# Pediatric Cough Guidelines

To improve the quality of clinical practice
and patient care in Pakistan

PCB
PEDIATRIC
COUGH
ADVISORY
BOARD

Guidelines for the diagnosis and treatment
of acute and chronic cough

# Recommendation At Glance

## PPA (Pulmonary Group)

| Intervention | Outcome | Harms | Comment |
|---|---|---|---|
| Physical Intervention[1] e.g.handwashing | Reduced risk with hand washing & disinfectants | No harms noted | Likely beneficial |
| Honey [20-27] | Benefitover placebo & dextromethorphan | No adverse event | some benefit |
| Nasalirrigation[30] | No difference in nasal symptom score | Nasalirritation, Drynose, Intolerance | Unclear benefit |
| Humidifield air[31] | Fewer participants with persistent symptoms | Mask Discomfort & nasal congestion | Unclear benefit |
| Ivy Leaf extract[32-35] (DEV 5-7.5:1) | Benefit over placebo | No evidence of harms | Possibly benefit |
| Intranasal ipratropium[15] | Improved rhinorrhea but not nasal congestion | Increased epistaxis, nasal dryness & mouth dryness | Possibly benefit |
| Antihistamine, combination therapy[11] | Best evidence for antihistamine-decongestant combination | Increased adverse events (insomnia / dry mouth) | Likely beneficial in older children; no effect in children <5 years |

# Preface

Cough is the most common symptom in paediatric medicine. On an average in developing countries each child suffers from 8 to 10 episodes of cough annually ,especially during winter. Aetiology of cough is extremely variable but the most common reason according to WHO is URTI and rarely under lying pneumonia and other serious pathologies. Ironically being the common symptom there are no set guidelines and every paediatrician treats it in his own ways The magnitude of the problem increases because of lack of regulations and over the counter availability of medicines including different groups of antibiotics.Taking lead from guidelines framed by various paediatric societies of different countries Pulmonology group of PPA took up a huge challenge to develop indigenous guidelines for our children. The group started the activity about one and half year ago and after many hectic meetings involving many learned PPA members and numerous deliberations has come up with an initial draft.We have tried to address the most commonly asked questions about definition, aetiology, diagnosis and various management modalities both for acute and chronic cough in children. This is by no means a final draft and group will welcome and appreciate any suggestions or any contributions from our colleagues ,friends and teachers both from within and outside Pakistan. I sincerely hope that once these guidelines are finalised it will go a along way in rationalising treatment for this common problem.

With best wishes and regards.
Prof . Waqar Hussain

**Pakistan Pediatric Association-Pulmonary Group**
**Expert Panel contributing in National Cough Guidelines**

Patron:Prof.Waqar Hussain
Chairman: Prof. Imran Iqbal
Convener: Assoc: Prof. Ghulam Mustafa
Members:
1.Prof. Sultan Mustafa
2.Prof. Khalid Mahmood
3.Prof. Muhammad Ali
4.Prof. Salma Sheikh
5.Prof. Ejaz Khan
6.Prof. Bashir Abroo
7.Prof. Irshad Ahmad

**Editor**: Prof. Dr. Sultan Mustafa

## Cover design:

We would recommend that the reader verify any procedures, treatment and drug dosages described in this book. Editor, contributors and publisher are not responsible for any injury and\or damage to patients or property arising from any error in or omission from this publication.

## Introduction: Why these guidelines?

Cough is the most common symptom with which the parents bring their children to a doctor, [1]. The normal children, when they are well, cough 11 times/day on an average (range 1-34), and this increases in frequency and severity during winter, when upper respiratory tract infections (URTI) are frequent. The prevalence of cough has been reported in 28% boys & 30 % girls [2]. Cough can impact a child's activity level and ability to sleep well, play or attend school and is often a source of parental anxiety [3]. Cough in children is different from that in adults in terms o duration, presentation, etiology and management [4]. The cough & cold medicines are the most commonly used medicines in children, though the evidence suggests that they are not effective. Given the wide spectrum of etiology of cough, it isnecessary to find out and treat the underlying cause. These guidelines are the clinical statement of the Pediatric pulmonary group of the Pakistan Pediatric Association regarding management of cough in children. These guidelines are needed because there exist no guidelines for children younger than 15 years though it is the commonest symptom in children and is not usually correctly diagnosed or treated.

Therefore these guidelines have been formulated for managing cough in children at primary and secondary care levels. We will discuss acute, sub-acute & chronic cough.

## Guidelines development Methodology:

We formed the Pediatric Cough Advisory Board (PCAB) from the members of the Pediatric Pulmonary Group (PPG).
The patron, president & convener had a preliminary meeting at Lahore in 12 January 2016. A tentative plan of action was formed. The ten members were chosen from all over the country, from representing all the provinces. They had a joint meeting at Lahore on 14th February 2016. The whole plan of action was formulated. The tasks were assigned and it was decided to have 3 Skype meetings in the coming weeks to discuss the issues and progress on the guidelines. After the meetings and having received the inputs from the various members, first draft of guidelines was prepared. This draft was discussed at PCAB meeting at Lahore on 13th July 2016. After incorporating the suggested changes, it was sent via e-mails to all the PCAB members. After their approval, the same was circulated to the rest of the members of the pulmonary group-PPA to get further inputs from all of them.The input was also sought from the General physicians & residents.

## Definitions:

### Cough (tussis):

By definition it is a "forceful expulsion of air from the lungs, frequently to clear the lung airways of fluids, mucus, or other material, and associated with a characteristic sound". Cough is a protective reflex and enhances innate immunity of the respiratory system by improving mucociliary clearance[5] so it is wise not to suppress it without identifying and treating its underlying cause. It can be voluntary and/or involuntary.

The sensitivity of the cough receptors is modulated by disease state. Up-regulation of cough receptors has been demonstrated after viral upper respiratory tract infection (URTI), asthma, gastroesophageal reflux disease (GERD) and treatment with angiotensin converting enzyme inhibitors. This causes cough to be triggered through relatively non-specific provocation [8].

Cough can be classified on the basis of duration of symptoms, expected etiology or characteristic of cough. Below definitions are based on the duration of presentation in children (Figure 1) [9].

### Acute Cough: Cough lasting for less than 3 weeks.

Acute cough is mostly associated with viral upper respiratory tract infections and does not require specific diagnostic evaluation. Between 35% and 40% of school age children continue to cough 10 days after the onset of a common cold, and 10% of preschool children continue to cough 25 days after a respiratory tract infection. So we have used the duration of 3 weeks for acute cough.

### Acute Prolonged Cough: Cough for more than 3 weeks but less than 8 weeks.

The children with pertussis or post viral infection run a protracted course and do not warrant further investigations [11]. This cough resolves slowly and though not acute yet needs caution before starting work up for the chronic cough.

## Chronic Cough: Cough lasting for more than 8 weeks

This may further be divided in recurrent & persistent [12]. The studies are not consistent to define duration of chronic cough [13]. It is important to use definitions of cough duration in the context of individual patient presentations, as some serious etiologies of cough require early attention and intervention [14].

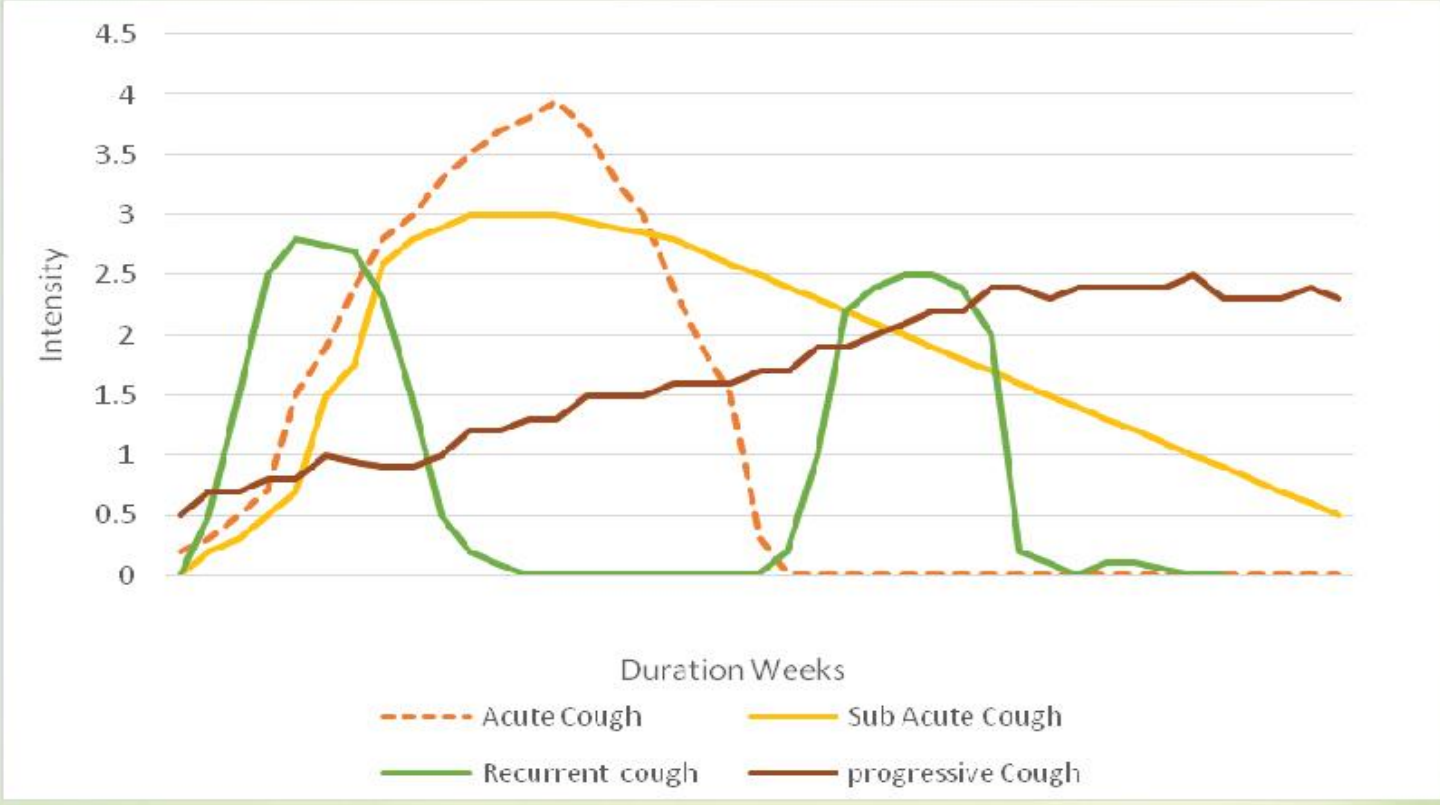
## Specific cough:

