

COUGH INSIGHTS

ISSUE 1



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A comprehensive range for the
Management of Cough



Solvin LS

Levosalbutamol 1 mg + Guaiphenesin 50 mg +
Ambroxol 30 mg / 5 ml Syrup



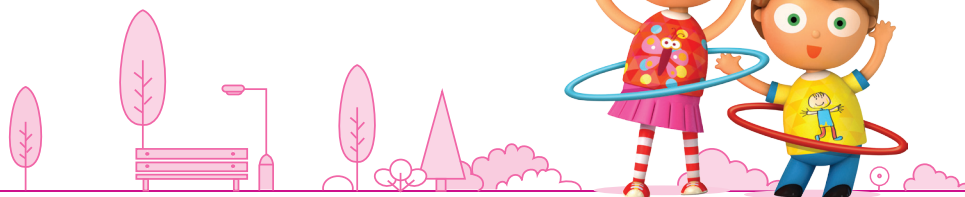
M-Solvin

Ambroxol 15 mg + Guaiphenesin 50 mg + Terbutaline
1.25 mg / 5 ml Syrup



**Solvin
cough**

Dextromethorphan 10 mg + CPM 2 mg / 5 ml Syrup

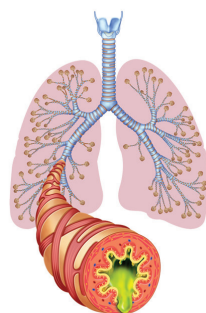


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CONTENTS

SECTION 1	EXPERT OPINION Potential role of combination therapy in alleviating productive cough	4
SECTION 2	PATIENT X-RAY Role of radiography in foreign body aspiration	7
SECTION 3	CHALLENGING CASE IN PEDIATRIC PULMONOLOGY A case report of a pediatric patient diagnosed with postinfectious bronchiolitis obliterans	9
SECTION 4	TREATMENT ALGORITHM Acute bronchitis in adult and pediatric patients	11
SECTION 5	GLOBAL UPDATE Clinical efficacy and tolerability of combination therapy with levosalbutamol, ambroxol, and guaiphenesin in the treatment of productive cough	12
SECTION 6	ADVANCES IN COUGH SCIENCE Development and technical validation of a pediatric cough detection algorithm based on a smartphone Applicability of the LEOSound system in detecting wheeze and cough	13 14



COUGH
INSIGHTS

POTENTIAL ROLE OF COMBINATION THERAPY IN ALLEVIATING PRODUCTIVE COUGH



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OVERVIEW

- Cough during childhood is very common, and is one of the most common reasons for consultation in routine pediatric practice. Cough impacts negatively on child's daily activities and ability to sleep well, play or attend school and is often a source of anxiety for the parents. It affects the quality of life of the child and the parents or caregivers.^{1,2}
- Cough in children is different from that in adults in terms of duration, presentation, etiology and management. Cough can be defined based on duration of presentation, content, and sound quality (Box 1).^{2,3}

Box 1: Different types of cough^{2,3}

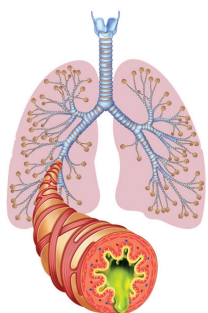
- Duration of cough
 - » Acute: cough lasting less than 4 weeks
 - » Chronic: cough lasting more than 4 weeks
- Quality of cough
 - » Sound pattern
 - Barking
 - Paroxysmal/spasmodic/whoop
 - » Nature of content
 - Dry/unproductive
 - Wet/productive

PRODUCTIVE OR WET COUGH

- Cough can be productive/wet or unproductive/dry. Productive cough suggests either an increase in respiratory tract secretions or abnormalities in its clearance mechanisms.^{4,5}
- A productive cough produces phlegm or mucus or sputum, which could likely be attributed to lower respiratory diseases, asthma or pneumonia, acute bronchitis, as well as chronic pulmonary disease like cystic fibrosis, and bronchiectasis.^{3,4}
- The burden of productive cough is more prevalent in developing nations; the incidence of productive cough in developing nations is about 20-30% as compared to 3-4% in the developed nations.⁴

Cough with wheeze

- Wheeze is a high-pitched whistling or rattling sound on expiration. It is caused by spasmodic narrowing of the distal airway.^{6,7}
- Wheezing is usually caused by an obstruction or narrowing of the small bronchial tubes in the chest. It can also be due to an obstruction in the larger airways or vocal cords. The most common causes of wheezing include problems with the lungs:⁷
 - » **Asthma:** Wheezing in asthma can be triggered by exposure to airborne allergens



