Parent questionnaire Physician score	Brompheniramine maleate (4 mg/5 ml 3 times daily for 2 days) Phenylephrine (5 mg/5 ml 3 times daily for 2 days) Propanolamine (5 mg/5 ml 3 times daily for 2 days)	No superior benefit was noted among treatment group and placebo group	Adverse events were rare bith in treatment and placebo group: Sleepiness Loose stool Hyperactive

(Continues)

Table 1 Continued.

Investigated drug	Authors	N. pts	Age of pts	Diagnosis	Primary Outcome Measures	Interventions	Results	Safety
Levodropropizine	Tamburrano et al. 1989	180	0.5 and 12 years	Not stated	Not stated	Levodropropizine for 1 week	Not stated	Adverse events were reported: not specifically stated
	Fiocchi et al. 1991	12	2 to 8 years	Asthmatic cough	Nocturnal sleeping quality	Levodropizine for 4 weeks	Significant improvement	
	Banderali et al. 1995	254	2 to 14 years	Non-productive cough due to various causes	Coughing frequency Number of night awakenings due to cough	Levodropropizine vs. Dropropizine for 3 days	No superior benefit was noted among levodropropizine and dropropizine	Somnolence was twice as frequent in the dropopizine group
	Kim et al.	77	0.5-11 years	Non-recurrent/ slightly recurrent cough	Severity and frequency of cough	Levodropizine Dextromethorphan t.i.d. for 3 days	Levodropizine was superior in reducing severity and frequency	Dextrometorphan revealed sedation
	De Blasio	433	0.1-14 years	Acute cough associated with URTI	Cough intensity Resolution rate	Levodropizine Clorepastine-codeine No treatment For 6 days	Both medications reduced cough intensity Levodropizine had higher significant resolution rate	Codeine induced sedation
	Zanasi et al.	330	0.4-14 years	Acute cough caused by URTI	Severity, frequency, and type of cough	Levodropizine Antibiotics Combination of them	Levodropizine was superior than antibiotics in reducing cough	No relevant adverse events
Menthol	Paul et al. 2010	138	2 to 11 years	URTIs	Nocturnal cough Congestion Sleep difficulty	Vicks VapoRub (camphor, menthol, and eucalyptus) Petrolatum No treatment	Vicks VapoRub was over petrolatum for cough severity Vicks VapoRub was over no treatment for all outcomes	Adverse effects were more common in the Vicks VapoRub group: Burning sensation of the skin Burning sensation of the eyes Burning sensation of the nose
Honey - food	Cohen et al. 2012	300	1 to 5 years	Nocturnal cough	Cough frequency Cough severity Bothersome cough Child and parental sleep quality	Eucalyptus honey (10 gr) Citrus honey (10 gr) Labetiae honey (10 gr) Placebo (10 gr)	Significant symptom reductions in all honey groups compared to placebo	No differences between treatment arms

	Paul et al. 2007	105	12 to 18 years	URTIs Nocturnal symptoms Illness duration of 7 days or less	Nocturnal cough Sleep quality	Honey (single dose) Dextromethorphan (single dose) No treatment	Significant symptom reductions in honey group	Adverse effects were more common both in honey and dextromethorphan: Hyperactivity Nervousness Insomnia
	Shadkam et al. 2010	139	24 to 60 months	URTIs	Nocturnal cough Sleep quality	Honey (2.5 mL, single dose) Dextromethorphan (2.5 mL, single dose) Diphenhydramine (2.5 mL, single dose)	Significant symptom reductions in honey group	Not investigated
Medical device made of complex natural substances (Grindelia, Helichrysum, Plantago and honey)	Canciani et al. 2014	102	3 to 6 years	Acute cough	Day- and night-time cough scores	Polysaccharide-resin-flavonoids and honey (5 ml doses, 4 times a day, for 8 days) Placebo	Significant day- and night-time cough scores reductions in Polysaccharide-resin-flavonoids and honey group (5 ml doses, 4 times a day, for 8 days)	Adverse events related to the treatment were not registered
	Cohen et al. 2017	150	2-5 years	Acute cough due to common cold	Cough frequency Cough severity Quality of sleep	Polysaccharide-resin-flavonoids and honey (5 ml doses, 4 times a day, for 3 days) Carbocysteine	Polysaccharide-resin-honey-flavonoids group was more effective in improving all outcomes	Mild digestive symptoms in 5 and 6 patients respectively
Erdosteine	Balli et al. 2007	158	Not explicitly stated	URTIs	Cough (primary), Polypnea Rhonchi and rales Body temperature	Erdosteine plus amoxicillin (for 7 +/- 2 days) Placebo plus amoxicillin (for 7 +/- 2 days)	Significant cough reduction in erdosteine plus amoxicillin group	Adverse events were not reported
Mucolytics	Nespoli et al. 1989	40	2 to 12 years	Acute febrile bronchitis	Cough score	Letosteine (25 mg 3 times daily for 10 days) Placebo	Significant reduction in cough score in letosteine group	Adverse events were not reported
	Albrecht et al. 2012	378	12 and older	URTIs	Spontaneous symptom severity scores	Guaifenesin (1600 mg twice daily for 7 days) Placebo	Significant reduction in spontaneous symptom severity scores in treatment group	No significant difference in adverse effects among groups