A cough in which there is a clear identifiable cause. The symptoms and signs are suggestive of an underlying etiology.

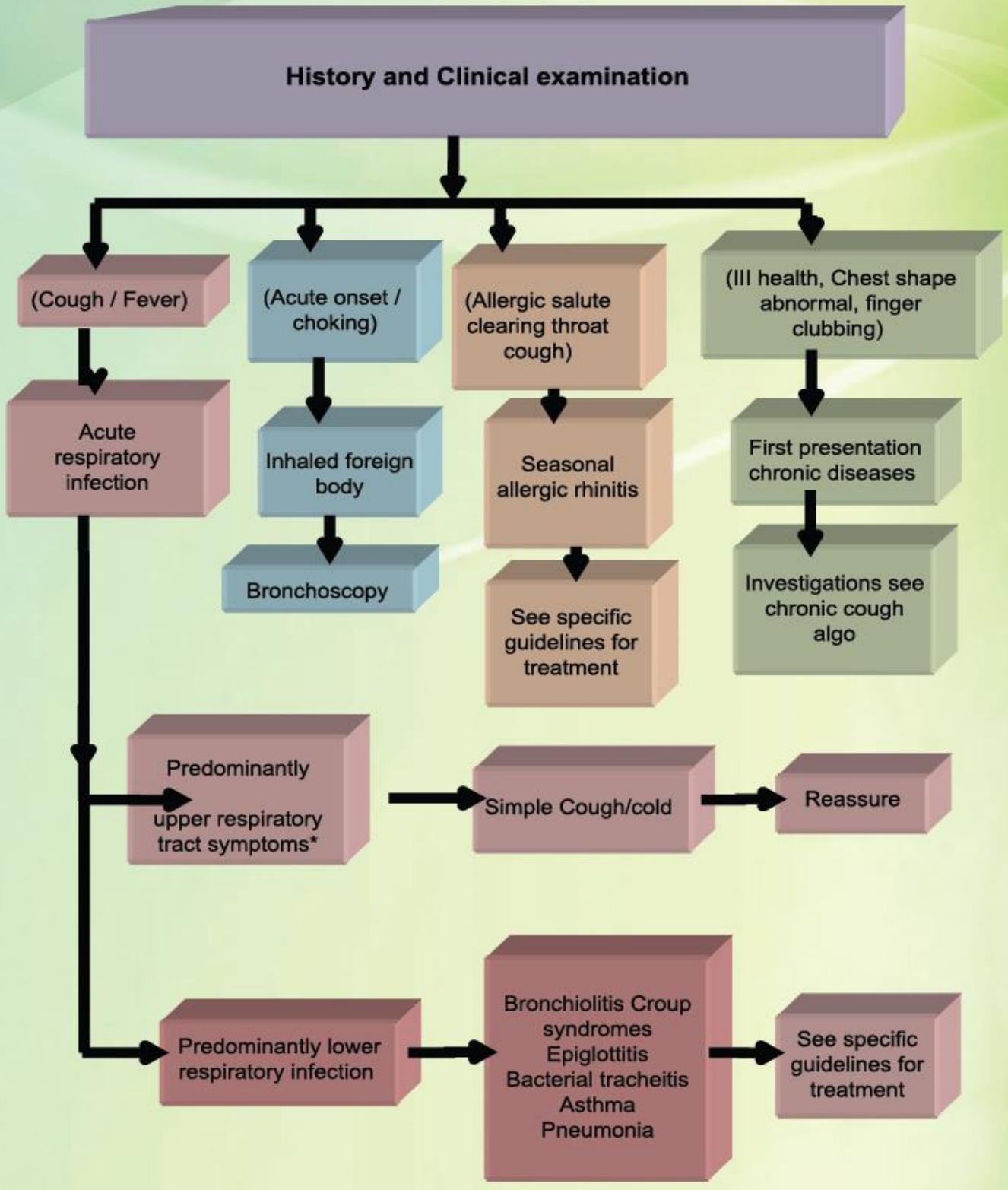
## Non-specific cough:

The isolated, dry cough without an identifiable etiology in a child having no symptoms/signs of chronic lung disease. The majorities are due to non-serious etiology (e.g. post-viral cough and/or increased cough receptor sensitivity) and may spontaneously resolve. (Figure 1 Modified from Marais et al) [15].

## Figure 1: Types of Cough



# Figure 2: Algorithm for Acute Cough



# Table: Questions to address in cough evaluation

| Question | Examples | Diagnosis |
|---|---|---|
| **How did the cough start?** | Sudden acute onset | Retained inhaled foreign body |
| | Cough and cold | Infective cause (e.g. post-viral) |
| **When did the cough start?** | Neonatal onset (especially if in first few days of life) | Aspiration |
| | | Congenital malformation |
| | | Cystic fibrosis |
| | | Primary ciliary dyskinesia |
| | | Lung infection in utero |
| **What triggers the cough?** | Exercise, cold air, early morning | Asthma |
| | Lying down | Postnasal drip, gastro-esophageal reflux disease |
| | Feeding | Recurrent pulmonary aspiration |
| **What is the quality of the cough?** | Productive ("moist or wet") | Chronic suppurative lung disease (bronchiectasis) e.g. cystic fibrosis |
| | Paroxysmal spasmodic cough with or without an inspiratory "whoop" and vomit | Pertussis or pertussis-like illness |
| | Hemoptysis | Cystic fibrosis |
| | | Other bronchiectasis |
| | | Retained inhaled foreign body |
| | | Tuberculosis |
| | | Tumor |
| | | Pulmonary haemosiderosis |
| | | Pulmonary arteriovenous malformation |
| | "Bizarre honking cough" in a child exhibiting indifference to the cough and which increases with attention | Psychogenic cough |
| | Dry repetitive cough, disappears with sleep | Habit cough |
| | Brassy, barking or "seal-like" | Tracheal or glottic cause (e.g. tracheomalacia and/or bronchomalacia) |
| | Cough producing casts of the airways | Plastic bronchitis |

# Table: Questions to address in cough evaluation

| | | |
|---|---|---|
| **Is the cough progressively worsening?** | | Inhaled foreign body |
| | | Lobar collapse |
| | | Tuberculosis |
| | | Rapidly expanding intrathoracic lesion |
| | | Cystic fibrosis<br>Pulmonary haemosiderosis<br>Tumor<br>Arteriovenous malfornation |

# Table: Questions to address in cough evaluation

| | | |
|---|---|---|
| **Is the cough an isolated symptom?** | Isolated cough (otherwise well) | Non-specific isolated cough |
| | | Recurrent viral bronchitis |
| | | Psychogenic cough |
| | Associated wheezing present | Asthma |
| | | Retained inhaled foreign body |
| | | Recurrent pulmonary aspiration |
| | | Airways compression or tracheobronchomalacia |
| | | Bronchiolitis obliterans or interstitial lung disease |
| | | Neonatal chronic lung disease and rarely |
| | | Cardiac disease with either congestive heart failure or large left to right shunts |
| | Associated ill health, recurrent pneumonia or pulmonary infiltrates | Cystic fibrosis |
| | | Immune deficiencies |
| | | Primary ciliary disorders |
| | | Recurrent pulmonary aspiration |
| | | Retained inhaled foreign body |
| | | Tuberculosis |
| | | Persistent bacterial bronchitis |
| | | Anatomical disorder |
| | Associated shortness of breath and restrictive lung defect | Interstitial lung disease |
| | Lying down | Postnasal drip, gastro-esophageal reflux disease |
| | Feeding | Recurrent pulmonary aspiration |