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- » **Bronchitis:** Inflammation of the lining of the bronchial tubes
- » **Bronchiolitis:** Most common in young children
- » **Pneumonia:** Inflammation of the lungs caused by a virus or bacteria
- » **Respiratory syncytial virus (RSV):** Seasonal lung infection that can lead to bronchiolitis or pneumonia
- » **Foreign body aspiration**

› In case of wheezing due to bronchitis or asthma, a bronchodilator is often prescribed to help open the airways and reduce inflammation enabling to breathe better.⁷

SUPPORTIVE CARE WITH COMBINATION THERAPY FOR ALLEVIATING PRODUCTIVE COUGH

- › In respiratory conditions associated with excess mucus production, there is need for a comprehensive formulation that may expel the mucus out of the airways and provide symptomatic relief to the patient.^{3,8}
- › Bronchodilatory cough formulations containing fixed dose combination of bronchodilator with mucolytics and/or expectorants are often prescribed for cough management.⁸

Levosalbutamol

- › Levosalbutamol is the therapeutically active isomer of salbutamol and has all the β_2 agonist activity. It acts as a bronchodilator and it has approximately 2-fold greater affinity than racemic salbutamol for the β_2 adrenergic receptor. It has approximately 100-fold greater binding affinity than S salbutamol.⁹
- › By interacting with β_2 adrenoceptors, levosalbutamol also exerts bronchoprotective and antiedematous properties and inhibits activation of mast cell and eosinophils. In many studies, levosalbutamol has been found to be well-tolerated and effective in pediatric patients in the need of bronchodilation.⁹
- › Levosalbutamol activates the adenylate cyclase leading to an increase in the intracellular concentration of 3',5'-cyclic adenosine monophosphate (cyclic AMP). Increased cyclic AMP activates protein kinase A; the kinase phosphorylates a calcium channel,

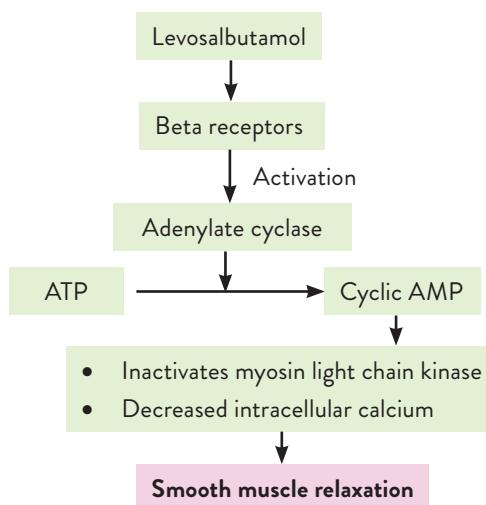
“ **Levosalbutamol acts as a bronchodilator and it has been found to be well-tolerated and effective in pediatric patients in the need of bronchodilation** ”

which promotes calcium influx and thus activates contractile proteins. In bronchial smooth muscle, the increase in protein kinases and phosphorylation leads to bronchial smooth muscle relaxation because of decreased calcium influx and increased calcium uptake in the sarcoplasmic reticulum (Figure 1).⁹⁻¹¹

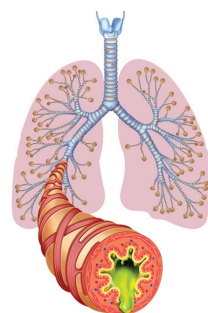
Ambroxol

- › Ambroxol is the active metabolite of bromhexine hydrochloride. It acts as a mucolytic agent; besides, it also increases bronchial secretion and reduces the viscosity of tenacious sputum and expedites its removal by coughing. It also upturns the clearance of mucociliary secretions.^{4,12}
- › In addition, ambroxol also exerts many other beneficial effects, such as surfactant-stimulatory effect, anti-inflammatory effect, anti-oxidant

Figure 1: Mechanistic approach to the bronchodilatory effect of levosalbutamol⁹⁻¹¹



Abbreviations: AMP; adenosine monophosphate, ATP; adenosine triphosphate.