(Continues)

Table 1 Randomized clinical trials (RCTs) on antitussive drugs for pediatric population with acute cough.

Investigated drug	Authors	N. pts	Age of pts	Diagnosis	Primary Outcome Measures	Interventions	Results	Safety
Dextromethorphan	Taylor et al. 1993	57	18 months to 12 years	Night cough due to URTIs	Parent questionnaire Cough score	Dextromethorphan (15 mg/5 ml as single dose for 3 days) Codeine (10 mg/5 ml as single dose for 3 days) Placebo	No superior benefit was noted among treatment groups	No significant difference in adverse effects among groups: Drowsiness Diarrhoea Hyperactivity
	Korppi et al. 1991	50	Not specifically stated	URTIs	Cough frequency Cough severity	Dextromethorphan plus salbutamol (1.5 mg/ml 5 ml 3 times daily for children under 7 years; 10 ml 3 times daily for older children) Placebo	No superior benefit was noted among treatment groups	No significant difference in adverse effects among groups: mild adverse effects (not stated)

* URTIs: upper respiratory tract infections.

was reported in the active treatment group than in the placebo group.[11,12]

Local anesthetics

Local anesthetics, including lignocaine, lidocaine, and benzonatate, are locally delivered to the airways where, by blocking sodium (Na)V+ channels in sensory nerves, they attenuate capsaicin-induced cough in humans. However, their effects are also associated with oropharyngeal anesthesia that causes an increased risk of aspiration of airway secretions and food.[13]

Nebulized lidocaine has been proposed as an effective antitussive in the treatment of acute cough resistant to conventional therapy. Concentrations ranging between 1% and 4% have proven to be efficient. Nebulized lidocaine also appears to be well tolerated by patients with minimal adverse effects, such as dysphonia, oropharyngeal numbness, and bitter taste.[14]

Benzonatate, a long-chain polyglycol derivative, is a nerve conduction blocker that, by inhibiting afferent vagal fibers from pulmonary stretch receptors located in the bronchial tree, exerts an antitussive effect. Currently, it has been adopted by oncologists for the treatment of refractory cough in children older than 10 years old. Benzonatate is administered orally and absorbed systemically with an onset of action of 15–20 min and with a 3–8-hour duration of action.[15] The recommended dose is 100–200 mg every 8 hours as required, with a maximum daily dose of 600 mg. Although cases of seizures cardiac arrest have been attributed to benzonatate use, its side effect profile is considered as relatively benign.[15]

Levodropropizine

Levodropropizine is a non-opioid agent whose peripheral antitussive action results both from modulation of the airway sensory nerves and inhibition of the release of the neuropeptides from C-fibers.[16] The lack of a central depressant action by levodropropizine has recently been confirmed by Mannini et al.[17] in a clinical study assessing the effects on the respiratory responses to a standard CO_2 re-breathing testing. Unlike dihydrocodeine, levodropropizine did not affect the hyperventilatory response to hypercapnia, demonstrating the absence of depression of the central mechanisms involved in the genesis of respiratory rhythm, thus supporting the peripheral action and favorable safety profile of levodropropizine especially in children.

