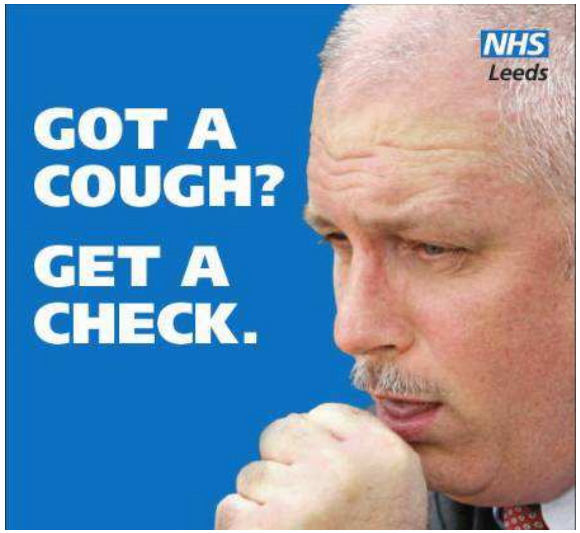
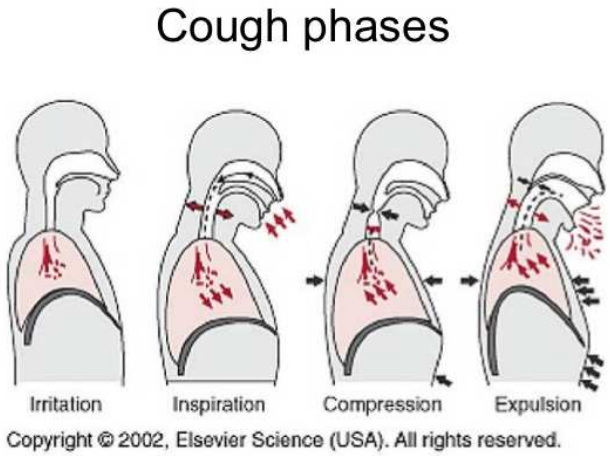
COUGH

PROF. G. ZULIANI



Definitions



Cough is a ***3-phase expulsive motor act*** characterized by:

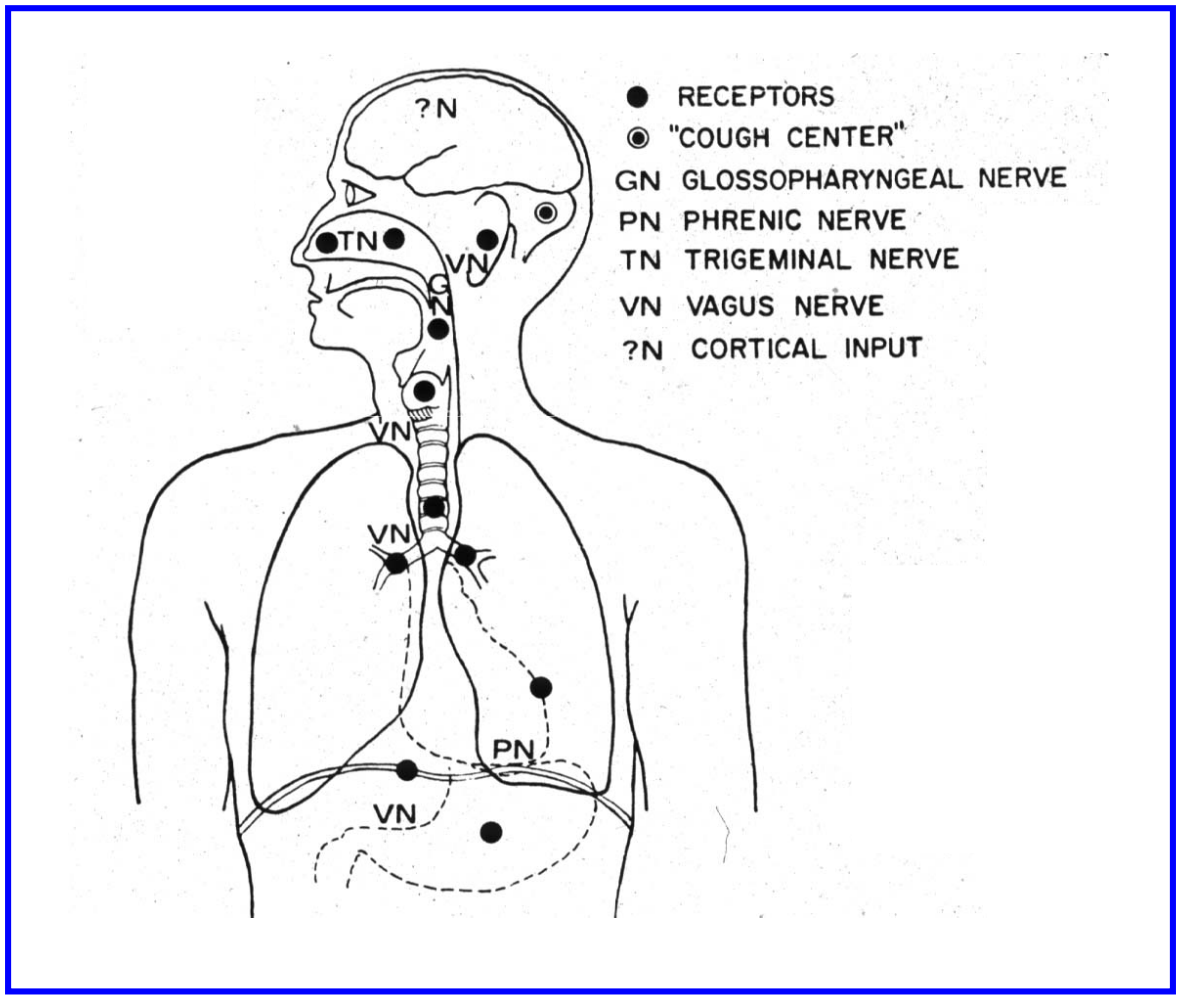
1. an inspiratory effort (inspiratory phase), followed by
2. a forced expiratory effort against a closed glottis (compressive phase), followed by
3. opening of the glottis and rapid expiratory airflow (expulsive phase) ***(Physiological)***