# Table: Common Differential diagnosis in a child presenting with acute cough

| Condition | Features |
|---|---|
| **URTI** | Short duration<br>Coryza |
| **Sinusitis** | Headache<br>Sinus tenderness |
| **Pneumonia** | Cough with fast breathing or/and<br>Lower chest wall indrawing |
| **Asthma or wheeze** | Recurrent episodes of shortness of breath or wheeze<br>Night cough or cough and wheeze with exercise<br>Response to bronchodilators<br>Known or family history of allergy or asthma |
| **Bronchiolitis** | Cough<br>Wheeze and crackles<br>Age usually < 1 year |
| **Pertussis** | Paroxysms of cough followed by whoop, vomiting,cyanosis or apnoea<br>No symptoms between bouts of cough<br>No fever<br>No history of DPT vaccination |
| **Foreign body** | History of sudden choking<br>Sudden onset of stridor or respiratory distress<br>Focal areas of wheeze or reduced breath sounds |
| **Croup** | Inspiratory stridor<br>Current measles<br>Barking character to cough<br>Hoarse voice |
| **Diphtheria** | No history of DPT vaccination<br>Inspiratory stridor<br>Grey pharyngeal membrane<br>Cardiac arrhythmia |

# Table: Indications for performing a chest radiograph in a child with acute cough

| Indication | Features | Likely common diagnoses |
|---|---|---|
| **Uncertainty about the diagnosis of pneumonia** | Fever and rapid breathing in the absence of wheeze/stridor<br>Localizing signs in chest<br>Persisting high fever or unusual course in bronchiolitis<br>Cough and fever persisting beyond 4–5 days | Pneumonia<br>N.B. Chest radiograph is not always indicated: use to resolve uncertainty or in more severe cases. |
| **Possibility of an inhaled foreign body** | Choking episode may not have been witnessed but cough of sudden onset or presence of asymmetrical wheeze or hyperinflation | Inhaled foreign body<br>Expiratory film may help in acute bronchial obstruction, but normal chest radiograph does not exclude foreign body.<br>Bronchoscopy is the most important investigation. |
| **Pointers suggesting that this is a presentation of a chronic respiratory disorder** | Failure to thrive<br>Finger clubbing<br>Overinflated chest<br>Chest deformity | See section on chronic cough |
| **Unusual clinical course** | Cough is relentlessly progressive beyond 2–3 weeks<br>Recurrent fever after initial resolution | Pneumonia<br>Enlarging intrathoracic lesion<br>Tuberculosis<br>Inhaled foreign body<br>Lobar collapse |
| **Is there hemoptysis?** | | Acute pneumonia<br>Chronic lung disorder (e.g. cystic fibrosis)<br>Inhaled foreign body<br>Tuberculosis<br>Pulmonary haemosiderosis<br>Tumor<br>Arteriovenous malformation |

## Prolonged acute cough in Children

### Why the term "Prolonged Acute Cough".

There are no studies that clearly define when a cough may be labeled as chronic cough [83]. American and Australian use the term chronic cough when it lasts more than 4 weeks [13,84] while others use this term when it lasts beyond 8 weeks [14].

The cough that goes beyond 2-3 weeks in children may be pertussoid or transient post viral syndrome and tends to abate in 8 weeks or at the minimum starts abating during this time. So these children actually require a period of observation from 3-8 weeks before further investigations. As this period is neither an acute period nor it requires to be dealt like a chronic, therefore we decided to adopt this term for the cough lasting between 3-8 weeks. The clinically well children in whom the cough is improving during 3-8 weeks may not require further workup. But if:

- The cough is getting worse over time
- The child already has signs of chronic lung disease
- An inhaled foreign body is suspected

Then the above policy of 'wait & see' is not appropriate and immediate investigations are warranted. The diagnoses that have to be kept in mind for a progressively worse cough are:

- Retained inhaled foreign body
- Pertussis
- Lobar collapse secondary to mucus plug
- Expanding mediastinal neoplasm
- Tuberculosis (often with accompanying weight loss)

### Causes of Prolonged Acute Cough:

These are the causes where complete resolution is expected over time.

### 1.Post infectious or Post viral Cough:

This is a non-specific cough that starts as cough & cold and then persists. This is by far the most common type of cough. In majority of children this resolves spontaneously [83]. No therapeutic intervention is recommended or required [14].

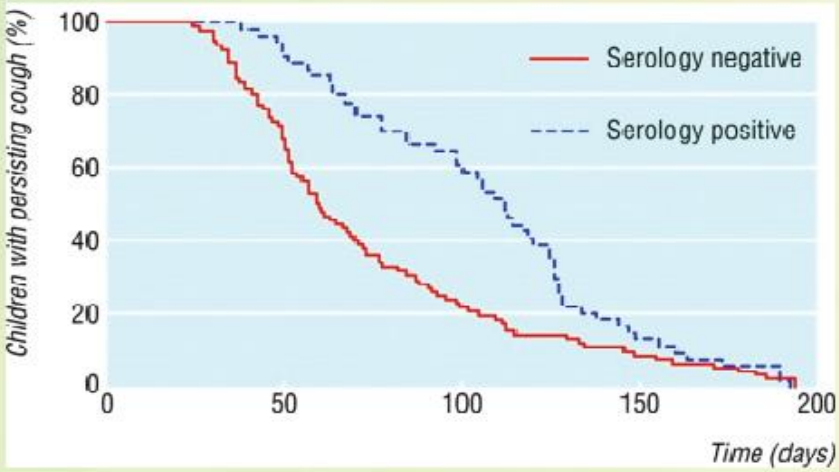
## 2.Acute Bronchiolitis:

Acute bronchiolitis is the most common acute lower respiratory infection in children less than 2 years. They present with tachypnea, dry cough, rhonchi, occasional crepts and audible wheeze. Though it is a self-limiting disease yet a significant number have persistent respiratory symptoms like cough in the post-acute phase [85]. The most significant concern of parents is a dry and irritating cough of bronchiolitis that is present in Respiratory Syncytial Virus (RSV) positive infants [86 85,87].Systematic reviews have not found any benefit with the use of inhaled glucocorticoids or leukotriene antagonists during acute phase to prevent post-bronchiolitis wheezing or cough [88,89].

## 3. Pertussis:

Although the infants less than 2 months are more at risk for severe pertussis but older children & adolescents are also affected and have prolonged acute cough [90,91]. It has been estimated that 32-37% of prolonged acute cough is due to pertussis [92 93,94]. The median duration of cough in children 5-16 years with serological evidence of pertussis has been estimated as 112 days (Range 38-191) [92,93]. In the same study pertussis negative (mostly mycoplasma positive) had cough with median duration of 58 days (range24-192). The important point is that the diagnosis of pertussis needs to be considered even when the classical pertussis symptoms are not present [94]. Almost all these children had complete resolution of cough. So if some child is started with inhaled steroids for this prolonged cough, they would seem to benefit from inhaled steroids but actually the resolution would have occurred due to the natural course of the cough.

**Figure :3**



The macrolides in pertussis may work if given in the beginning of the disease [95]. They may be given within 6 weeks of onset of cough for infants less than 1 year and within 3 weeks in children above 1 year of age [96]. Antibiotics have shown to lessen the duration of infectiousness [97]. But after this 'window' period macrolides do not alter the course of illness or infectiousness.

**4.Patients recovering from complicated acute pneumonia (e.g. empyema):**
Around one third of children treated with empyema can have prolonged acute cough even after 4 weeks. This may be due to the residual of disease and may benefit from a prolonged course of antibiotics after discharge for 1–4 weeks or longer [98,99].

**5.Rhinosinusitis:**
Nasal secretions that continue more than 10 days with/without a wet or dry cough diagnose the rhinosinusitis. The atopic children are more likely to have chronic rhinosinusitis. The symptoms continue for 4-8 weeks and unlike adults may not have facial pain or discomfort.
Antibiotics (amoxicillin-clavulanate) may be of benefit in bacterial sinusitis but more side effects are observed [100 101,102].

**6.Retained Inhaled foreign body:**
The history of choking and then prolonged recurrent cough with persistent pneumonia leads to the suspicion of foreign body aspiration (FBA). The diagnosis may be delayed when the aspiration is not observed or the typical triad of cough, wheeze and diminished breath sound is not present . This delay in diagnosis and removal may lead to episodic chronic cough and recurrent pneumonias. The virtual bronchoscopy is promising for diagnosing such children [105].
The treatment is immediate removal of foreign body endoscopically.