In a meta-analysis collecting seven RCTs focused on levodropropizine and evaluating its efficacy in the treatment of acute cough in children, Zanasi et al.[18] showed that levodropropizine was an effective antitussive drug with statistically significant better efficacy outcomes when compared to central antitussive drugs (e.g., codeine, cloperastine, and dextromethorphan) in terms of reducing cough frequency and intensity, and sleep-related outcomes. In particular, five studies investigated the role of levodropropizine in children and adolescents, as reported in Table 1. Fiocchi et al. evaluated asthmatic children (2–8 years) in an RCT placebo-controlled study.[19] Levodropropizine, administered for 5 days, significantly improved the quality of sleep. Banderali performed a large RCT double-blind study, including 258 children and adolescents (2–14 years old), to compare levodropropizine with dropropizine for the treatment of non-productive cough.[20] Both medications were found effective on cough, but dropropizine caused twice somnolence. Kim evaluated 77 children (6 months to 11 years old) with non-recurrent/slightly recurrent cough accompanied by acute or chronic bronchitis in an RCT double-blind study.[21] This trial compared levodropropizine with dextromethorphan administered for 3 days and found that levodropropizine was more effective in reducing the severity and frequency of cough. De Blasio, in an observational study conducted on 433 children and adolescents, evaluated the effectiveness of levodropropizine or central antitussive agents (cloperastine/codeine) in reducing acute cough associated with URTI also in comparison with no treatment.[22] Levodropropizine was more effective in the resolution time than central agents. Zanasi et al. conducted a prospective observational study in 330 children and adolescents to compare levodropropizine, antibiotics, the combination of both, or no treatment, to treat acute cough caused by URTI[23] and found that levodropropizine was more effective than antibiotics in reducing cough. Currently, levodropropizine is indicated for short-term symptomatic treatment of acute cough both in children older than 2 years and adults.[24]

Menthol

Produced by the peppermint plant *Mentha x piperita*, l-menthol is the most biologically active isomer used as an antitussive drug. The activity of menthol is through a specific receptor called transient receptor melastatin 8 (TRPM8), a member of the transient receptor potential family of nociceptors, mainly located on afferent sensory neurons and acting by blockade of sodium channels.[25] Moreover, the antitussive activity of menthol is also mediated by the activation of nasal sensory afferents as opposed to those pulmonary.[26] Although this popular topical preparation has been used in adults and children for more than a century, clinical evidence regarding the activity of menthol from RCTs is very sparse and no clinical studies have been conducted by the modern standard. The evoked cough was reduced in children by inhalation of menthol vapor but not significantly when compared with placebo.[27]

Honey

Honey, a supersaturated sugar solution, is a cheap, popular, and safe demulcent cited by the World Health Organization (WHO) as a potential treatment for URTIs-associated cough in children.[27] Due to its viscosity, honey increases saliva production and swallowing, thus sending an irritative stimulus to the cortical neural network also interfering with the cough reflex. Additionally, honey shows several properties such as anti-inflammatory, antioxidant, antibacterial, and metabolic activities.[28]

Accumulating evidence supports the beneficial effects of honey for symptomatic relief of nocturnal URTIs-associated cough, in reducing cough duration and severity, and in improving sleep quality for both children and their parents.[29-31] In their systematic review, Malesker et al. suggested that honey may offer more relief for cough symptoms in children older than 1 year when compared to no treatment, diphenhydramine, or carbocysteine, but its efficacy is lower than dextromethorphan.[32,33]

Medical device composed of complex natural substances

A new category of cough products is that of substance-based medical devices; they exert their primary effects with a physiological and non-pharmacological mechanism.

Moreover, honey, when administered in addition to specific substances, such as resins, polysaccharides, saponins, flavonoids, and sugars, appeared superior also to the placebo in the treatment of cough persisting more than 7 days.[34] Specifically, 102 children aged 3–6 years, randomly assigned to the treatment group and placebo group, experienced a significant improvement both in day-time and night-time cough scores and, interestingly, severe adverse events or other safety reasons were not recorded in the treatment group.[34] In light of these findings, the authors hypothesized that honey, although not showing specific pharmacological properties, can act effectively as a mechanical barrier limiting the injury caused by external micro-organisms and irritants on the upper respiratory tract mucosa, inhibit the stimulation of nerve endings, and exert an indirect anti-inflammatory action, resulting in the recovery of the damaged tissue. Probably, these effects may be potentiated by the components present in the product, including *Grindelia, Plantago*, and *Helichrysum*, which exert anti-inflammatory and cytoprotective adjunctive effects. This compound contains a polysaccharide-resin-honey polymer; thus, this syrup may exert a marked antitussive activity as confirmed by a randomized, single-blinded, multicenter study.[35] This trial included 150 children with acute cough due to URTI; patients were treated with this honey-based polymer or carbocysteine for four consecutive days. The polysaccharide-resin-honey syrup induced a more rapid and greater improvement in all measured parameters, such as nocturnal and daytime cough, and quality of sleep for both children and parents.