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“ Productive cough can be managed using combination therapy with bronchodilators, expectorants, and mucolytics ”

effect, and local anesthetic effect. Ambroxol effectively ameliorates bronchial symptoms (severity and frequency of cough) among pediatric patients.^{13,14}

Guaiphenesin

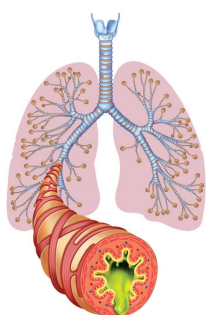
- Guaiphenesin is an expectorant and mucokinetic, which alleviates cough discomfort by increasing sputum volume and decreasing its viscosity; it reduces the surface tension and adhesiveness of sputum, thus promoting effective cough.^{4,15}
- By reducing the adhesiveness and viscosity of sputum, it increases the efficacy of cough reflex, ciliary actions and mucociliary removal for accumulated bronchial secretions from the lower and upper airway. Further, it also enhances the rate of mucociliary clearance to expel mucus.^{4,16}

Evidence-based efficacy of combination therapy

- Available evidence suggests that productive cough can be managed with combination therapy of bronchodilators plus expectorants plus mucolytics. A phase IV clinical trial by Kiran *et al*⁴ conducted among pediatric patients demonstrated that combination therapy with levosalbutamol, ambroxol hydrochloride, and guaiphenesin was effective and well-tolerated for the treatment of productive cough associated with bronchospasm in conditions such as bronchitis and bronchial asthma, and also in conditions associated with tenacious mucus, wheezing and chest congestion.
- Thus, supportive care with cough formulation containing a bronchodilator, a mucokinetic, and an expectorant can be a potential choice of treatment for productive cough.^{4,8}

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ROLE OF RADIOGRAPHY IN FOREIGN BODY ASPIRATION

OVERVIEW

- Foreign body (FB) ingestion is a common presenting complaint in pediatric patients.¹
- Infants and young children between the ages of 6 months and 3 years lack molar teeth, have uncoordinated swallowing mechanisms, and, most importantly, engage with their surroundings by placing objects in their mouths, thus they are vulnerable to foreign body aspiration.²
- FBs such as coins, toy parts, jewellery pieces, and button-type batteries are commonly ingested by children.¹
- Fortunately, 80-90% of ingested foreign objects that reach the stomach pass through without incident.
- The remainder may become obstructed in the esophagus or another region of the alimentary tract, putting the pediatric patient at risk of serious complications such as aspiration, obstruction, bleeding, perforation, fistulisation, sepsis, and death.
- The initial pediatric patient assessment aims to determine the type of object ingested, its location in the body, and the presence of any associated complications.¹

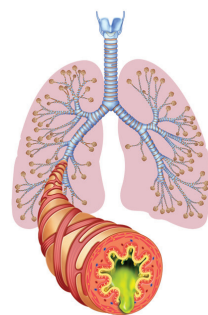
RADIOGRAPHY IN FOREIGN BODY ASPIRATION

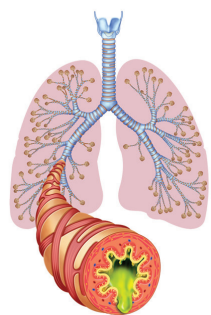
Chest X-rays

- Chest X-rays are among the most common radiological investigations performed on children in both inpatient and outpatient settings, and accurate interpretation is required to guide management.³
- Plain radiographs play an important role in assessing ingested FBs in pediatric patients. They are very

useful in confirming the diagnosis of FB ingestion because most ingested FBs are radiopaque.¹

- When an FB has been swallowed, anteroposterior and lateral neck, anteroposterior and lateral chest, and abdominal radiographs should be obtained to perform a thorough examination and rule out the presence of an ingested FB.
- Because some FBs, particularly those of discoid shape, cannot be identified in a single projection, lateral and anteroposterior radiographs are important.¹
- Because most aspirated FBs are radiolucent, radiographs are normal. The radiopacity of an FB affects its radiologic visualisation.
- Many objects, including meat, tiny bones, aluminium, glass, plastic, and wood, may be radiolucent and thus not visible on plain radiographs.¹
- Despite the fact that only 10% of aspirated foreign bodies are radiopaque, indirect signs of aspiration such as air trapping, focal airspace disease, pleural effusion, mediastinal shift, pneumothorax, or subcutaneous emphysema are important imaging surrogates.
- The most common indirect sign of aspiration is unilateral hyperinflation. This finding should be followed up with bilateral decubitus radiographs to rule out air trapping with the side of foreign body aspiration failing to deflate in the dependent position.
- However, lateral decubitus radiography has only 68–74% sensitivity and 45–67% specificity. As such, negative chest radiography in the setting of high clinical suspicion should prompt further evaluation with computed tomography.²