## 7.Persistent bacterial bronchitis (PBB):

The diagnostic criteria for PBB is:

i.wet cough >four weeks duration

ii.identifiable lower airway bacterial infection on broncho-alveolar lavage (BAL) culture

iii.response to antibiotics (amoxicillin/clavulanate) with resolution of cough within two weeks

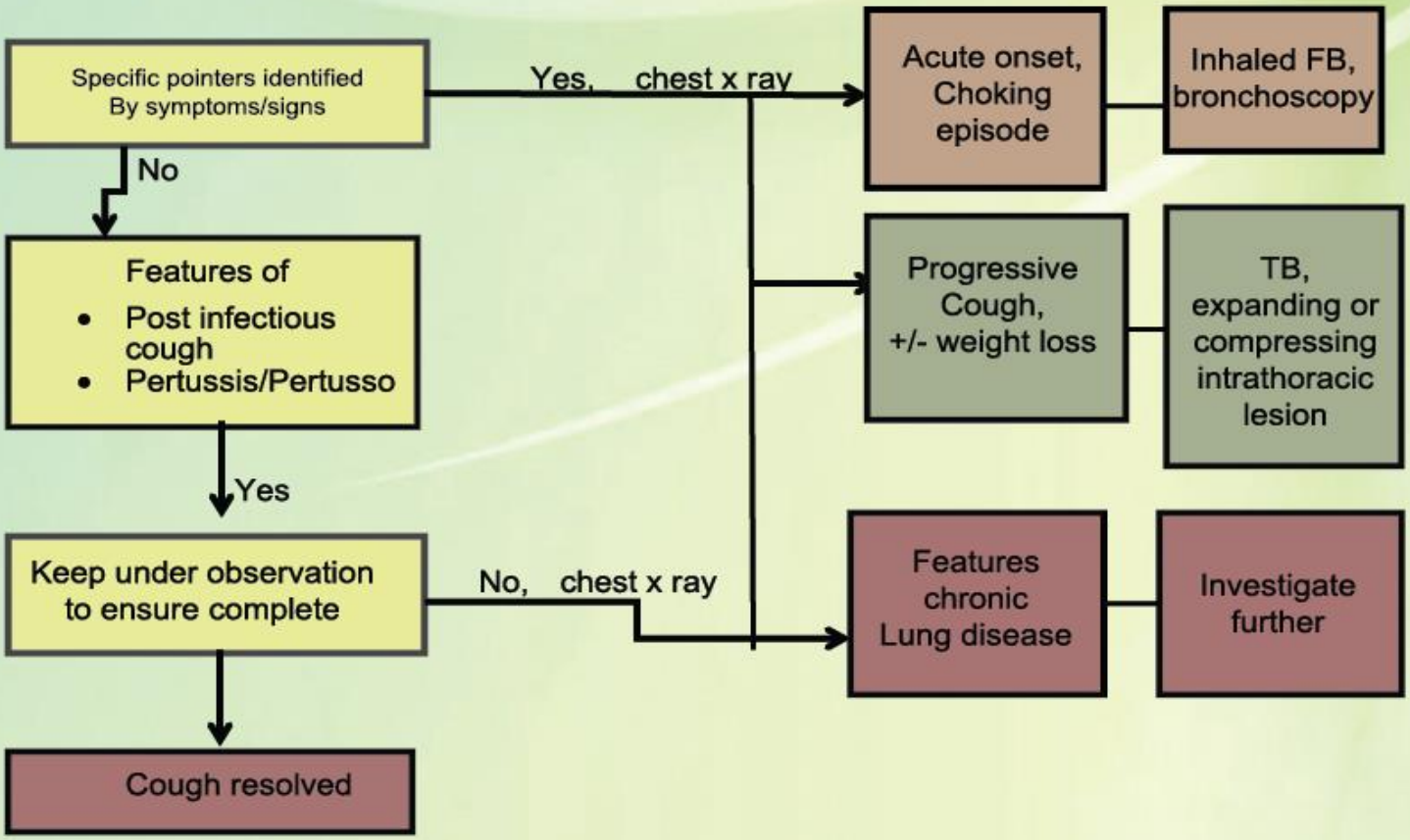
iv.the absence of an alternative specific etiology [106,107,108.]

An association has been found between PBB of infancy and airway malacia (tracheal, bronchial) [109,110,111.] This cough resolve with a 2-week course of antibiotics (amoxicillin-clavulanate) though at times may need 4–6 weeks course. The investigations are warranted to look for immunodeficiency or chronic suppurative lung disease when this becomes recurrent or if it does not resolves [112,113.] The other diseases that lead to chronic coughing include cystic fibrosis, immune deficiencies, primary ciliary dyskinesia and recurrent pulmonary aspiration.

## Conclusion:

These are only the common causes of prolonged acute cough. There are reasonable numbers of children who keep coughing after 3 weeks of common cold. If they are clinically well in the absence of a serious illness and the cough is resolving then 'wait & see' is the best policy. The work up should not be delayed if there is a possibility of retained inhaled foreign body, the cough is worsening or in the presence of chronic lung disease. A prolonged wet cough that develops after the common cold has resolved may be indicative of persistent bacterial bronchitis or rhinosinusitis. As a guide

## Figure 4: Algorithm for Prolonged Acute Cough



## Table: Patterns, causes and potential investigations of chronic or frequently recurrent cough in otherwise healthy children

| | Pattern | Cause | Potential investigations |
|---|---|---|---|
| Frequently recurring viral bronchitis | Episodic, frequent in winter, associated with "head colds", may occur "back-to-back" | Viral infections | None |
| | | Crowded living conditions, ETS and attendance in child care nursery | Chest radiography |
| | | | Examine during a period when symptom-free |
| Post viral cough | Troublesome cough (day and night) following a respiratory infection and slowly resolving over next 2–3 months | Viral respiratory infections, *Chlamydia* and *Mycoplasma* infections | None, chest radiography, serology |
| | | | Consider trial of asthma therapy (some mild asthmatics have prolonged recovery from each viral infection) |
| Pertussis and pertussis-like illness | Troublesome spasmodic cough after initial respiratory infection that slowly resolves over 3–6 months. Vomiting clear tenacious mucus. Older child may complain of difficulty catching breath | *Bordetella pertussis,* parapertussis, adenovirus, influenza, parainfluenza | Nil |
| | | | Chest radiograph, positive serology or culture may be helpful in reducing requirements for further investigation |
| Cough variant asthma | Isolated cough (no wheezing) due to asthma. Confidence in diagnosis increased when strong atopic background present and cough responds rapidly to anti-asthma medication but relapses when stopped | Asthma | None, chest radiograph. Is airways obstruction present and reversible? |
| | | | BHR or BDR tests, |
| | | | Is there eosinophillic inflammation? Induced sputum, allergy tests, FeNO, response to asthma medication |
| Allergic rhinitis, postnasal drip and sinusitis – cough likely due to concomitant tracheobronchial inflammation | Not fully accepted as a cause of cough. Cough when "head hits the pillow" or constant throat clearing by day. May have transverse nasal crease of "allergic salute" | Causes of allergic rhinitis | ENT examination, often no investigations needed |
| | | | Chest radiography, allergy tests |
| | | | Response to antirhinitis treatment within 2 weeks |
| | | | CT scan of sinuses |
| Psychogenic cough | Usually an older child/ adolescent(1) Tic-like "habit cough" persisting after head cold or during times of stress(2) Bizarre disruptive honking cough with child exhibiting "la belle indifference". Cough goes away with concentration or sleep | Underlying stress | It is important to do investigations to assure the doctor and parent that no major disease is being missed. However, it is important not to keep performing futile investigations that may reinforce the underlying problem |
| | | Bizarre honking cough usually serving a purpose with some secondary gain | |

## Chronic Cough in Children

This is the cough that lasts for more than 8 weeks. This cough usually has a specific diagnosis and so needs to be treated according to the specific protocols as have been devised.

### Investigations:

The relevant investigations have been enlisted in the table-6.

### Management:

The outline of management is shown in figure 5.

- The efforts should be made to make a specific diagnosis and then follow the guidelines accordingly to treat the chronic cough (tuberculosis, asthma, cystic fibrosis, immunodeficiency, primary ciliary dyskinesia etc).
- The use of algorithmic guidelines may be helpful in better evaluation and management of the children with cough 114. One is given in figure 5.
- The habit (psychogenic) cough can be treated with psychotherapy, such as suggestion and/or behavioral therapy. Organic causes need to be excluded.

### When to refer for sub-specialist advice?

A child needs referral to a pediatric pulmonologist in the following conditions:

- Chronic non-specific cough.
- Partially resolved, prolonged (>3 months) or recurrent protracted bronchitis.
- Foreign body inhalation suspected.
- Congenital/developmental defect suspected.
- Persistent hypoxemia associated with cough.