Cough is a forced expulsive maneuver, usually against a closed glottis and which is associated with a characteristic sound ***(Clinical)***

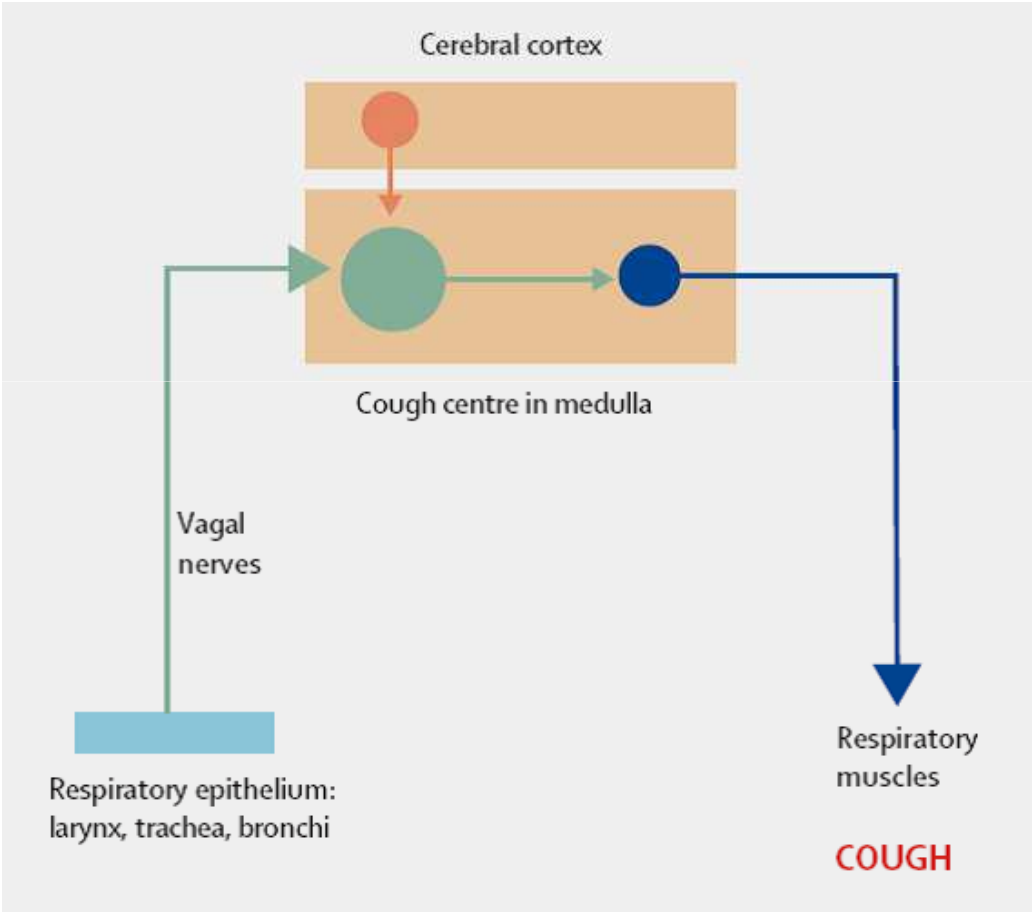
Three Categories of Cough

- **Acute Cough** = < 3 Weeks Duration
- **Subacute Cough** = 3 – 8 Weeks Duration
- **Chronic Cough** = > 8 Weeks Duration