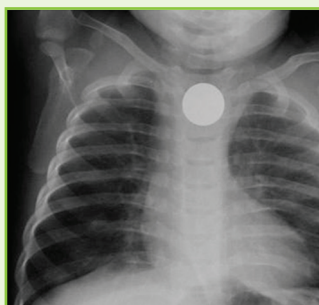


TRACHEAL VERSUS ESOPHAGEAL FOREIGN COINS: DIAGNOSTIC DILEMMA

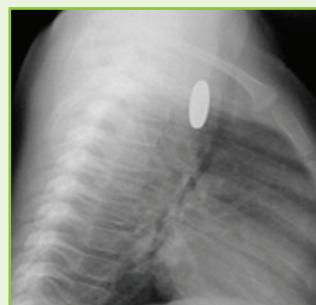
Anteroposterior (AP) and lateral chest X-rays can help to confirm the diagnosis of a coin lodged in the esophagus. Esophageal coins align so as to appear as a circular disc (en face) on the AP view and as a thick line (on edge) on the lateral view. On the other hand, coins lodged in the trachea align to appear on edge on the AP view and en face on the lateral view.⁴

Esophagus

A radiopaque foreign body (coin) lodged at the proximal portion of the thoracic esophagus



Anteroposterior view



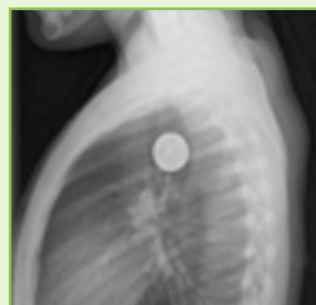
Lateral view

Trachea

A radiopaque foreign body (coin) lodged in the trachea



Anteroposterior view



Lateral view

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A CASE REPORT OF A PEDIATRIC PATIENT DIAGNOSED WITH POSTINFECTIOUS BRONCHIOLITIS OBLITERANS

OVERVIEW

- Bronchiolitis obliterans is a chronic obstructive respiratory disease characterised by stenosis or occlusion of the bronchioles and smaller airways.
- It has a poor prognosis, and the patient may require home oxygen therapy and/or lung transplantation.
- Bronchiolitis obliterans is clinically similar to bronchial asthma, and it is possible that bronchiolitis obliterans is misdiagnosed as bronchial asthma in some cases.
- Fujita Y *et al* reported a pediatric case of postinfectious bronchiolitis obliterans misdiagnosed as bronchial asthma.

CASE PRESENTATION

A 7-year-old girl was admitted to the hospital due to exertional dyspnea.

PAST MEDICAL HISTORY

- At 1 year of age, she was admitted to the hospital with a respiratory syncytial (RS) virus infection, which was detected in samples from the patient's nasopharynx using a rapid antigen test.
- She was readmitted due to wheezing and respiratory distress next month. She was diagnosed with

bronchial asthma on the basis of the following findings: dry cough, wheezing, chest tightening and progressive breathing difficulties.

- She was treated with inhaled corticosteroids.
- Despite continued treatment, she required frequent readmissions due to wheezing, respiratory discomfort, and tachypnea:
 - » At the age of **1 year: 6** times
 - » At the age of **2 years: 5** times
 - » At the age of **3 years: 7** times
 - » At the age of **4 years: 6** times
 - » At the age of **5 years: 1** time
 - » At the age of **6 years: 6** times

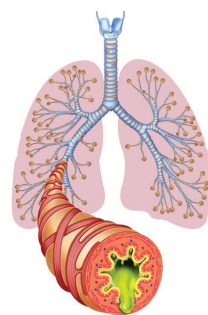
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Reports of the blood tests of the patient

Parameters	Lab examination values
White blood cell count	6,900/ μ L
Eosinophils	9.6%
KL-6 level	204 IU/mL
Total immunoglobulin E (IgE) level	681 UA/ mL
House dust mite-specific IgE level	6.85 UA/mL
Aspergillus-specific IgE level	< 0.1 UA/mL



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Radiography	
Methods	Findings
Chest X-ray	Hyperinflation, indicating air trapping
High-resolution chest computed tomography	Depicted mosaic perfusion
Ventilation-perfusion scintigraphy	Revealed a ventilation perfusion mismatch

INVESTIGATIONS

- Respiratory function test results indicated obstructive airway disease
- The administration of bronchodilators did not improve the respiratory function
- The fractional nitric oxide concentration in the exhaled breath was normal
- Sputum culture showed no pathogenic bacteria
- The patient had no respiratory problems during infancy, and a chest CT scan revealed no typical findings indicative of bronchopulmonary dysplasia (BPD)
- She had no episodes with signs and symptoms indicative of cystic fibrosis, such as meconium ileus, intestinal disorder, and recurrent respiratory infections.