Generally speaking, children receiving honey showed no or minimal risk of adverse effects such as abdominal pain, nausea, and vomiting, which are common unspecific side effects recorded also in placebo groups.[36] However, honey administration is not recommended in children younger than 1 year for a high risk of infantile botulism.[37]

Glycerol

Glycerol, also known as glycerine or glycerin, is a colorless, odorless, viscous liquid that is found naturally in all cells in the form of triglycerides and it occurs naturally in most products of fermentation.[38] Due to its properties of lubrication, demulcent activity, and sweetness, glycerol contributes up to 85% of the benefit of cough syrups.[39] The humectant properties of glycerol are due to the presence of three hydrophilic alcoholic hydroxyl groups in its chemical structure that can attract and bind to molecules of water, and, additionally, to exert a plasticizing effect preventing drying out mucosal dryness. Moreover, because of its hydroxyl groups, glycerol shows solubility characteristics similar to aliphatic alcohols and this justifies it as a very common and useful solvent for cough medicines. It has been reported that the major effect of cough syrups is related to the intrinsic properties of the syrup rather than the active ingredients, and glycerol, usually at 0.75g/5 mL concentration, can be considered as the only "active" ingredient of the cough syrup, although it does not have any known pharmacological actions. Glycerol is also viscous and acts as a thickening or bodying agent in cough syrups. Finally, glycerol has lubricant and demulcent properties that make it capable of forming a soothing film over mucosa, decreasing friction between moving surfaces, and relieving pain and inflammation. Glycerol administration has not been associated with adverse effects, except in very high concentrations when a dehydrating effect is apparent.[38]

To the best of our knowledge, only one randomized, placebo-controlled, double-blind, efficacy and safety study was performed to investigate the efficacy of glycerol in adult patients suffering from dry cough.[40] The authors reported that the group receiving filmogen glycerol showed a significant decrease in the mean scores of dry cough severity and frequency, throat pain, irritation, swelling, and redness when compared to placebo.[40]

No data are available in the pediatric population affected by acute cough; however, although at present RCTs are required to determine the efficacy of glycerol as a cough treatment in children and infants from 6 months, several health authorities, such as the World Health Organization and the Medicines and Healthcare products Regulatory Agency, promote the use of cough syrups containing glycerol.[41,42] It is plausible that glycerol's effectiveness in improving acute cough depends on pathophysiologic mechanisms similar to honey. Both compounds exert a relevant demulcent activity.

Mucolytics and expectorants

Erdosteine is a homocysteine analog currently used in chronic obstructive pulmonary disease treatment because of its peculiar activities on bronchial secretions and positive effects on bacterial adhesiveness.[15] Additionally, due to its abilities to influence mucus consistency and enhance mucociliary function, erdosteine has been successfully tested both in animal models and humans as a mucolytic drug.[43] Pivotal studies documented that erdosteine was able to significantly reduce oxidative stress, inhibit pro-inflammatory mediators release and restore the beta (ß)2-adrenoceptors functions.[44,45] The clinical effects of erdosteine in addition to antibiotic treatment in children with acute cough were demonstrated by Balli et al.[46] In a multicenter, randomized, double-blind and placebo-controlled trial, 158 children with URTIs were randomized to erdosteine plus amoxicillin treatment (n=78) and placebo plus amoxicillin (n = 80) for 7 ± 2 days. The efficacy parameters were cough (primary), polypnea, rhonchi, rales, and body temperature. The erdosteine group showed a significant reduction in the severity of cough when compared to placebo. Moreover, neither adverse events nor adverse changes in laboratory parameters were observed in the treated group.[46]

Widely prescribed for treating acute cough, carbocisteine (S-carboxymethyl L-cysteine) and N-acetylcysteine are mucolytics thought to reduce mucus viscosity due to their ability to increase the concentration of chloride in airway secretions, reduce airway tachykinins, and also decrease cough reflex hypersensitivity.[46]

Carbocisteine is a muco-regulating drug that acts on the formation of mucus by modifying the composition of secretions in the bronchial glands and restoring the

physiological characteristics of viscosity and elasticity by restoring the right balance between mucin proteins.[47,48] Changes in mucus rheology improve the mucociliary function and promote antibiotics diffusibility during chronic bronchitis.[49]

Furthermore, carbocisteine has shown an anti-adhesive action against viruses and bacteria, Specifically, carbocisteine was able to inhibit respiratory syncytial virus infection by reducing ICAM-1 expression,[50] and to alter the surface structure of *Streptococcus pneumoniae,* resulting in a decrease in attachment.[51]