Anatomic sites of afferent cough receptors

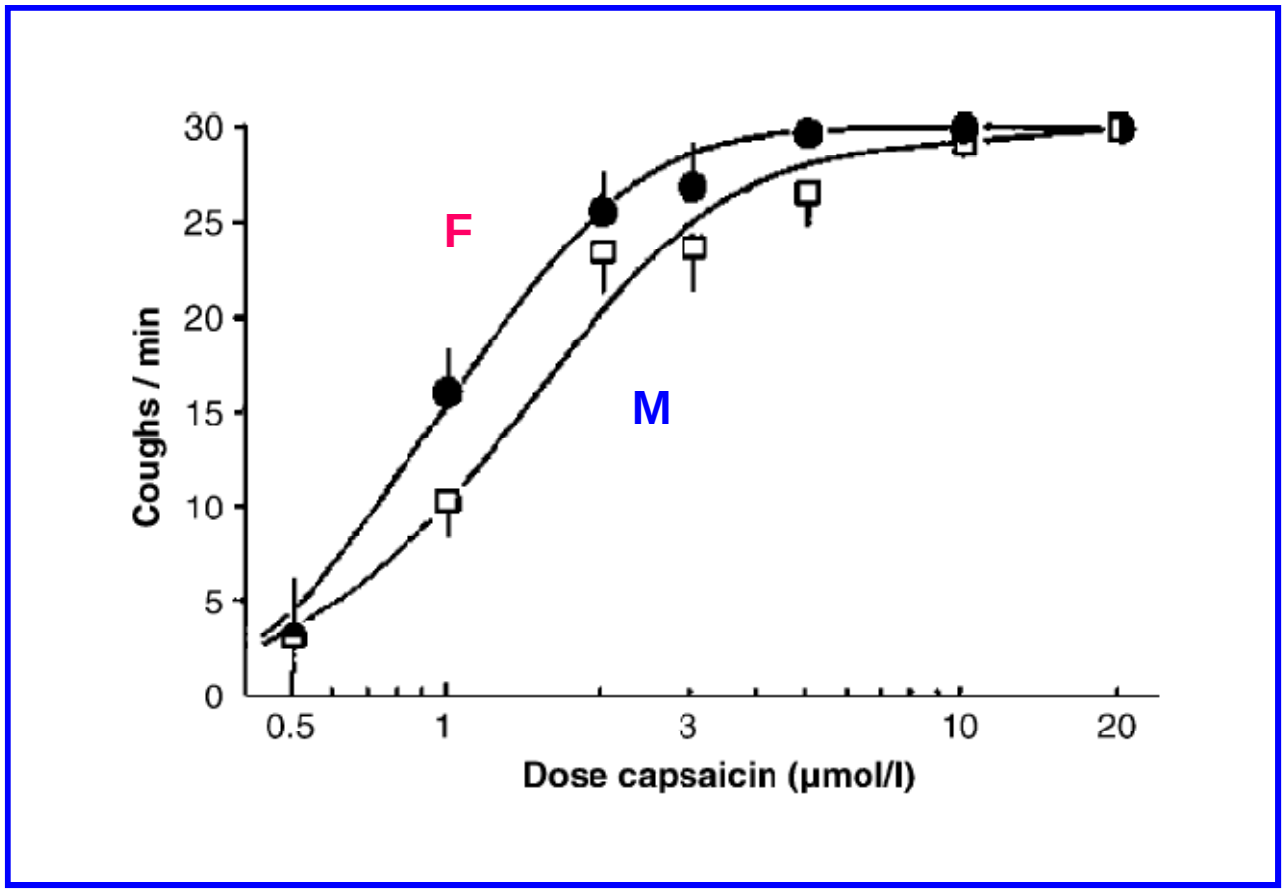


Mechanism of Cough



Eccles R. Lancet Infect Dis

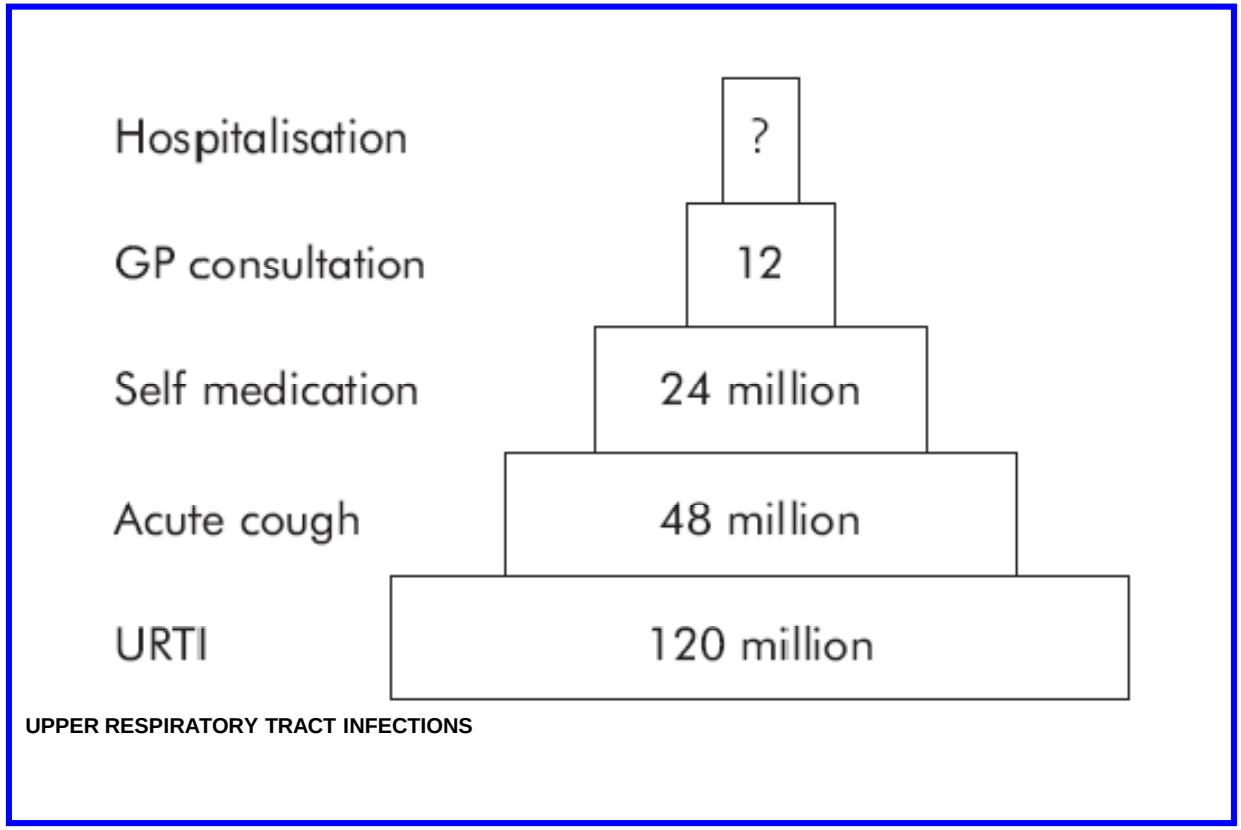
Cough reflex hypersensitivity



Morice *et al*. Lancet

Acute cough

Incidence of acute cough



UPPER RESPIRATORY TRACT INFECTIONS

Thorax 2006;**61**(Suppl I):i1–i24.

Differential Diagnosis of Acute Cough

- Upper Respiratory Tract infections: viral syndromes, sinusitis viral/bacterial
- Allergies
- Exacerbation of COPD
- Pneumonia
- Left Ventricular Heart Failure
- Foreign Body Aspiration

Table 1 Common serious conditions presenting with isolated cough

- Neoplasm
- Infection, e.g. tuberculosis
- Foreign body inhalation
- Acute allergy – anaphylaxis
- Interstitial lung disease