DIAGNOSIS

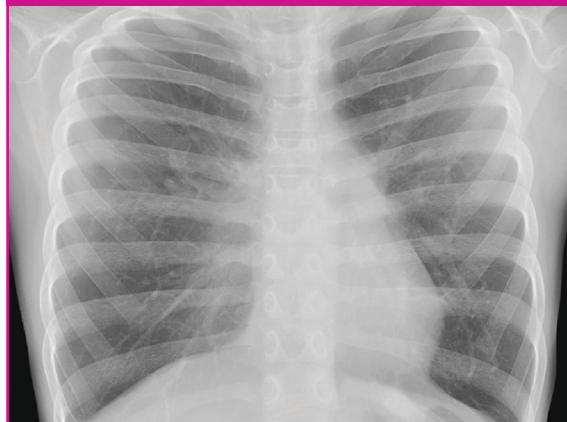
Postinfectious bronchiolitis obliterans due to RS virus

TREATMENT

- She was treated with systemic methylprednisolone for 5 days and her symptoms of dyspnea gradually improved
- No significant improvement was seen in pulmonary function test after 1 month
- However, she was readmitted to the hospital, and her quality of life continued to deteriorate because of exertional dyspnea.

This case report demonstrates that proper treatment during early stage can improve the prognosis of bronchiolitis obliterans. Although, if symptoms of

Chest X-ray reveals hyperinflation, indicating air trapping



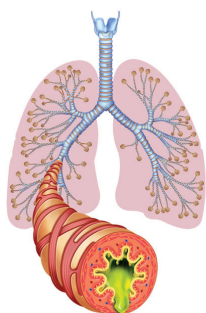
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If symptoms of patient do not respond to bronchial asthma treatment, pediatricians should consider other diseases similar to bronchial asthma, such as bronchiolitis obliterans, in the differential diagnosis

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patient do not respond to bronchial asthma treatment, pediatricians should consider other diseases similar to bronchial asthma, such as bronchiolitis obliterans, in the differential diagnosis.