However, the evidence for antitussive activity of mucolytics is limited and the RCTs published on mucolytic drugs do not meet the stated quality criteria both in children and adults. Moreover, when cough severity has been reported as an outcome measure in placebo-controlled trials, no significant clinical effects have been demonstrated neither for carbocisteine nor N-acetylcysteine.[52-54]

Specifically, only one trial involving 40 children and comparing the mucolytic letosteine with placebo has been identified by Smith et al. in a systematic review.[10] Letosteine significantly decreased the symptom score with a good safety profile.[55]

Fever, bronchospasm, and gastrointestinal disorders are adverse effects frequently reported after oral administration of N-acetylcysteine. When administered in combination with ampicillin, erythromycin, and tetracyclines, N-acetylcysteine can also inactivate them.[15]

Guaifenesin (or glyceryl guaiacolate), ipecac, terpene hydrate, and ammonium chloride are expectorants most frequently prescribed to patients with acute cough. By influencing the cholinergic innervation of airway mucous glands, they promote an increase in the volume of bronchial secretions; however, because vagal stimulation also irritates the gastric mucosa, nausea and vomiting are common adverse effects. In their RCT involving in 378 participants with URTIs, Albrecht et al.,[56] by comparing extended-release guaifenesin with placebo, did not report significant differences in daily cough as well as in total spontaneous symptom severity scores among two groups.

Bromhexine and its metabolite ambroxol modulate the activity of mucus secretion through the induction of hydrolytic depolymerization of mucoprotein fibers.[57] However, scientific data on their use in acute cough are very sparse. Studies in the pediatric population have been performed only without a control group or an active comparator in an open design.[10] There are no studies that have identified outcomes with the use of expectorants in the pediatric population, although their use is approved by the Food and Drug Administration (FDA) in children and adults.[10]

Central antitussive drugs: opioids and non-opioids

Opioids

Codeine Numerous preparations containing codeine, as a single agent or in combination with other active molecules, are available for the symptomatic treatment of acute cough for children older than 12 years without compromised respiratory function. Codeine, also called methylmorphine, is a weak opioid that, acting directly on the cough center in the medulla, suppresses the cough reflex. However, literature data do not support the efficacy of codeine in the treatment of acute cough, as current evidence finds codeine to be no more effective than a placebo for acute cough in the pediatric population.[10]

Moreover, as codeine is metabolized into morphine in the liver by cytochrome P450 2D6 (CYP2D6), the safety profile of codeine raises greater concerns, especially in CYP2D6 "ultra-rapid metabolizers" patients who convert codeine to morphine at a faster than normal rate, reporting high serum morphine levels and a higher risk of developing toxic effects such as life-threatening respiratory depression. In this regard, post-marketing studies revealed 9 fatal cases and 41 serious cases associated with codeine administration in the pediatric population.[58] In July 2015, the FDA warranted codeine-containing medications to treat coughs and colds in children younger than 18 years of age because of the potential for serious side effects, including slowed or difficult breathing.[59]

Non-opioids

Dextromethorphan Due to its binding to N-methyl-D-aspartate (NMDA) receptors in the brain, dextromethorphan $HBr^{(+)}$-3-methoxy-17-methyl-morphinan hydrobromide monohydrate, the dextro-isomer of levorphanol methyl ether, was thought to be effective for reducing acute cough; however, due to the lack of proof in the pediatric population, its clinical efficacy is currently questioned. Four double-blind, randomized, placebo-controlled studies in pediatric patients (n=327) affected by acute cough did not report a significant effect of dextromethorphan in reducing cough frequency, impact on the child or parental sleep, and parent-recorded symptom scores.[10] Moreover, when compared to placebo, dextromethorphan was frequently associated with numerous reports of serious adverse events, such as dystonia, anaphylaxis, and bullous mastocytosis at standard doses and psychosis, hallucinations, ataxia, somnolence, peripheral neuropathy, cerebellar degeneration, and death at higher doses.[10] Furthermore, the potential for accidental overdose and abuse of dextromethorphan pushed investigators to review the efficacy and safety of antitussive drugs containing dextromethorphan, especially in the pediatric population where there is a paucity of studies.[60]

Caramiphen Originally developed as a muscle relaxant due to its anticholinergic properties, caramiphen edisylate shows central antitussive effects when administered orally, although not consistently. In the adult population, three double-blind controlled trials confirmed that caramiphen was antitussive but less effective than codeine.[61-63] Due to the lack of consistent evidence about its efficacy, the FDA removed caramiphen from the market.[15]

Carbetapentane or pentoxyverine Usually administrated in combination with guaifenesin and H1-receptor antagonists, carbetapentane 2-[2-(diethylamino)-ethox^{y}ethyl-1-phenylcyclopentanecarboxylate] is commonly used to treat acute cough. Probably, it exerts its antitussive activity mainly in the CNS by binding to sigma, kappa, and mu-opioid receptors.[64] To the best of our knowledge, no studies of carbetapentane or pentoxyverine as a treatment in acute cough were identified in children.[15]

New drugs for the treatment of acute cough

A better understanding of the mechanisms involved in cough reflex has allowed new potential therapeutic targets to be identified, such as channels/receptors expressed by airway sensory nerves, as well as to expand the therapeutic range currently available in the treatment of acute cough.

