

Cough is an important natural defense mechanism of the respiratory tract, and it is one of the most common reasons for adults seeking medical treatment.

Under normal conditions, cough serves an important protective role in the airways and lungs as it helps in preserving the gas-exchanging functions of the lung by facilitating clearance of aspirate, inhaled particulate matter, accumulated secretions, and irritants that are either inhaled or formed at sites of mucosal inflammation. Impaired cough reflex can have dire consequences.

On the contrary, cough is an important mechanism for the spread of life-threatening acute and chronic respiratory tract infections and it also adversely affect the quality of life in asthma, COPD, GERD, ILD, LRTIs including pulmonary tuberculosis and other lung diseases.

These contrasting functions and consequences of cough highlight the importance of early diagnosis and adoption of balanced therapeutic measures.

**MECHANISM OF COUGH PRODUCTION**

The cough reflex consists of three phases: an inhalation, a forced exhalation against a closed glottis, and a violent release of air from the lungs following opening of the glottis, usually accompanied by a distinctive sound. Coughing may be voluntary or involuntary.

Cough receptors- Chemosensitive receptors and Mechanosensors receptors are located in the respiratory tract from the hypopharynx & larynx to the segmental bronchi:

Table 1: Common causes of cough	
<b>Acute infections:</b> Tracheobronchitis, Bronchopneumonia, Viral Pneumonia and Acute on Chronic Bronchitis	<b>Tumours:</b> Bronchogenic and alveolar cell carcinomas, and benign airway and mediastinal tumours
<b>Chronic infections:</b> Bronchiectasis, Tuberculosis & cystic fibrosis	<b>Foreign body</b>
<b>Airway disease:</b> Asthma, chronic bronchitis, COPD & chronic post-nasal drip	<b>Cardiovascular:</b> Left ventricular failure, pulmonary infarction and aortic aneurysm
<b>Parenchymal disease:</b> Interstitial fibrosis, emphysema	<b>Other disease:</b> Reflux oesophagitis, recurrent aspiration
	<b>Drugs:</b> ACE inhibitors

Vagal sensory nerve plays major role in regulation of cough response, whereas bronchopulmonary sensory nerves innervating other viscera, as well as somatosensory nerves innervating chest wall, diaphragm and abdominal muscles also contribute in regulation of cough response.

Sensory afferent pathways finally terminate at the brainstem, at the nucleus of the solitary tract, and the spinal trigeminal tract. Voluntary control of cough is possible because of the influence of higher cortical centers on the cough centre. Efferent signals are then sent to the muscles that produce the forced expiratory effort.

**CAUSES OF COUGH (TABLE 1)**

Cough is a common symptom present more or less with all respiratory disorders. It is also present in cardiovascular, Gastro Intestinal diseases and some disorders related to chest wall. In India pulmonary tuberculosis should always be consider as an important cause of sub acute or chronic cough.

Depending upon the onset & duration arbitrary causes of cough can be divided

- Acute Cough - Acute or short-lived cough, which often occurs in association with upper respiratory tract infection, is usually self-limiting and usually resolves within three weeks.
- Sub acute Cough - Cough lasting between 3 to 8 weeks' period. Cough in tuberculosis, M. Pneumoniae & B. Pertusis infections infection can be kept in this category.
- Chronic Cough (CC)- Lasts more than 8 weeks duration. It is a common warning symptom of almost all chronic respiratory and some non-respiratory illnesses with an estimated prevalence of 10 % to 20% of the population. Most patients with CC have dry cough or with minimum expectoration (LI 1-4). It poses a great diagnostic and management challenge, due to its variant etiologies.

Arbitrarily Chronic Cough can be further divided in:

- a. Causes easy to recognize after clinical examination, chest radiography, and spirometry:
  - Upper & lower respiratory tract infections (bacterial including tuberculosis)
  - Asthma (most cases)
  - COPD

- Pulmonary tuberculosis
  - Sarcoidosis
  - Interstitial lung disease
  - Lung cancer
  - Inhaled foreign body, and
  - Heart failure
- b. Causes difficult to recognize after clinical examination, chest radiography, and spirometry/ remained unrecognized:
- Viral infections of the upper respiratory tract
  - Upper airway cough syndrome (UACS); postnasal drip syndrome)
  - Gastroesophageal reflux disease (GERD)
  - Cough-variant asthma,
  - Eosinophilic bronchitis
  - Mediastinal tumors
  - Pleural diseases
  - Early interstitial fibrosis
  - Use of an angiotensin converting enzyme-inhibitor (ACEI)
  - Psychogenic
  - Idiopathic (or unexplained) cough.

The latest American College of Chest Physicians (ACCP) Consensus Guidelines, which analyzed the data of 11 studies worldwide, reported that postnasal drip(or UACS), GERD, and cough-variant asthma were the most common causes of chronic cough in difficult to recognize causes of cough, comprising two-thirds of all diagnoses.