Table 3 Causes of acute cough with a normal chest radiograph

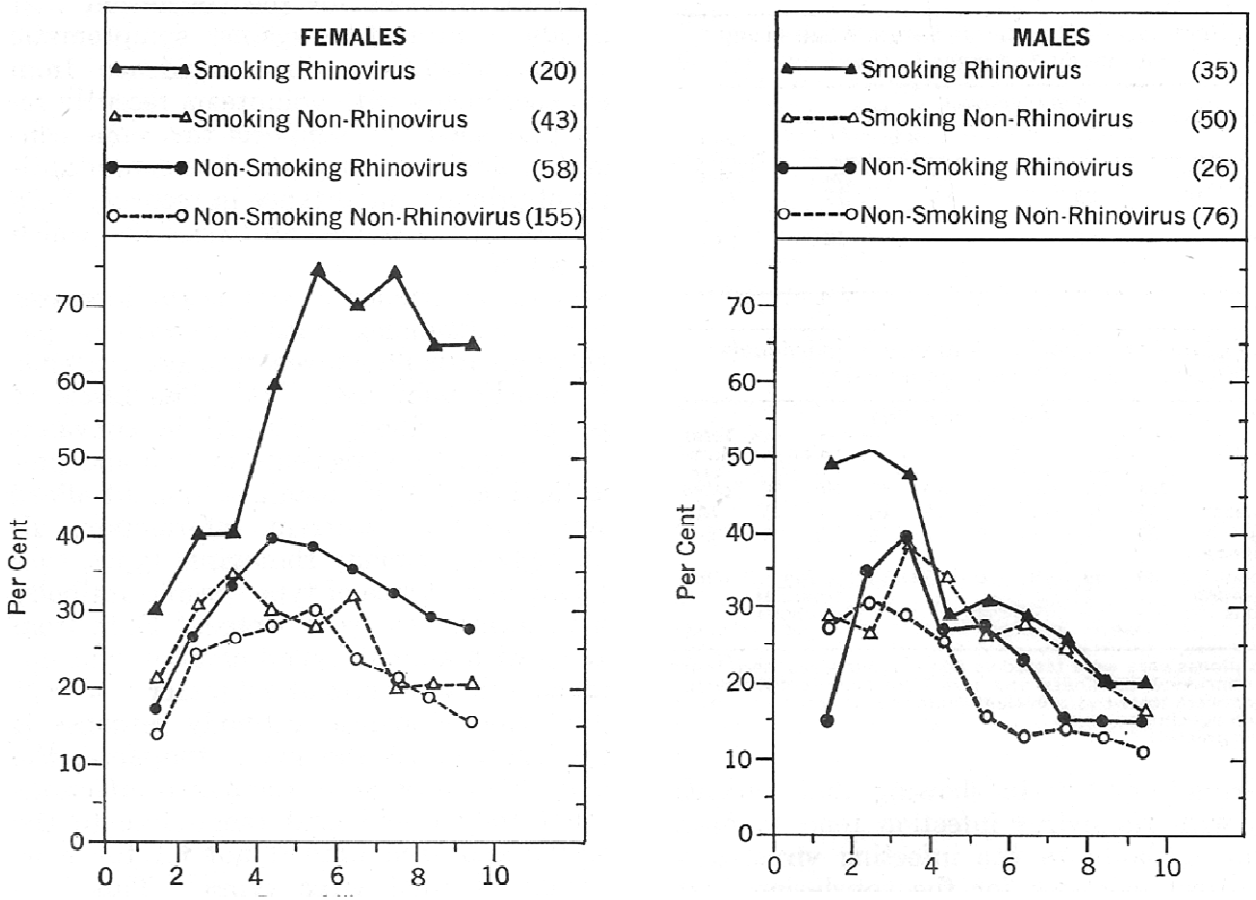
- Viral respiratory tract infection
  - Respiratory syncytial virus
  - Rhinovirus
  - Influenza
  - Parainfluenza
  - Adenovirus
  - Respiratory corona virus
  - Metapneumovirus
- Bacterial infection (acute bronchitis)
- Inhaled foreign body
- Inhaled toxic fume

BTS GUIDELINES BRITISH THORACIC SOCIETY

Recommendations for the management of cough in adults

A H Morice, L McGarvey, I Pavord, on behalf of the British Thoracic Society Cough Guideline Group

Effect of Gender and Smoking on Cough in the Common Cold



JAMA 1967; 202:494-500

Cough in Viral Infection

- Upper respiratory viral infections are the most common cause of cough:
  - **83% within first 48 hours**
  - **26% on day 14**
- Arises from the stimulation of the cough reflex in upper airway by post-nasal drip and/or clearing of the throat

Cough in Viral Infection

Signs and symptoms include:

- *rhinorrhea*
- *sneezing*
- *nasal obstruction*
- *post nasal drip*
- *irritation of the throat*
- *+/- fever*
- *normal chest exam*
  - Diagnostic testing is not indicated in a immunocompetent patient as there is a very low yield = over 97% of CXR are normal

Acute cough

- In the **elderly,** classic signs and symptoms may be minimal, so consider also the possible diagnosis of:

  - ***Pneumonia***
  - ***CHF***
  - ***Asthma***
  - ***Aspiration***

Acute cough

Table 2 Symptoms associated with acute cough prompting a chest radiograph

- Haemoptysis
- Breathlessness
- Fever
- Chest pain
- Weight loss

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Subacute Cough Differential Diagnosis

- Post-infectious
- Bacterial Sinusitis
- Asthma

Post Infectious Cough

- Post-infectious cough:
  - Begins with respiratory tract infection
  - NOT diagnosis of pneumonia
  - Ultimately resolves without treatment
  - Results from PND or clearing of throat
  - With or without bronchial hyper-responsiveness