Purinergic receptors

Purinergic receptors are adenosine 5′-triphosphate (ATP)-activated ion channels commonly expressed on airway sensory afferent nerves. Particularly, the subtypes P2X receptor has recently attracted the attention of many researchers as a promising drug target. Gefapixant, previously known as AF-219/MK7264, is a P2X3 receptor antagonist shown to cause a 75% reduction in cough frequency when compared with placebo at high doses (600 mg bd); however, all enrolled patients were experiencing taste disturbances such as hypogeusia and dysgeusia.[65] Successively, a phase 2b trial revealed that gefapixant was effective in reducing cough frequency also at lower doses (30–50 mg) with less taste disturbance.[66] Large-scale phase III trials on adults with refractory cough are ongoing to evaluate both the cough-modifying effect and safety of P2X3 receptor antagonist therapy.[67,68] Currently, RCTs on its use in the pediatric population are still not available.

Transient receptor potential receptors

Initially discovered in *Drosophila* in the 1960s,[69] transient receptor potential (TRP) channels are a family of cation channels expressed on airway sensory afferent nerves, epithelial cells, and smooth muscle cells,[70] and directly activated by multiple stimuli such as temperature, light, pressure, osmolality, and pain.[71] The TRP channel can be scholastically divided into six subfamilies of which TRPV1, TRPV4, transient receptor ankyrin 1 (TRPA1), and TRPM8 are of particular interest regarding cough reflex.

TRPV1 is a polymodal channel expressed on C-fibers sensory neurons and induced by temperature, pro-inflammatory mediators, acidity, and capsaicin. Two compounds (SB-705498 and XEN-D0501) have been tested in RCTs performed in adult patients with chronic cough and, although a significant reduction in capsaicin-induced cough reflex was detected, both TRPV1 antagonists failed to reduce cough frequency.[72,73]

TRPV4 is an osmosensor whose activation has been associated with the release of ATP and P2X3 receptors activation.[74] The efficacy of TRPV4 has been tested in a clinical trial with the TRPV4 antagonist, GSK2798745, but it was stopped early as the interim analysis suggested a lack of efficacy.[75]

Activated by irritant chemicals, TRPA1 has been demonstrated to evoke cough reflex both in *in vivo* models and in humans via the inhalation of cinnamaldehyde.[76] However, a clinical trial with the TRPA1 antagonist, GRC 17536, failed to test its efficacy on cough frequency.[77]

To date, the evidence for an antitussive role of the TRPM8 receptor, activated by cooling compounds such as menthol, icilin, and eucalyptol, is inconclusive.[78]

Gamma-aminobutyric acid B ($GABA^B$) receptor agonists

By acting on neuronal pathways influencing cough reflex, Lesogaberan, a peripherally acting $GABA_B$ receptor agonist, has been proved to be effective in reducing citric acid-evoked cough in a preclinical model but not in humans.[79]

Sodium cromoglycate

In patients affected by lung cancer and angiotensin-converting enzyme inhibitor-induced cough,[80,81] inhaled sodium cromoglycate revealed a positive antitussive effect, presumably through the G-protein-coupled receptor-mediated reduction of C-fibers activity. In a randomized placebo-controlled trial, where high-dose cromoglycate (PA101) was delivered via eFlow nebulizer, a reduction in cough was observed only in patients with idiopathic pulmonary fibrosis but not in chronic idiopathic cough subjects.[82]

Central neuronal receptors antagonists

Central neuronal receptors have recently been proposed as an attractive strategy in the treatment of cough. Neurokinin receptor antagonism 1 (NK 1) and alpha (α)7 acetylcholine receptor agonism, previously developed for chemotherapy-induced nausea and vomiting, and schizophrenia, respectively, were shown to play a role in the CNS in evoking cough. Clinical data on their effects on cough frequency are still awaited.[83, 84]

Discussion

Despite the scientific knowledge regarding neurophysiological pathways involved in cough reflex having significantly advanced in recent years, the diagnostic and therapeutic management of acute cough still remains nebulous and contradictory. Aiming to provide clarity on disease management, we performed an updated review about the therapeutic management of acute cough in the pediatric population and proposed a diagnostic algorithm to offer a practical guide for the pediatrician (Figure 1).