### Upper airway cough syndrome (UACS)

The ACCP 2006 guidelines has suggested the term 'UACS' instead of the previously described 'postnasal drip syndrome', because it can also occur as a result of irritation or inflammation of the upper airway structures that directly stimulate the cough receptors independently or in addition to the postnasal drip. Rhinitis or rhinosinusitis commonly appears in the reported causes of cough in these patients. Common clinical signs and symptoms associated with UACS are: a feeling of drainage in the posterior pharynx, frequent throat clearing, nasal discharge, cobblestone appearance of the oropharyngeal mucosa, and mucopurulent secretions in the oropharynx.

In case patients do not respond to empirical treatment, sinus imaging, preferably with a CT scan, is indicated.

### Asthma

Chronic dry cough, usually in the case of cough-variant asthma, often occurs at night, may present as a predominant symptom or even the only symptom in patients with asthma. In asthma dry cough can be explained by two mechanisms: sensitization of cough

receptors by increased levels of inflammatory mediators and stimulation of cough receptors through constriction of the bronchial smooth muscle.

Asthma as the cause of chronic dry cough has to be considered in patients who do not respond to empirical treatment for postnasal drip. Spirometry is the most reliable test for establishing the diagnosis of asthma. Other tests e.g. Bronchoprovocation tests, sputum eosinophil count or increased exhaled nitric oxide (NO) concentration may also be required for making diagnosis.

### Non-asthmatic Eosinophilic Bronchitis (NAEB)

NAEB also presents in a similar manner e.g. cough and sputum eosinophilia with or without dyspnea. Major characteristic distinguishing asthma from NAEB is the absence of variable airflow obstruction (spirometry) and bronchial hyperresponsiveness. In the absence of objective tests, a trial of inhaled / oral corticosteroids should be considered in patients with unexplained chronic cough in order to rule out asthma and NAEB. Additional treatment options for patients with cough-variant asthma include long-acting bronchodilators, antileukotrienes, and/or low-dose theophylline. Patients with NAEB have a good response to corticosteroids, but not to bronchodilators.

### Gastro-esophageal reflux disease (GERD)

Gastroesophageal reflux disease (GERD) is reported as a cause of chronic cough in as many as 40% of the patients. These patients have cough alone or with gastrointestinal symptoms, such as, heartburn and regurgitation. GERD associated cough has been postulated to occur through three major mechanisms: oesophageal-tracheobronchial cough reflex, laryngo-pharyngeal reflux, and micro aspiration.

In up to 75% of the cases, patients with GERD-related cough may present with no gastrointestinal symptoms. Some patients may need pH monitoring of reflux events and objective cough recording. Most of these patients respond to anti-reflux diet & lifestyle changes, a prokinetic agent (e.g. metoclopramide), with a proton pump inhibitor (PPI)

It has been reported that 5 to 10 % of patients seeking medical advice and from 0% to 46% of patients referred to specialty cough clinics for CC, have persistent cough of unexplained origin. These patients have CC that persists often for many months or years, despite exhaustive investigations and treatment of known causes are often labeled as Unexplained Chronic Cough (UCC).

In recent past number of unconventional causes of unexplained chronic cough has been described.

### Non-acid reflux and chronic cough

A subgroup of patients with CC suggestive of GERD, have failed to respond to intense acid suppression treatment and improved chronic cough after antireflux surgery, suggesting the involvement of a non-acidic gastric component.

CC due to non-acid reflux causes, a hypersensitive

Table 2: History Taking in Chronic Cough		
Symptoms	Variable	Related pathology/disease
Onset & Duration	Recent (Acute)	URTI, Viral resp. infections
	Long standing (Chronic)	TB, Asthma, COPD, Bronchiectasis, ILD, Pertussis, Foreign body, Drugs
Character	Brassy	Pressure on the trachea
	Hollow/Bovine	Laryngeal nerve palsy causing vocal cord dysfunction
	Barking	Acute Epiglottitis
Nocturnal	Early morning	Bronchial asthma
Precipitating factors	Triggers	Usually in asthma
Relieving factors	Precipitating factors	Usually in asthma
Sputum	Presence (Volume, Consistency, Pattern)	Infections including pulm. tub., COPD, CF, Bronchiectasis, Asthma
	Dry	GERD, Drugs (e.g. ACEI)
Haemoptysis	Colour, Volume,	Pulm. Tub., Heart Failure, RHD- MS, Lung Cancer, Suppurative lung diseases including Bronchiactasis, etc
Association	Breathlessness, Sputum, Chest pain, Wheeze, Hoarseness, Post nasal drip	Asthma, COPD, CV dis.
		Infections including pulm. tub., COPD, CF, Bronchiectasis,
		Lobar pneumonia, pulm. embolism, pleuritis
		Asthma
		Laryngeal diseases
		Allergic Rhynitis, Sinusitis

cough reflex, possibly through the stimulation from the neurogenic airway inflammation and mast cell activation. Impedance-pH monitoring is a powerful tool that helps in detecting acid and non-acid reflux events in patients on PPI therapy.

### Sleep apnea and chronic cough

Several recent studies have suggested a possible association between chronic cough and obstructive apnea. It is proposed that increase in trans-diaphragmatic pressure during apnea episodes, which causes lower esophageal sphincter insufficiency may lead to GERD; also snoring and apnea may induce epithelial injury.