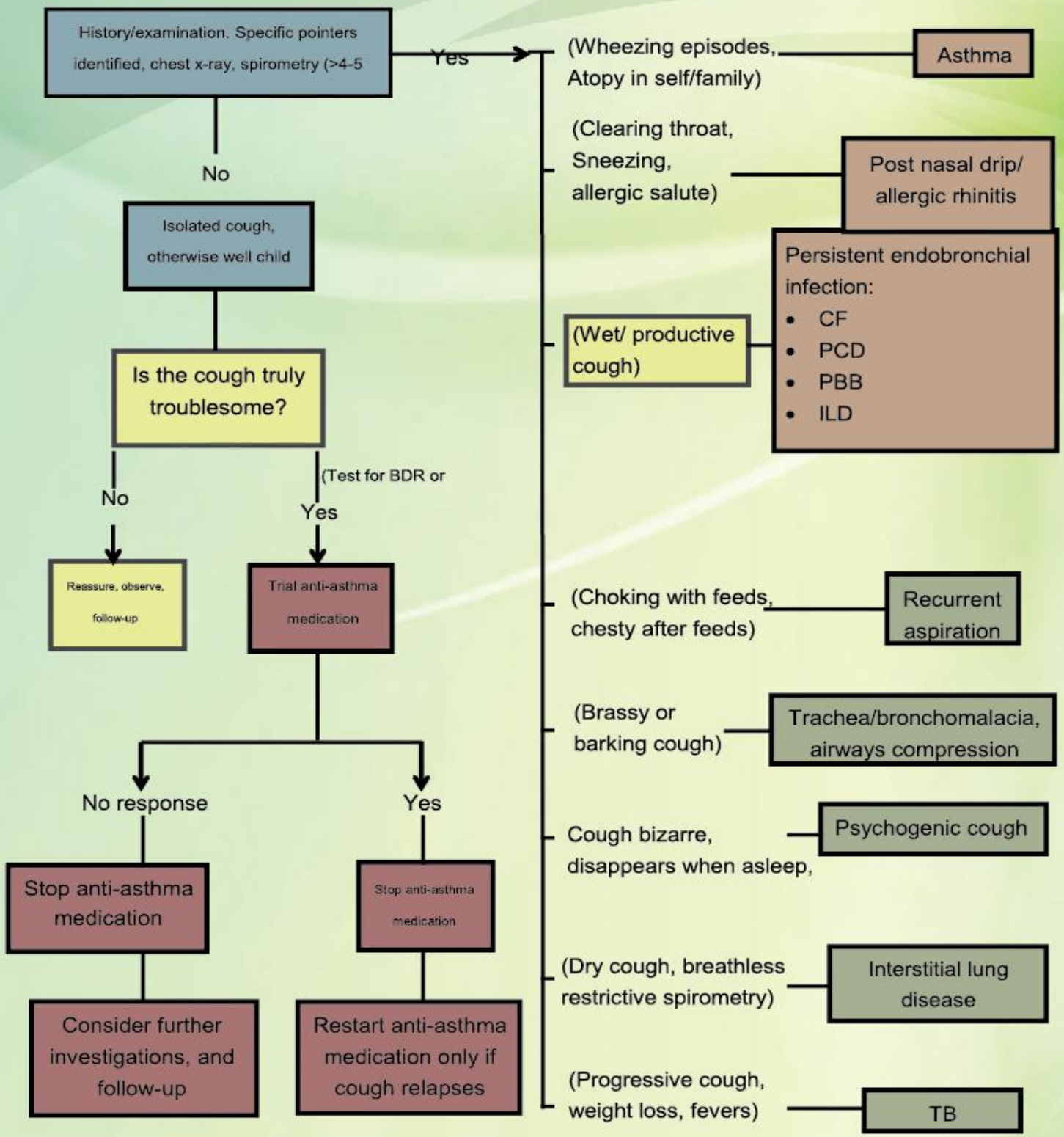
### Conclusion:

The differential diagnosis of chronic cough differs in children than from adults. We need to standardize the protocols for treating various causes in our circumstances. We also need to produce our own evidence base so as to apply to our children. This is possible when we nurture a research ecosystem.

## Table: Potentially serious lung disorders with chronic coughing

| Condition | Investigations |
|---|---|
| Asthma | Lung function studies, bronchoprovocation studies, FeNO, Specific allergen assessment. Skin prick test, |
| Tuberculosis | Chest radiography, Mantoux, early morning gastric aspirates and gamma interferon tests |
| Protracted bacterial bronchitis | Chest radiography, Bronchoscopy & Bronchoalveolar Lavage (BAL), sputum for culture<br>Exclusion of other causes in this table.<br>Response to 4–6 weeks antibiotic and physiotherapy |
| | HRCT scan |
| Recurrent pulmonary aspiration: Laryngeal cleft or 'H' type TEF fistula. GER, Hiatal hernia. Post-TOF repair with swallowing incoordination<br>Neuromuscular or neurodevelopmental disorder | Barium swallow, video fluoroscopy, 24 h pH studies, milk isotope scan, fat-laden macrophage index* on Bronchoalveolar lavage if bronchoscopy indicated. Esophagoscopy with biopsy may be indicated. |
| | NB. There is little evidence that GER alone is a cause of cough in otherwise healthy children |
| | |
| Retained inhaled foreign body | Chest radiography and HRCT scan(virtual bronchoscopy) may show focal lung disease & foreign body. |
| | Rigid bronchoscopy is both diagnostic and therapeutic and is almost always indicated if the history is suggestive of inhaled retained foreign body |
| Immune deficiencies | Differential white cell counts, immunoglobulin levels and subsets, functional antibody responses and lymphocyte subset analysis |
| Anatomical disorder (e.g. bronchomalacia) or lung malformation (e.g. cystic congenital thoracic malformation) | Bronchoscopy and CT scan |
| Cystic fibrosis | Sweat test, nasal potential difference, assessment of pancreatic function, genotyping |
| Primary ciliary disorders | Screening FnNO, saccharine test, Technicium scan for nasal cilia motility. cilial ultrastructure and function, culture of ciliated epithelium |
| | |
| Interstitial lung disease | Spirometry (restrictive defect), chest radiography and HRCT scan, lung biopsy |

**Figure 5: Algorithm for Chronic Cough**



## Recommended Management:

The health professionals & parents do have faith in many over the counter drugs, though the evidence does not support their pharmacologic efficacy [30]. The parents demand "some" medicine as they are not satisfied with "nothing doing" approach. Many of the physicians advise these medicines as a placebo as they don't have time to educate the parents. But being custodians of the patients' health, the health professionals are duty bound not to prescribe medicine for which there is no real proof of efficacy.

## Supportive Care:

For cough related to URTI only supportive measures are required like:

. Antipyretics
. Good hydration/ Increased fluid intake
. Positioning with the head elevated
. Humidified air [39]
. Hand washing
. The correct hand washing for child and care provider is essential to prevent the spread of the infection.
.Saline nasal washes [40]

**These supportive therapies are safe and not expensive. They should be the mainstay of treatment for children with cough and colds.**

## Pharmacology:

**Antihistamines and intranasal steroids:** are beneficial for children with an allergic cough in the pollen season for treating allergic rhinitis. An RCT has indicated that antihistamines are beneficial for reducing cough frequency and intensity during the pollen season [63]. Intra-nasal steroids may have an efficacy advantage over anti-histamines [64].

## Non Pharmacology:

**Honey:** The honey has shown to be effective and safe for relieving thesymptoms of cough and cold in upper and lower respiratory tract infections due to its demulcent, antioxidant and anti-microbial properties [48,75 -81].

## Ivy Leaf:

**The ivy leaf extracts (DEV 5-7.5:1) have shown to be effective and efficacious for reducing the cough in children[65 -74,] with a caveat of study design and lack of placebo control.**

## Parental Education:

It is very important to educate the parents and medical profession about the natural course of disease. In most children the cough resolves in 2 weeks but in a minority it takes 4 weeks to settle down [28,29,82.]

## The parents need to be apprised of:

| Category | Generics |
|---|---|

.The cause of the illness
.The expected length of time for symptoms to last
.Symptoms and signs of complications
.Lack of efficacy of medications in children
.The likely adverse effects of the medicines
.For which signs they have to re-consult.
.(e.g. ongoing fever, tachypnea).

The information obtained from Internet needs to takencautiously. All the information is not equally reliable. In an evaluation of 19 website only one site had most of the content that was correct [83].

## Non-recommended but commonly used cough medicines for children.

Over-the-counter (OTC) medications are not more effective than placebo for acute cough. They potentially have side effects so the PPA-pulmonary group also recommends to avoid them in children less than 4 years of age [30]. Many of these are not recommended for children less than 12 or 6 years of age in various countries [42 -45]. The data show no efficacy (no benefit) of OTC cough medicines when compared to placebo in children for brompheniramine, diphenhydramine, chlorpheniramine, guaifenesin, clemastine, phenylephrine, codeine, phenylpropanolamine, dextromethorphan, or salbutamol (oral) [46,47]. The various combinations like dextromethorphan/ diphenhydramine or brompheniramine/ phenylephrine also have not shown to be effective in trials or Cochrane review [48 -50 44,45.]