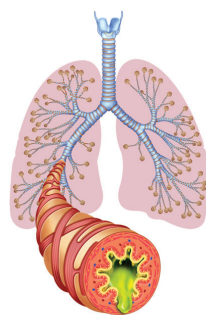
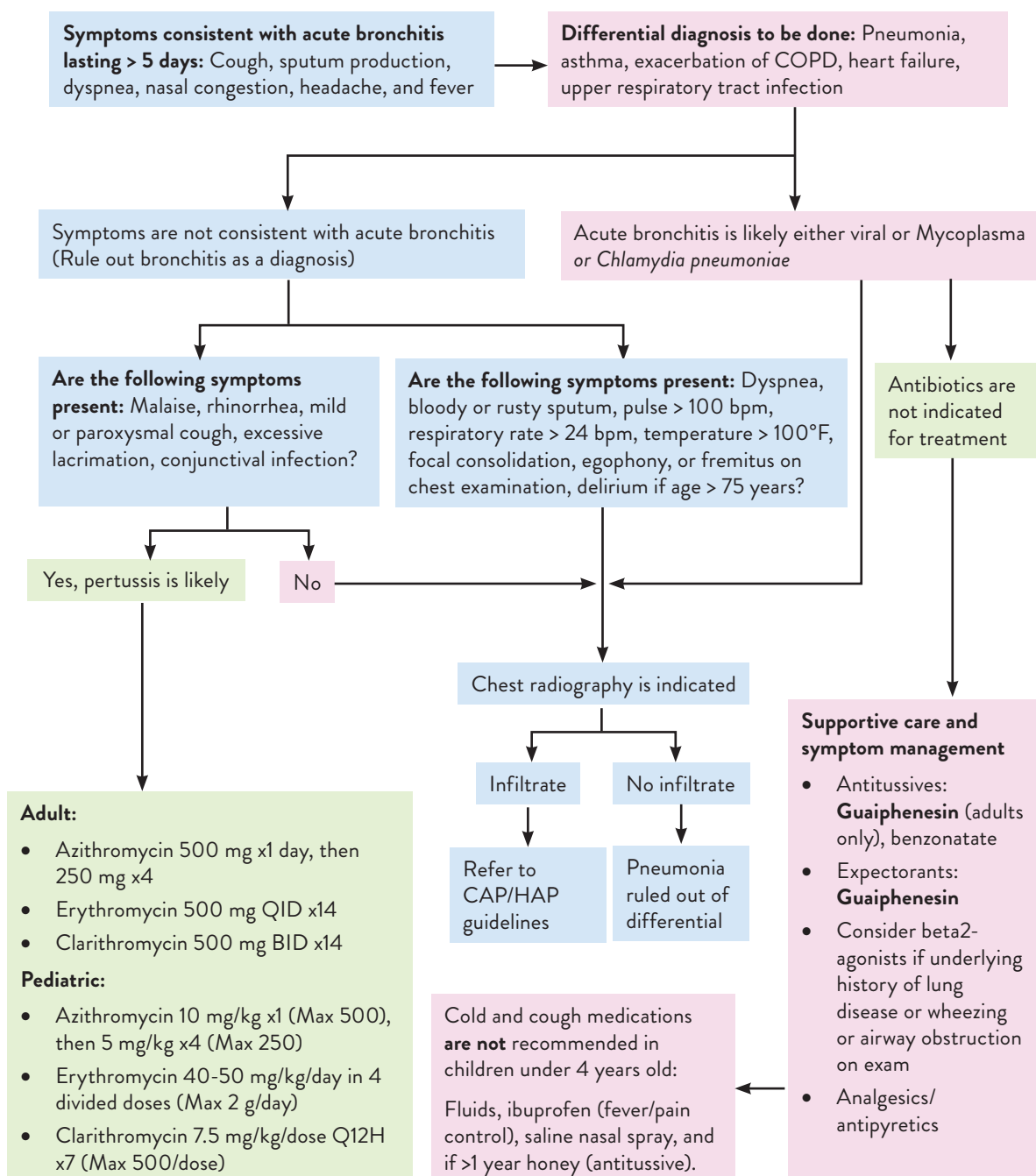
Source: Fujita Y, Miyamoto K, Imataka G, Yoshihara S. Postinfectious Bronchiolitis Obliterans Misdiagnosed as Bronchial Asthma in a Pediatric Patient. *Tohoku J Exp Med.* 2021;254(4):257-260.



SECTION 4

TREATMENT ALGORITHM

ACUTE BRONCHITIS IN ADULT AND PEDIATRIC PATIENTS



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Abbreviations: COPD; chronic obstructive pulmonary disease, CAP; community-acquired pneumonia, HAP; hospital-acquired pneumonia, QID; four times a day, BID; twice a day.

Source: Acute Bronchitis for Adult and Pediatric Patients Algorithm. Available at: https://www.hqi.solutions/wp-content/uploads/2018/07/Outpatient-Acute-Bronchitis-Treatment-Algorithm-for-Adults_VA-SASI_07-2018_508.pdf. Accessed on 04/04/2022.

CLINICAL EFFICACY AND TOLERABILITY OF COMBINATION THERAPY WITH LEVOSALBUTAMOL, AMBROXOL, AND GUAIPHENESIN IN THE TREATMENT OF PRODUCTIVE COUGH

Cough is one of the most frequent symptoms that most of the clinicians face while treating pediatric patients. Cough can be of two types, i.e. productive and unproductive cough. Productive cough is the cough with respiratory tract secretions and unproductive cough is the cough with no respiratory tract secretions.

Productive cough is a symptom which is mostly observed in developing countries. Productive cough can be treated with the combination of bronchodilator, expectorant and mucolytics.

AIM

To test the efficacy and tolerability for the combination of levosalbutamol, ambroxol hydrochloride, and guaiphenesin for the treatment of productive cough associated with bronchospasm in conditions such as bronchitis and bronchial asthma as well as all conditions associated with tenacious mucus, wheezing and chest congestion.

METHODOLOGY

A Phase IV clinical trial was conducted with a total of 325 patients; 149 patients were of age group 2 to 12 years and 176 were of age below 1 year.

RESULTS

- At baseline (visit 1), the mean cough severity score (CSS) was 6.624 which was reduced to 3.744 after initiating the treatment with the study drug combination at visit 2 (day 3) and it was further reduced to 1.049 at visit 3 (day 5). (Figure 1)
- As compared to baseline, there was reduction in mean CSS of 43.478% and 84.163% at visit 2 and visit 3, respectively (Figure 2).