### Vocal cord dysfunction and chronic cough

Patients with vocal cord dysfunction commonly experience stridor and dysphonia, owing to episodic, uncontrollable narrowing of the cords during inspiration may experience dyspnea and cough and are commonly misdiagnosed as asthma. The diagnosis of vocal cord dysfunction can be made with the use of direct laryngoscopy and flattening of the inspiratory flow-volume loop on spirometry.

### Psychogenic or Habitual Cough

A habitual cough is a diagnosis of exclusion. Many patients with this condition do not cough during sleep and enjoyable distractions. It is suggested that some of these patients may have more than one potential aggravating factor for production of cough.

### Cough hypersensitivity syndrome: The new paradigm

In this view, CC is considered as a single syndrome with a common intrinsic mechanism of cough hypersensitivity. It is suggested that there is increased expression of cough receptors in the airways of these patients with CC, and common diseases, such as rhinitis, eosinophilic bronchitis, asthma or gastroesophageal acidic refluxes are believed to be triggers rather than causes for production of cough.

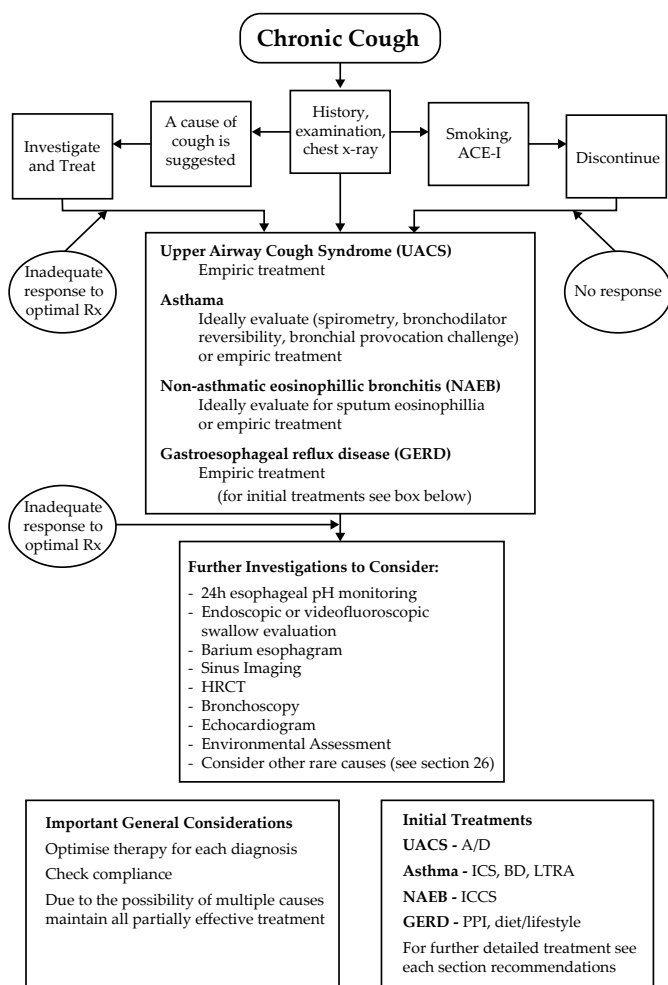
## CLINICAL EVALUATION

### History

Relevant points in history taking in a patient of Chronic Cough are given in Table 2.

## INVESTIGATIONS

- ESR, TDLC, TEC
- Sputum examination – AFB, malignant cell, eosinophils, fungus & culture sensitivity
- X-ray chest, X-ray PNS
- Spirometry – Reversibility test, Broncho-provocation tests,
- Exhaled nitric oxide (NO) concentration
- Laryngoscopy & Bronchoscopy
- Impedance-pH monitoring
- HRCT/Contrast CT – chest, sinuses



**Fig. 1: Algorithm for the management of Chronic Cough (Chronic Cough: in patients of  $\geq 15$  years of age cough lasting  $> 8$  weeks); [ACE-I; ACE-inhibitor; BD = Bronchodilator; LTRA = Leukotrienes receptor antagonist; PPI = Proton Pump Inhibitor]; Cited from: De Blasio F, Virchow JC, et al. Cough management: a practical approach. *Cough* 2011; 7:7. © 2011 De Blasio et al; licensee BioMed Central Ltd. [This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.]**

- ECG, ECHO

### QUANTITATIVE ASSESSMENT OF CHRONIC COUGH

- Subjective quality of life questionnaires
- Leicester Cough Questionnaire (LCQ),

- Cough-specific Quality of Life Questionnaire (CQLQ),
- Adverse Cough Outcome Survey (ACOS)
- Chronic Cough Impact Questionnaire (CCIQ)
- Cough and Sputum Assessment Questionnaire (CASA-Q).
- Parent Cough-specific Quality-of-Life questionnaire (PC-QOL) for children.
- Cough diary scores and Visual analog scales,
- Objective ambulatory cough monitoring systems. Several sound based monitoring systems are in use for ambulatory patients e.g. Leicester, Vitalojak and Coughcount cough monitors.

The management of chronic cough is depicted in Figure 1.

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