**Table: Non-recommended but commonly used cough medicines for children.**

| | |
|---|---|
| **Antihistamines** | Brompheniramine maleate |
| | Chlorpheniramine maleate |
| | Dexchlorpheniramine maleate |
| | Diphenhydramine hydro- chloride |
| | Oxylamine succinate, |
| | Pheniramine maleate |
| | Promethazine hydrochloride, |
| | Triprolidine hydrochloride |
| ***Antitussives:*** | Codeine phosphate |
| | Dextromethorphan hydrobromide, |
| | Dihydrocodeine tartrate |
| | Pentoxyverine citrate, |
| | Pholcodine |
| ***Mucolytics*** | Ammonium chloride |
| | Bromhexine hydrochloride |
| | Guaifenesin, (guaiphenesin) |
| | Ipecacuanha |
| ***Decongestants:*** | Phenylephrine hydrochloride |
| | Pseudoephedrine hydrochloride |
| | Oxymetazoline hydrochloride |
| | Xylometazoline hydrochloride |

## Codeine.

The codeine is an opiate receptor agonist and its active ingredient is morphine. It is commonly used as an analgesic in pediatrics. Its antitussive effect is probably by direct suppression of the medullary cough center in the brainstem by raising the cough threshold. This does not suppress cough completely, even in adults, and has serious adverse effects, especially in overdose.

The suggested dose in children is 1mg/kg/day given in 4 divided doses (max 60 mg/day) but efficacy or safety of this dose is not confirmed.For cough, the use of codeine is not safe. The Cochrane review 2002 concluded that evidence does not exist for or against the effectiveness in acute cough.

## Pholcodine

No studies could be found in children investigating the effectiveness of pholcodine for acute cough. **Safety**

Recent studies have shown that exposure to pholcodine cough syrup causes a large increase in levels of IgE antibodies towards pholcodine, morphine and suxamethonium thus increasing the potential future risk of allergic reactions to neuromuscular blocking agents (via these IgE binding to quaternary ammonium ion epitopes)..

## Dextromethorphan

Dextromethorphan elevates the threshold for cough in the medullary cough center. It is centrally acting non-opioid drug with little analgesic or addictive properties. This drug can lead to dilation of pupils without significant respiratory depression. It may also slightly elevate blood pressure. Since liver with CYP2D6 enzyme metabolizes it, its efficacy, safety and toxicity depend on the slow or fast or ultra-fast metabolism of the drug.The combination of dextromethorphan and pseudoephedrine and antihistamines or adrenergic agents is likely to be more toxic [10]. Therefore it is best to avoid it for acute cough in children.

## First Generation Antihistamines:

They are classified in several groups based on their chemical structure. Each class has somewhat different properties & side effects but most of them cause drowsiness, dry mouth, dizziness and irritability [12]. They impair cognition and affect school/work performance. At times the children do experience paradoxical stimulation [11,13,14]. The acute toxicity of oral antihistamines is dose-dependent. Mild symptoms (somnolence,

anticholinergic signs, tachycardia, nausea, vomiting) occur in 60% of patients. Moderate symptoms (isolated and spontaneously resolving agitation, confusion, hallucinations, and electrocardiographic disturbances) develop in 25% of patients. Severe symptoms (delirium, psychosis, seizures, and coma) occur with larger doses

They should be used very cautiously in children with asthma as they lead to the thickening of the secretions and make it harder for the children to clear them up [12,19].

**diphenhydramine**

There is significant evidence and reports of cases to support diphenhydramine being the most cardiotoxic of the antihistamines [10,21]. Numerous cases of toxicity have been reported in children.

**Second-Generation Antihistamines:**

(terfenadine, astemizole, loratadine, cetirizine, desloratadine)

They penetrate blood-brain barrier poorly and so are considered to be non-sedating [12]. They are long-acting selective histamine-1-receptor antagonists and have less anticholinergic actions or side effects [11]. They are not effective in reducing nasal congestion [13]. They cause headaches, gastrointestinal problems, weight gain, sinus tachycardia, palpitations and serious ventricular arrhythmias

**Phenylephrine:** It is modified epinephrine and very commonly used in cough syrups. It is a sympathomimetic agent with a powerful postsynaptic alpha-adrenergic receptor stimulant and has minimal effect on the beta-receptors of the heart. This causes constriction of most of the vascular beds thus increasing peripheral resistance that results in increased systolic & diastolic blood pressures [11]

**Pseudoephedrine:**

This has sympathomimetic properties like phenylephrine so the toxicity and clinical effects are expected to be similar to those seen with phenylephrine. The data shows toxic ingestions in children that are more common in children less than 2 years of age. The common cause of overdoses is taking more than one combination products inadvertently or use for extended periods of time [11].

## Expectorants for acute cough in children

The expectorants make the secretions thinner and stimulate the flow of respiratory fluid. This ciliary flow and coughing carries this fluid towards the pharynx. These drugs did not show any benefit in clinical settings when given at recommended doses [13].

There is very limited evidence for all of the expectorants in acute cough or in acute upper respiratory tract infections [19]. Some of the expectorants are discussed as under.

## Guaifenesin.

There are no studies in children that demonstrate its effectiveness or benefit in acute cough [12]. The four studies in adults, mainly with chronic respiratory conditions, showed equivocal evidence [10]. Controlled studies in adults did not demonstrate changes in sputum quality or volume or in cough frequency, though patients did perceive a decrease in sputum thickness and quantity [12].

## ammonium chloride

There are a few reports of toxicity from in cough mixtures, including metabolic acid-base abnormalities with abuse, disorientation, confusion & coma.

## Bromhexine:

Is an expectorant/mucolytic agent. There are no placebo-controlled trials demonstrating effectiveness of bromhexine in children. Adult studies are mainly negative for its effects on cough and of marginal benefit at best .

## Ipecacuanha:

There are no studies of ipecacuanha for acute cough in children. Adolescent and young adults with eating disorders occasionally abuse **ipecacuanha**[31,32].

## ipratropium bromide:

The ipratropium bromide is an anticholinergic bronchodilator with some cough suppressant activity due to allergy. A review of their use in adult respiratory conditions only recommended the use of ipratropium bromide for cough suppression in patients with cough due to an upper respiratory tract infection or chronic bronchitis [33,34] [10,35]. Their use in combination with cough suppressants is also questionable.

These guidelines have been presented in 23rd Biennial International Pediatric Conference-Nov 11-13 ,2016 Serena Islamabad

## References


1. Hay AD, Heron J, Ness A, ALSPAC study team. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. Fam Pract. 2005;22(4):367-74.

2. Burr ML, Anderson HR, Austin JB, Harkins LS, Kaur B, Strachan DP et al. Respiratory symptoms and home environment in children: a national survey. Thorax. 1999;54(1):27-32.

3. Cornford CS, Morgan M, Ridsdale L. Why do mothers consult when their children cough? Fam Pract. 1993;10(2):193-6.

4. Chang A. Cough: are children really different to adults? Cough ;7. http:/ www.coughjournal.com/content/1/1/7. 2005.

5. Bartlett JA, Fischer AJ, McCray PB. Innate immune functions of the airway epithelium. Contrib Microbiol. 2008;15:147-63.

6. Chang HQ, Yang XE, Fang YY, Pu PM, Li ZK, Rengel Z. In-situ nitrogen removal from the eutrophic water by microbial-plant integrated system. Journal of Zhejiang University. Science. B. 2006;7(7):521-31.

7. Hegland KW, Troche MS, Davenport PW. Cough expired volume and airflow rates during sequential induced cough. Frontiers in physiology. 2013;4:167.

8. Connell F, Thomas V, Studham J, Pride N, Fuller R. O' Capsaicin cough sensitivity increases during upper respiratory infection. Respir Med 279e86. 1996;90

9. Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. Br J Gen Pract. 2002;52(478):401-9.

10. Hay AD, Wilson A, Fahey T, Peters TJ. The duration of acute cough in pre-school children presenting to primary care: a prospective cohort study. Fam Pract. 2003;20(6):696-705.

11. Irwin RS, Madison JM. The diagnosis and treatment of cough. N Engl J Med. 2000;343(23):1715-21.

12. Sherrill DL, Guerra S, Minervini MC, Wright AL, Martinez FD. The relation of rhinitis to recurrent cough and wheezing: a longitudinal study. Respir Med. 2005;99(11):1377-85.

13. Chang AB, Glomb WB, ). Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):260S-83S.

14. Shields M, Bush A, Everard M, McKenzie S, Primhak R. Chest ;260Se83S. British Thoracic Society Guidelines: recommendations for the assessment and management of cough in children. Thorax 63Suppl Illiii1e15. 2008;129

15. Marais BJ, Gie RP, Obihara CC, Hesseling AC, Schaaf HS, Beyers N. Well defined symptoms are of value in the diagnosis of childhood pulmonary tuberculosis. Arch Dis Child. 2005;90(11):1162-5.