As viral URTIs are the most common causes of acute cough, up to 90% of cases do not need to be treated. No curative (antiviral) treatment is available, and antibiotics have repeatedly been shown to neither improve symptoms nor prevent complications, thus resulting in them being ineffective in patients without preexisting lung disease.[15] Taking these considerations into account, children with acute cough without cough pointers can be safely managed using a “wait, watch, review” approach, consisting of parental reassurance and close clinical observation.

A pathologically excessive cough commonly causes significant complaints both to the patient and the whole family; thus, investigating the reasons of parental anxiety and offering reassurance are crucial in the management of acute cough. Providing parents with information and educating on expected illness duration might reduce anxiety, additional consultations, and the need for OTC medication use.[85-87] In this regard, it has been demonstrated that whether parents are insistently requiring medication prescriptions and/or the physician perceives that the child’s parents expect one, there is an increased risk

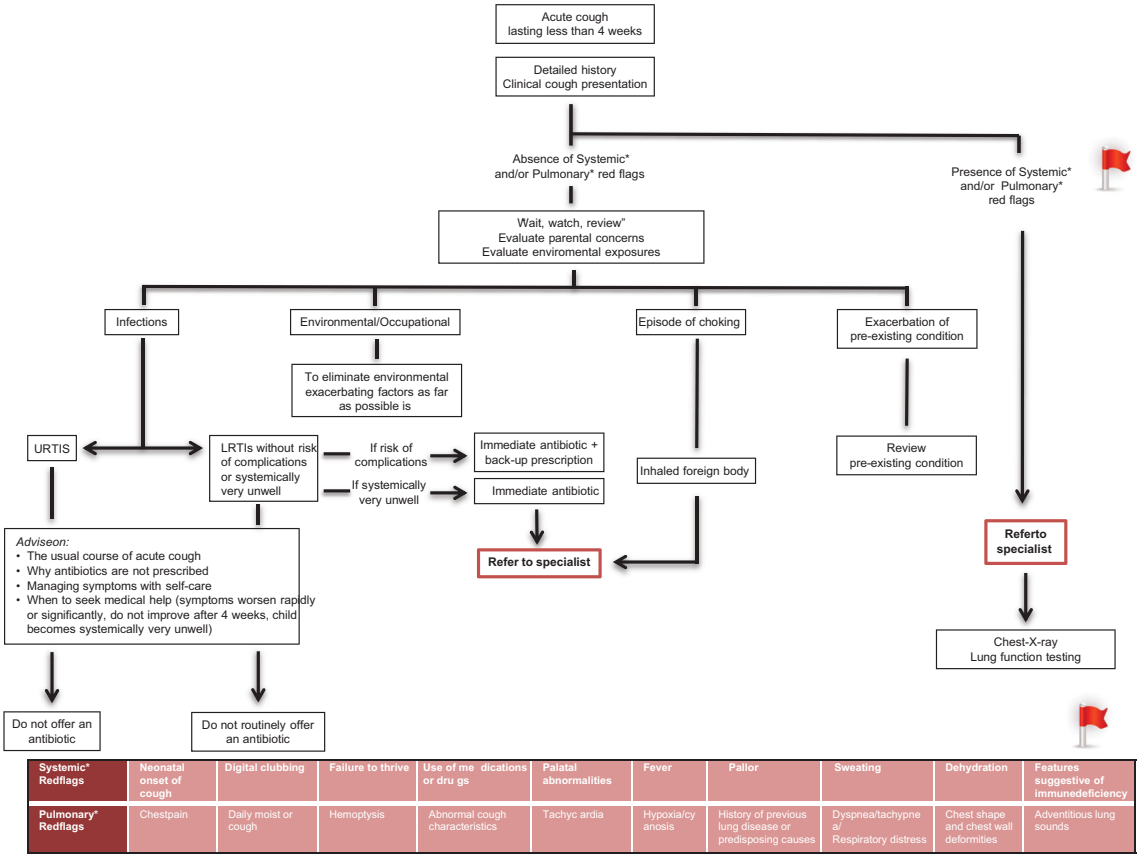

Figure 1 Flow chart of acute cough assessment for children. URTIs: upper respiratory tract infections; LTRIs: lower respiratory tract infections.