Onset of cough after experimentally induced common cold

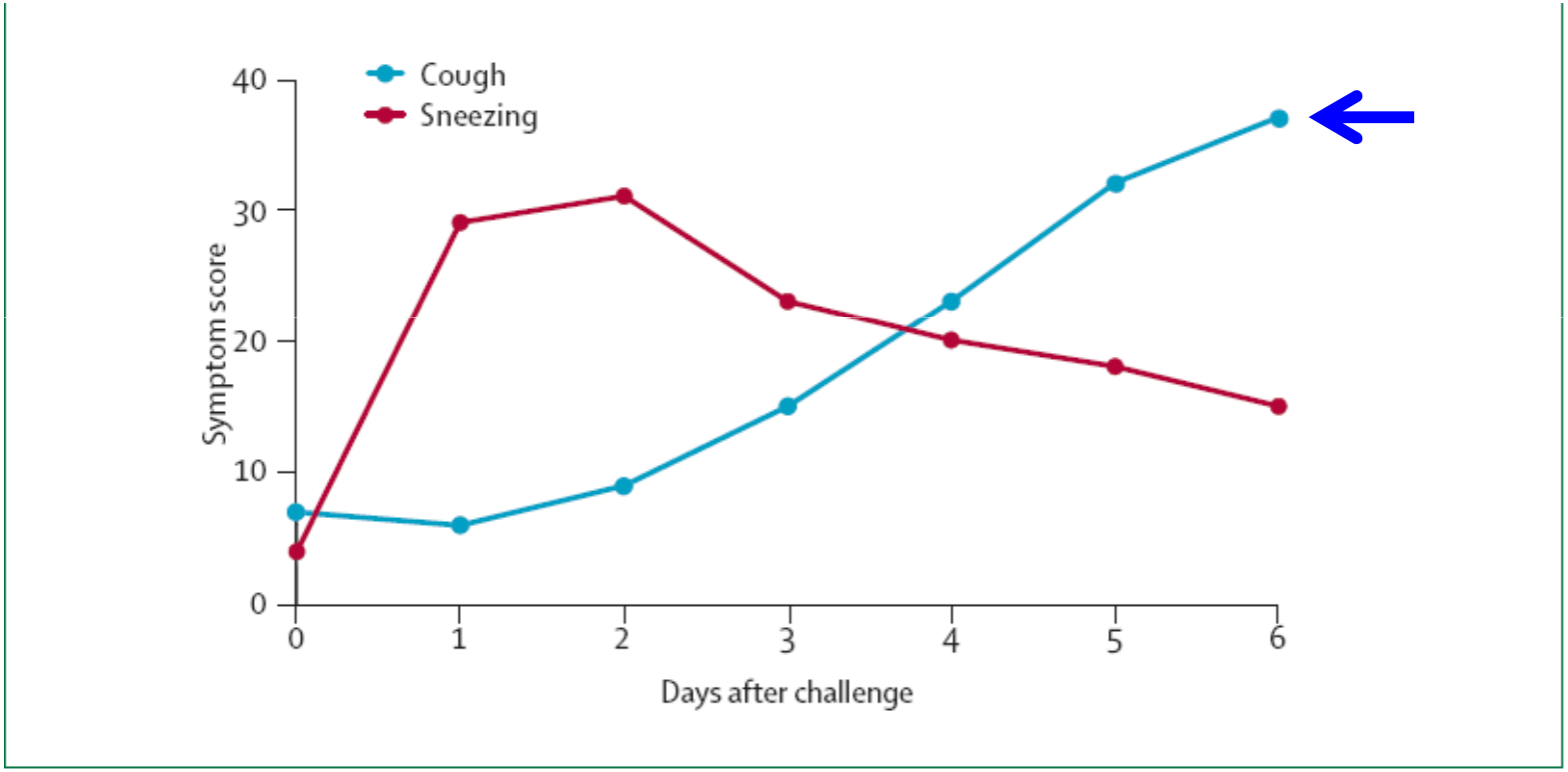

Figure 5: Time course of symptoms of sneezing and cough using challenge with infected nasal secretions to infect human volunteers

Eccles R. Lancet Infect Dis

Summary – acute cough

Acute cough

Key points

- Acute cough is defined as one lasting less than 3 weeks.
- Acute cough is the commonest new presentation in primary care and is most commonly associated with viral upper respiratory tract infection.
- In the absence of significant co-morbidity, an acute cough is normally benign and self-limiting.
- It is the commonest symptom associated with acute exacerbations and hospitalisations with asthma and COPD.
- The cost of acute cough to the UK economy is estimated to be at least £979 million. This comprises £875 million to loss of productivity and £104 million cost to the healthcare system and the purchase of non-prescription medicines.

Recommendations

- Indications for further investigation include haemoptysis, prominent systemic illness, suspicion of inhaled foreign body, suspicion of lung cancer.
- Patients report benefit from various over-the-counter preparations; there is little evidence of a specific pharmacological effect.