16. Leder K, Sinclair MI, Mitakakis TZ, Hellard ME, Forbes A. A community-based study of respiratory episodes in Melbourne, Australia. Aust N Z J Public Health. 2003;27(4):399-404.

17. Chang AB, Harrhy VA, Simpson J, Masters IB, Gibson PG. Cough, airway inflammation, and mild asthma exacerbation. Arch Dis Child. 2002;86(4):270-5.

18. Monto AS. Studies of the community and family: acute respiratory illness and infection. Epidemiol Rev. 1994;16(2):351-73.

19. Narayanappa D, Rajani H S, Mahendrappa K, Ravikumar V G.. Prevalence of asthma in urban school children in Jaipur, Rajasthan. Indian Pediatr. 2012;(49):835-6.

20. Hay A, Wilson A. The natural history of acute cough in children aged years in primary care: a systematic review. Br Pract 4019. 2005;52:0-4.

21. Shakil Ahmad. Acute bronchiolitis in children; epidemiologic and clinical features. Professional Med. 2013;20(5):707-12.

22. Janjua NZ, Mahmood B, Dharma VK, Sathiakumar N, Khan MI. Use of biomass fuel and acute respiratory infections in rural Pakistan. Public Health. 2012;126(10):855-62.

23. Nizami SQ, Bhutta ZA, Hasan R. Incidence of acute respiratory infections in children 2 months to 5 years of age in periurban communities in Karachi, Pakistan. J Pak Med Assoc. 2006;56(4):163-7.

24. McCormick A, Charlton J, Fleming D. Assessing health needs in primary care. Morbidity study from general practice provides another source of information. BMJ. 1995;310(6993):1534.

25. Ayres JG, Noah ND, Fleming DM. Incidence of episodes of acute asthma and acute bronchitis in general practice 1976-87. Br J Gen Pract. 1993;43(374):361-4.

26. Meza RA, Bridges-Webb C, Sayer GP, Miles DA, Traynor V, Neary S. The management of acute bronchitis in general practice: results from the Australian Morbidity and Treatment Survey, 1990-1991. Aust Fam Physician. 1994;23(8):1550-3.

27. Shields MD, Doherty GM. Chronic cough in children. Paediatr Respir Rev. 2013;14(2):100-5; quiz 106, 137.

28. Butler CC, Hood K, Kinnersley P, Robling M, Prout H, Houston H. Predicting the clinical course of suspected acute viral upper respiratory tract infection in children. Fam Pract. 2005;22(1):92-5.

29. Hay AD, Fahey T, Peters TJ, Wilson A. Predicting complications from acute cough in pre-school children in primary care: a prospective cohort study. Br J Gen Pract. 2004;54(498):9-14.

30. Lowry JA, Leeder JS. Over-the-Counter Medications: Update on Cough and Cold Preparations. Pediatr Rev. 2015;36(7):286-97; quiz 298.

31. Anon. Bronchiolitis. Clinical Evidence ;. . 2004;12:401-26.

32. . Scottish Intercollegiate Guidelines Network (SIGN). Bronchiolitis in children. 2006.

33. Perlstein PH, Kotagal UR, Bolling C, Steele R, Schoettker PJ, Atherton HD et al. Evaluation of an evidence-based guideline for bronchiolitis. Pediatrics. 1999;104(6):1334-41.

34. Anon. Croup. Clinical Evidence ;. . 2004;12:370-84.

35. British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN). British guideline on the management of asthma. Thorax 58Suppl 1. 2003;:1-83.

36. British Thoracic Society. BTS guidelines for the management of community acquired pneumonia in childhood Thorax 57Suppl 1. 2002;:377-470.

37. Lakhanpaul M, Atkinson M, Stephenson T. Community acquired pneumonia in children: a clinical update. 2004.

38. Singh M, Singh M. Heated, humidified air for the common cold. The Cochrane database of systematic reviews. 2013;(6):CD001728.

39. Kassel JC, King D, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. The Cochrane database of systematic reviews. 2010;(3):CD006821.

40. Kelly LF. Pediatric cough and cold preparations. Pediatr Rev. 2004;25(4):115-23.

41. Allan GM, Arroll B. Prevention and treatment of the common cold: making sense of the evidence. CMAJ. 2014;186(3):190-9.

42. Drug Safety and Availability > FDA Drug Safety Communication: Serious adverse events from accidental ingestion by children of over-the-counter eye drops and nasal sprays [Internet]. 2016 [cited 7/1/2016]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm325257.htm#healthcare

43. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. The Cochrane database of systematic reviews. 2012;(8):CD001831.

44. Smith S, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database Syst Rev.. 2014;11:10.

45. De Sutter AIM, Saraswat A, van Driel ML. Antihistamines for the common cold. The Cochrane database of systematic reviews. 2015;(11):CD009345.

46. De Sutter AIM, van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. The Cochrane database of systematic reviews. 2012;(2):CD004976.

47. Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med. 2007;161(12):1140-6.

48. Paul I. Therapeutic options for acute cough due to upper respiratory infections in children. Lung.. 2012;190(1):41-4.

49. Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics. 2004;114(1):e85-90.

50. Schroeder K, Fahey T. Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials. Arch Dis Child. 2002;86(3):170-5.

51. Bernard DW, Goepp JG, Duggan AK, Serwint JR, Rowe PC. Is oral albuterol effective for acute cough in non-asthmatic children? Acta Paediatr. 1999;88(4):465-7.

52. Smucry J, Flynn C, Becker L. Are b2 agonists effective treatment for acute bronchitis or acute cough in patients without underlying pulmonary disease? A systematic review. Pract. 2001;50(11)

53. Mertsola J, Viljanen MK, Ruuskanen O. Salbutamol in the treatment of whooping cough. Scand J Infect Dis. 1986;18(6):593-4.

54. Torre D, Tambini R, Ferrario G, Bonetta G. Treatment with steroids in children with pertussis. Pediatr Infect Dis J. 1993;12(5):419-20.

55. Pillay V, Swingler G. Symptomatic treatment of the cough in whooping cough. The Cochrane database of systematic reviews. 2003;(4):CD003257.

56. Christakis DA, Wright JA, Taylor JA, Zimmerman FJ. Association between parental satisfaction and antibiotic prescription for children with cough and cold symptoms. Pediatr Infect Dis J. 2005;24(9):774-7.

57. Arroll B, Kenealy T. Antibiotics for acute purulent rhinitis. BMJ. 2002;325(7376):1311-2.

58. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. The Cochrane database of systematic reviews. 2013;(6):CD000247.

59. Bergquist SO, Bernander S, Dahnsjö H, Sundelöf B. Erythromycin in the treatment of pertussis: a study of bacteriologic and clinical effects. Pediatr Infect Dis J. 1987;6(5):458-61.

60. Tiwari T, Murphy T, Moran J. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. CDC guidelines Morbidity and Mortality Weekly Report Recommendations and Reports MMWR 54RR14. 2005;:1-3.

61. Crowcroft NS, Pebody RG. Recent developments in pertussis. Lancet (London, England). 2006;367(9526):1926-36.

62. Ciprandi G, Tosca M, Ricca V, Passalacqua G, Fregonese L, Fasce L et al. Cetirizine treatment of allergic cough in children with pollen allergy. Allergy. 1997;52(7):752-4.

63. Rodrigo G. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2002;89:479-84.

64. Zeil S, Schwanebeck U, Vogelberg C. Tolerance and effect of an add-on treatment with a cough medicine containing ivy leaves dry extract on lung function in children with bronchial asthma. Phytomedicine. 2014;21(10):1216-20.

65. Fazio S, Pouso J, Dolinsky D, Fernandez A, Hernandez M, Clavier G et al. Tolerance, safety and efficacy of Hedera helix extract in inflammatory bronchial diseases under clinical practice conditions: a prospective, open, multicentre postmarketing study in 9657 patients. Phytomedicine. 2009;16(1):17-24.

66. Holzinger F, Beck S, Dini L, Stöter C, Heintze C. The diagnosis and treatment of acute cough in adults. Deutsches Arzteblatt international. 2014;111(20):356-63.

67. Schmidt M, Thomsen M, Schmidt U. Suitability of ivy extract for the treatment of paediatric cough. Phytother Res. 2012;26(12):1942-7.

68. Marzian O. [Treatment of acute bronchitis in children and adolescents. Non-interventional postmarketing surveillance study confirms the benefit and safety of a syrup made of extracts from thyme and ivy leaves]. MMW Fortschr Med.. 2007;149(27-28 Suppl):69-74.

69. Hofmann D, Hecker M, Völp A. Efficacy of dry extract of ivy leaves in children with bronchial asthma--a review of randomized controlled trials. Phytomedicine.. 2003;10(2-3):213-20.

70. Büechi S, Vögelin R, von E, Ramos M, Melzer J. Open trial to assess aspects of safety and efficacy of a combined herbal cough syrup with ivy and thyme. Forsch Komplementarmed Klass Naturheilkd.. 2005;12(6):328-32.