that an ineffective medication will be written. Thus, the child's parents should be correctly informed on the cause and course of the disease in order to appropriately evaluate medication prescription. Despite a number of evidence-based guidelines and systematic reviews published more than a decade ago, which do not recommend pharmacological treatment of acute cough in children,[88-91] a safe and effective antitussive therapy remains a significant area of unmet need.[92] Most cough suppressants used in adults present an unacceptable risk-benefit profile for pediatric use because of the potential for excessive sedation (narcotics as codeine and hydrocodone), dextromethorphan, and first-generation antihistamine or hyperstimulation (pseudoephedrine and phenylephrine).[89,92,93] Furthermore, although nonpharmacological, supportive care with analgesics, hot beverages, lozenges and honey are commonly used by many pediatricians, unfortunately these strategies are often ineffective (90). Since cough is frequently a highly distressing symptom with a significant impact on children's and parents' sleep and daily activities,[22] when symptomatic cough treatment is indicated to avoid a detrimental effect on well-being and quality of life of children and parents, peripherally acting antitussives such as levodropropizine should be preferred for the favorable efficacy and safety profile and risk-benefit ratio.[24,94] Moreover, an unnecessary prescription antibiotic therapy, also contributing to drug resistance development as likely to cause side effects, will be reserved for patients who are seriously ill and/or who need them.[95]

In parallel, it is equally important to record information on environmental exacerbating factors, such as exposure to tobacco smoke, and clinical history, as well as cough quality. It is crucial to attempt to eliminate environmental exacerbating factors as far as possible. In children, fully immunized whooping cough and influenza are less common. In URTIs, coryza and fever usually precede the appearance of cough; if URTIs symptoms, except cough, last for more than 10 days, acute rhinosinusitis should also be suspected.[96] An episode of choking suggests an inhaled foreign body. The acute cough could also be indicative of other conditions such as bronchiolitis, whooping cough, pneumonia, and asthma. Although it is a benign and self-limiting illness, the physician should not miss that up to 12% of children with acute cough can experience complications, even if it is commonly mild and easy to treat. Otitis media is the most common complication, followed by diarrhea and vomiting, and rash. About 5% of children can report bronchitis or pneumonia. Hospitalization is required in 1-2% of cases. Although there is sparse evidence regarding the predictive value of signs and symptoms in children with acute cough, studies have reported that children with chest sign and fever show a probability of complications of 18% and 28%, respectively, while children with neither chest signs nor fever have a probability of complications

of only 6%.[95] Taking these considerations together, when the child appears otherwise healthy or shows features of an underlying disease, such as finger clubbing, failure to thrive, chest wall deformities, adventitious lung sounds, and palatal abnormalities, or when symptoms worsen rapidly or significantly, the patient should be referred to a specialist and subjected to chest X-ray and, if older than 5 years, lung function testing.

Conclusions

An acute cough dramatically impacts the socioeconomic and healthcare system. On the one hand, in most cases, an acute cough does not raise minimal concerns among physicians as it is a benign and self-limiting disease and is generally caused by URTIs, while on the other hand, it is the most common symptom for which patients require medical visits, hospitalization, and spend large amount of money on healthcare. However, a symptomatic treatment of acute cough with antitussive agents is often needed in order to improve the quality of life, restore physical and social activities, and hopefully avoid the development of persistent cough.[94,98,99] Therapeutic options for the management of acute cough in children are limited because of the lack of data to support the efficacy of currently available antitussives in the pediatric population, as well as unacceptable side effects and safety concerns associated with most agents used in the management of adult cough (90, 92), Furthermore, frequently, patients adopt a "do-it-yourself" approach and also resort to OTC medicines, most of which do not show a clinically proven efficacy and reliability in supporting their use. Among the drugs currently used for the symptomatic treatment of cough, peripherally acting antitussives such as levodropropizine should be recommended especially in children for the favorable risk-benefit ratio.[24,92,94]

Despite the knowledge of cough reflex and factors that lead to a hypertussive status having significantly advanced in recent years, these findings have not yet been translated into clinical practice as well as in approved new medicines. The number of studies in each category of cough medications is very small, and availability, dosing, and treatment duration of OTC drugs vary significantly among studies. Recently, the peripheral and central neuronal pathways of cough reflex have been targeting for new and promising drugs in managing and reducing acute cough; however, their use should be supported by adequate research within this targeted age group. Therefore, the need for well-performed clinical trials focusing on new and reliable medications with proven efficacy and safety in acute cough is urgently required.

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