BTS GUIDELINES

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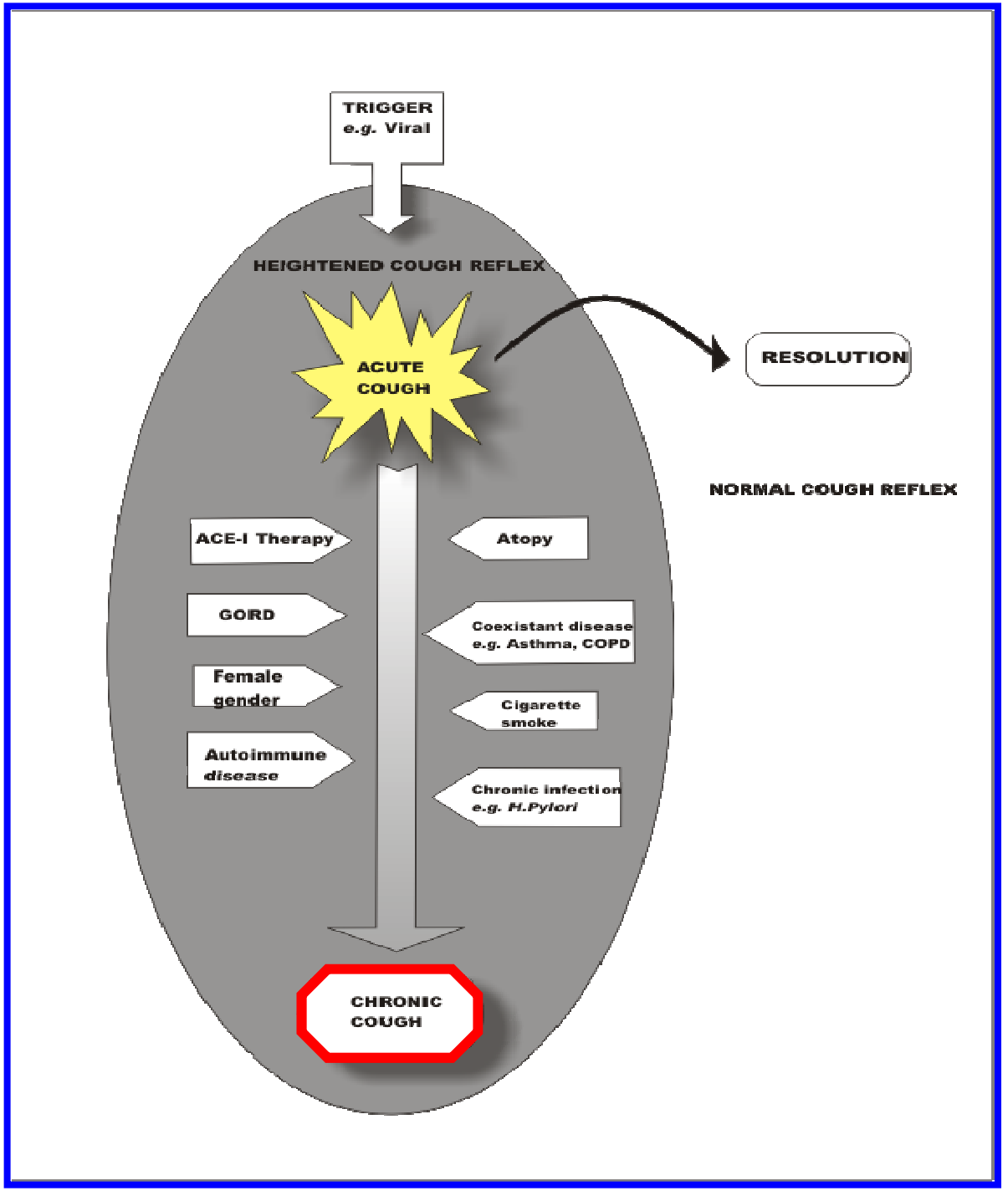
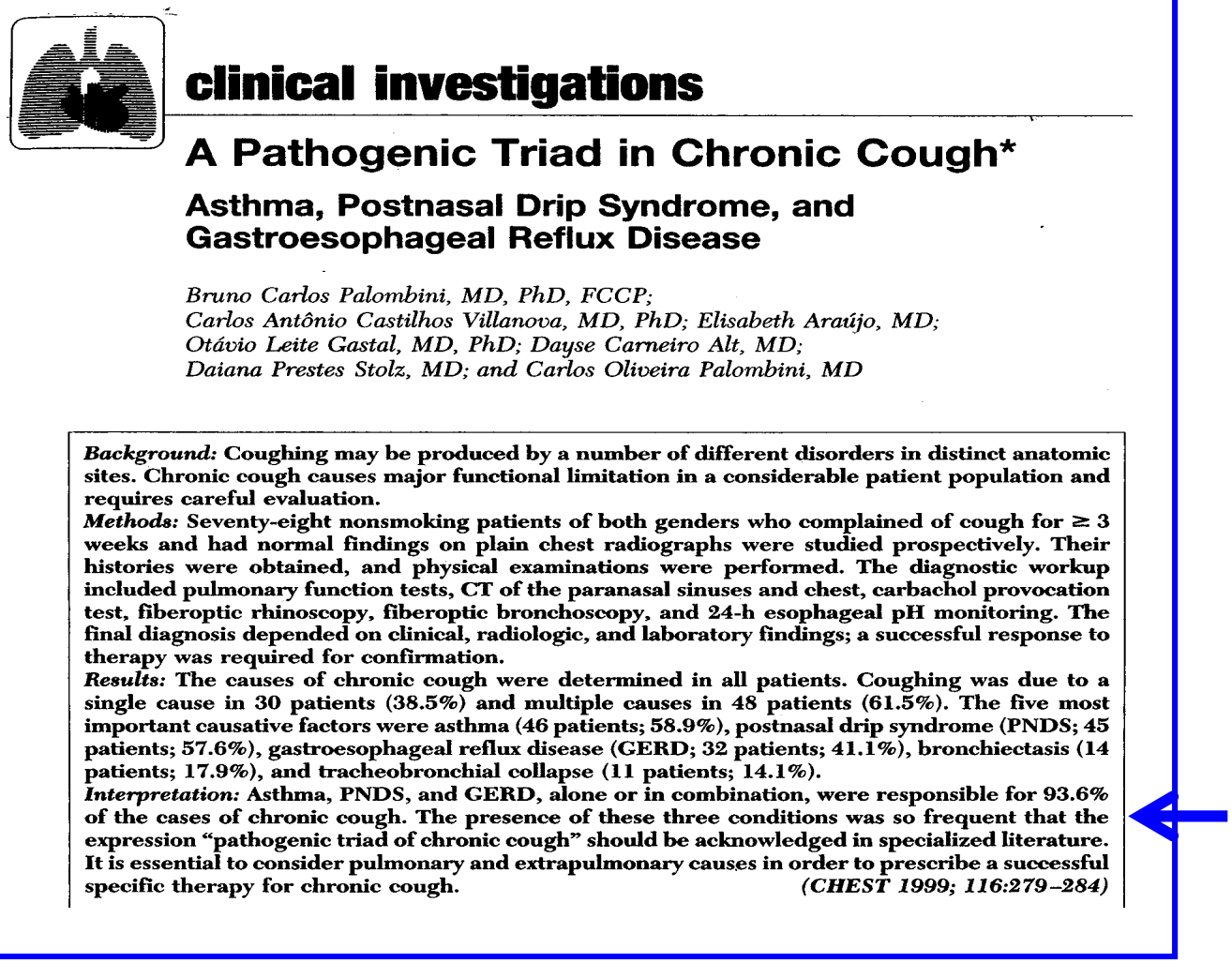
Chronic cough