71. Cwientzek U, Ottillinger B, Arenberger P. Acute bronchitis therapy with ivy leaves extracts in a two-arm study. A double-blind, randomised study vs. an other ivy leaves extract. Phytomedicine.. 2011;18(13):1105-9.

72. Kemmerich B, Eberhardt R, Stammer H. Efficacy and tolerability of a fluid extract combination of thyme herb and ivy leaves and matched placebo in adults suffering from acute bronchitis with productive cough. A prospective, double-blind, placebo-controlled clinical trial. Arzneimittelforschung.. 2006;56(9):652-60.

73. Holzinger F, Chenot JF. Systematic review of clinical trials assessing the effectiveness of ivy leaf (hedera helix) for acute upper respiratory tract infections. Evidence-based complementary and alternative medicine : eCAM. 2011;2011:382789.

74. Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextromethorphan, and diphenhydramine on nightly cough and sleep quality in children and their parents. J Altern Complement Med. 2010;16(7):787-93.

75. Goldman R. Honey for treatment of cough in children. Can Fam Physician.. 2014;60(12):1107-8.

76. Oduwole O, Meremikwu M, Oyo-Ita A, Udoh E. Cochrane in context: Honey for acute cough in children. Evid Based Child Health.. 2014;9(2):444-5.

77. Miceli S, Greco M, Monaco S, Varrasi G, Di L, Simeone G. Effect of multiple honey doses on non-specific acute cough in children. An open randomised study and literature review. Allergol Immunopathol (Madr).. 2015;43(5):449-55.

78. Waris A, Macharia M, Njeru E, Essajee F. RANDOMISED DOUBLE BLIND STUDY TO COMPARE EFFECTIVENESS OF HONEY, SALBUTAMOL AND PLACEBO IN TREATMENT OF COUGH IN CHILDREN WITH COMMON COLD. East Afr Med J.. 2014;91(2):50-6.

79. Cohen H, Rozen J, Kristal H, Laks Y, Berkovitch M, Uziel Y et al. Effect of honey on nocturnal cough and sleep quality: a double-blind, randomized, placebo-controlled study. Pediatrics.. 2012;130(3):465-71.

80. Oduwole O, Meremikwu M, Oyo-Ita A, Udoh E. Honey for acute cough in children. Cochrane Database Syst Rev.. 2012;:10.

81. Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. JAMA. 2005;293(24):3029-35.

82. Pandolfini C, Impicciatore P, Bonati M. Parents on the web: risks for quality management of cough in children. Pediatrics. 2000;105(1):e1.

83. Shields MD, Thavagnanam S. The difficult coughing child: prolonged acute cough in children. Cough (London, England). 2013;9(1):11.

84. Chang AB, Robertson CF, Van Asperen PP, Glasgow NJ, Mellis CM, Masters IB et al. A multicenter study on chronic cough in children : burden and etiologies based on a standardized management pathway. Chest. 2012;142(4):943-50.

85. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588-98.

86. Napierkowski DB. Diagnosing and treating respiratory syncytial virus bronchiolitis. Nurse Pract. 2016;41(9):1-4.

87. Swingler GH, Hussey GD, Zwarenstein M. Duration of illness in ambulatory children diagnosed with bronchiolitis. Arch Pediatr Adolesc Med. 2000;154(10):997-1000.

88. McNaughten B, Bourke TW. Optimising the management of bronchiolitis in infants. Practitioner. 2015;259(1784):13-5, 2.

89. Bourke T, Shields M. Bronchiolitis. BMJ Clin Evid. 2011;2011.

90. Plans P, Toledo D, Sala MR, Camps N, Villanova M, Rodríguez R et al. Effectiveness of acellular pertussis vaccination during childhood (<7 years of age) for preventing pertussis in household contacts 1-9 years old in Catalonia and Navarra (Spain). Eur J Clin Microbiol Infect Dis. 2016;

91. Cherry JD. Epidemic pertussis in 2012--the resurgence of a vaccine-preventable disease. N Engl J Med. 2012;367(9):785-7.

92. Wang K, Chalker V, Bermingham A, Harrison T, Mant D, Harnden A. Mycoplasma pneumoniae and respiratory virus infections in children with persistent cough in England: a retrospective analysis. Pediatr Infect Dis J. 2011;30(12):1047-51.

93. Harnden A, Grant C, Harrison T, Perera R, Brueggemann AB, Mayon-White R et al. Whooping cough in school age children with persistent cough: prospective cohort study in primary care. BMJ. 2006;333(7560):174-7.

94. Cornia PB, Hersh AL, Lipsky BA, Newman TB, Gonzales R. Does this coughing adolescent or adult patient have pertussis? JAMA. 2010;304(8):890-6.

95. Carbonetti NH. Pertussis Leukocytosis: Mechanisms, Clinical Relevance and Treatment. Pathogens and disease. 2016;

96. Tiwari T, Murphy TV, Moran J, National Immunization Program C. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. MMWR Recomm Rep. 2005;54(RR-14):1-6.

97. Heininger U. Update on pertussis in children. Expert Rev Anti Infect Ther. 2010;8(2):163-73.

98. Balfour-Lynn IM, Abrahamson E, Cohen G, Hartley J, King S, Parikh D et al. BTS guidelines for the management of pleural infection in children. Thorax. 2005;60 Suppl 1:i1-21.

99. Cohen E, Mahant S, Dell SD, Traubici J, Ragone A, Wadhwa A et al. The long-term outcomes of pediatric pleural empyema: a prospective study. Arch Pediatr Adolesc Med. 2012;166(11):999-1004.

100. Sabino HAC, Valera FCP, Aragon DC, Fantucci MZ, Titoneli CC, Martinez R et al. Amoxicillin-clavulanate for patients with acute exacerbation of chronic rhinosinusitis: a prospective, double-blinded, placebo-controlled trial. International forum of allergy & rhinology. 2016;

101. Poachanukoon O, Nanthapisal S, Chaumrattanakul U. Pediatric acute and chronic rhinosinusitis: comparison of clinical characteristics and outcome of treatment. Asian Pac J Allergy Immunol. 2012;30(2):146-51.

102. DeMuri GP, Wald ER. Clinical practice. Acute bacterial sinusitis in children. N Engl J Med. 2012;367(12):1128-34.

103. Ezer SS, Oguzkurt P, Ince E, Temiz A, Çalıskan E, Hicsonmez A. Foreign body aspiration in children: analysis of diagnostic criteria and accurate time for bronchoscopy. Pediatr Emerg Care. 2011;27(8):723-6.

104. Paksu S, Paksu MS, Kilic M, Guner SN, Baysal K, Sancak R et al. Foreign body aspiration in childhood: evaluation of diagnostic parameters. Pediatr Emerg Care. 2012;28(3):259-64.

105. Behera G, Tripathy N, Maru YK, Mundra RK, Gupta Y, Lodha M. Role of virtual bronchoscopy in children with a vegetable foreign body in the tracheobronchial tree. J Laryngol Otol. 2014;128(12):1078-83.

106. Wang Y, Hao C, Chi F, Yu X, Sun H, Huang L et al. Clinical characteristics of protracted bacterial bronchitis in Chinese infants. Scientific reports. 2015;5:13731.

107. Chang AB, Redding GJ, Everard ML. Chronic wet cough: Protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatr Pulmonol. 2008;43(6):519-31.

108. Craven V, Everard ML. Protracted bacterial bronchitis: reinventing an old disease. Arch Dis Child. 2013;98(1):72-6.

109. Paul SP, Sanapala S, Bhatt JM. Recognition and management of children with protracted bacterial bronchitis. Br J Hosp Med (Lond). 2015;76(7):398-404.

110. Narang R, Bakewell K, Peach J, Clayton S, Samuels M, Alexander J et al. Bacterial distribution in the lungs of children with protracted bacterial bronchitis. PLoS One.. 2014;9(9):10.

111. Kompare M, Weinberger M. Protracted bacterial bronchitis in young children: association with airway malacia. J Pediatr. 2012;160(1):88-92.

112. Marchant JM, Gibson PG, Grissell TV, Timmins NL, Masters IB, Chang AB. Prospective assessment of protracted bacterial bronchitis: airway inflammation and innate immune activation. Pediatr Pulmonol. 2008;43(11):1092-9.

113. Lim MTC, Jeyarajah K, Jones P, Pandya H, Doffinger R, Kumararatne D et al. Specific antibody deficiency in children with chronic wet cough. Arch Dis Child. 2012;97(5):478-80.

114. Chang AB, Robertson CF, van Asperen PP, Glasgow NJ, Masters IB, Teoh L et al. A cough algorithm for chronic cough in children: a multicenter, randomized controlled study. Pediatrics. 2013;131(5):e1576-83.

PEDIATRIC COUGH ADVISORY BOARD

# Guidelines for the diagnosis and treatment of acute and chronic cough