Figure 1: Comparison of mean cough severity score at visit 1, visit 2 and visit 3

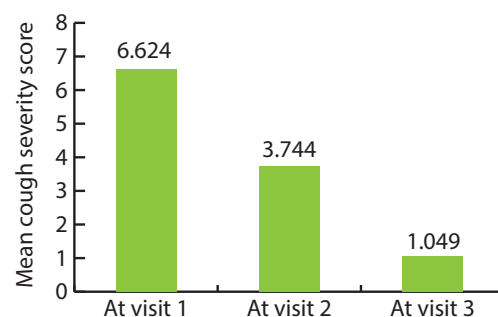
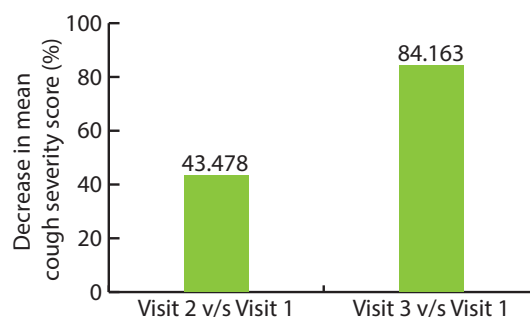


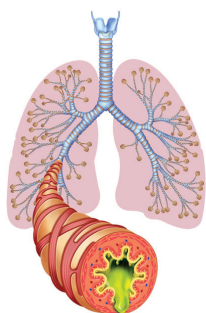
Figure 2: Reduction in mean CSS at visit 2 and 3 compared to visit 1



CONCLUSION

Combination of levosalbutamol, ambroxol hydrochloride, and guaiphenesin is effective and well-tolerated in the treatment of productive cough.

Source: Kiran MD, Pawaskar LJ, Sheikh SN. Efficacy and Safety for the Combination of Levosalbutamol, Ambroxol and Guaiphenesin for the Symptomatic Treatment of Productive Cough: Phase IV Clinical Trial. *Int. J. Inn. Res. Med Sci.* 2019;4(01),11-15.



DEVELOPMENT AND TECHNICAL VALIDATION OF A PEDIATRIC COUGH DETECTION ALGORITHM BASED ON A SMARTPHONE

Coughing is a common symptom of pediatric lung disease, and cough frequency has been linked to disease activity in a number of conditions. Cough detection software could be used to create a noninvasive digital biomarker for pediatric clinical trials or care.

AIM

To develop a smartphone-based algorithm that objectively and automatically counts cough sounds of children.

METHODOLOGY

The training set included 3228 pediatric cough sounds and 480,780 noncough sounds from publicly available sources, as well as continuous sound recordings of 7 patients admitted due to respiratory disease. The robustness of the algorithm was investigated by repeatedly classifying a recording with the smartphone-based algorithm during various conditions.

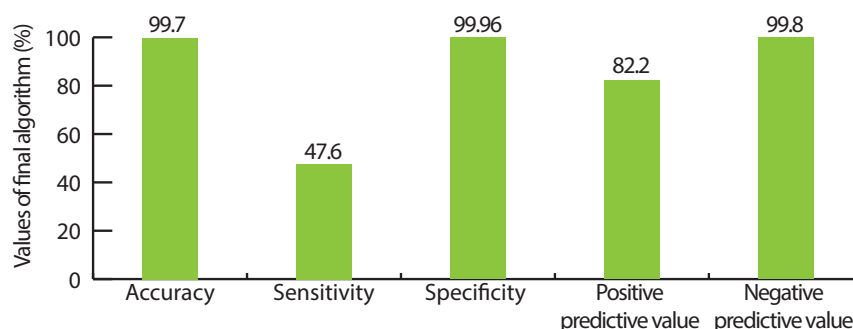
RESULTS

- In the validation dataset, the final algorithm achieved an accuracy of 99.7%, sensitivity of 47.6%, specificity of 99.96%, positive predictive value of 82.2%, and negative predictive value of 99.8% (Figure 1)
- In the validation dataset, the correlation coefficient between manual and automated cough counts was 0.97 ($p < 0.001$)
- The intra- and interdevice reliability of the algorithm was adequate, and the algorithm performed best at an unobstructed distance of 0.5-1 m from the audio source.

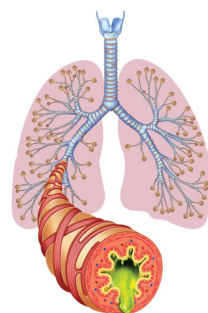
CONCLUSION

This novel smartphone-based pediatric cough detection application can be used in clinical care for long-term follow-up or as a digital endpoint in clinical trials.

Figure 1: Performance of the final smartphone-based algorithm in the validation dataset



Source: Kruizinga MD, Zhuparris A, Dessing E, et al. Development and technical validation of a smartphone-based pediatric cough detection algorithm. *Pediatr Pulmonol.* 2022;57(3):761-767.



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APPLICABILITY OF THE LEOSound SYSTEM IN DETECTING WHEEZE AND COUGH

Asthma, one of the most common chronic diseases in children, exhibits circadian variations, with symptoms worsening at night. The circadian oscillation of multiple genes that influence lung physiology, as well as variations in the local inflammatory response, contributes to the nocturnal aggravation of asthma activity.

AIM

To determine the applicability of the LEOSound system for the clinical use in children and to investigate and validate the software algorithms for automated classification of coughing and wheezing.

METHODOLOGY

A total of 115 children and adolescents with and without respiratory conditions were evaluated to record the airway sounds overnight.

RESULTS

- There was general acceptance across all age groups, and a technically successful recording was obtained in 98 children, corresponding to 92,976 sound epochs of 30 s each or a total of 774 h of lung sounds
- The cough index and the wheeze index (events per hour) of individual patients showed a strong positive correlation.

AUTOMATED DETECTION OF COUGH

- Cough positive epochs: **1444**
- False discovery rate: **20.6%**
- Missed cough epochs rate: **10.3%**

On the level of single epochs

- Sensitivity for cough detection: **89.7%**
- Specificity for cough detection: **99.7%**
- Accuracy for cough detection: **99.5%**

AUTOMATED DETECTION OF WHEEZE

- Wheeze positive epochs: **6383**
- False discovery rate: **29.0%**
- Missed wheeze epochs rate: **2.4%**

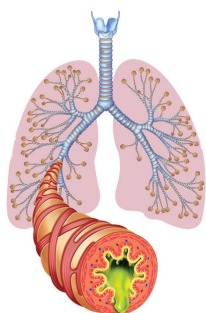
On the level of single epochs

- Sensitivity for wheeze detection: **97.6%**
- Specificity for wheeze detection: **97.9%**
- Accuracy for wheeze detection: **97.9%**

CONCLUSION

The LEOSound is an appropriate device for standardised detection of cough and wheezing, and thus a promising diagnostic tool for detecting nocturnal respiratory symptoms, particularly in children. However, in clinical routine use, a validation process to reduce false positive classifications is required.

Source: Urban C, Kiefer A, Conradt R, et al. Validation of the LEOSound® monitor for standardized detection of wheezing and cough in children. *Pediatr Pulmonol.* 2022;57(2):551-559.



COUGH
INSIGHTS

KEY-HIGHLIGHTS

Cough impacts negatively on child's daily activities and ability to sleep well, play or attend school and is often a source of anxiety for the parents

Bronchodilatory cough formulations containing fixed dose combination of bronchodilator with mucolytics and/or expectorants are often prescribed for cough management

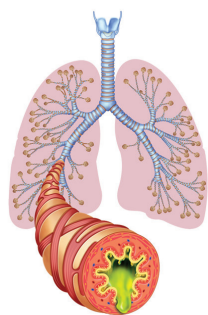
Levosalbutamol acts as a bronchodilator and it has been found to be well-tolerated and effective in pediatric patients in the need of bronchodilation

Ambroxol acts as a mucolytic agent; it increases bronchial secretion and reduces the viscosity of tenacious sputum and expedites its removal by coughing

Guaiphenesin is an expectorant and mucokinetic, which alleviates cough discomfort by increasing sputum volume and decreasing its viscosity

A phase IV clinical trial conducted among pediatric patients demonstrated that combination therapy with levosalbutamol, ambroxol hydrochloride, and guaiphenesin was effective and well-tolerated for the treatment of productive cough associated with bronchospasm in conditions such as bronchitis and bronchial asthma, and also in conditions associated with tenacious mucus, wheezing and chest congestion

Thus, supportive care with cough formulation containing a bronchodilator, a mucokinetic, and an expectorant can be a potential choice of treatment for productive cough.



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