TRIGGER
e.g. Viral
HEIGHTENED COUGH REFLEX
ACUTE COUGH
RESOLUTION
NORMAL COUGH REFLEX
ACE-I Therapy
GORD
Female gender
Autoimmune disease
Atopy
Coexistant disease e.g. Asthma, COPD
Cigarette smoke
Chronic infection e.g. H.Pylori
CHRONIC COUGH

Causes of chronic cough

- In immunocompetent patients, most cases of chronic cough are caused by:
  1. **Postnasal drip (PND)**
  2. **Asthma**
  3. **Gastroesophageal reflux (GERD)**
  - **Chronic bronchitis due to cigarette smoking**
  - **Bronchiectasis**
  - **Use of ACE inhibitors**

Most common causes of chronic cough in patients investigated in specialist clinics



clinical investigations

A Pathogenic Triad in Chronic Cough*

Asthma, Postnasal Drip Syndrome, and Gastroesophageal Reflux Disease

Bruno Carlos Palombini, MD, PhD, FCCP;
Carlos Antônio Castilhos Villanova, MD, PhD; Elisabeth Araújo, MD;
Otávio Leite Gastal, MD, PhD; Dayse Carneiro Alt, MD;
Daiana Prestes Stolz, MD; and Carlos Oliveira Palombini, MD

Background: **Coughing may be produced by a number of different disorders in distinct anatomic sites. Chronic cough causes major functional limitation in a considerable patient population and requires careful evaluation.**
Methods: **Seventy-eight nonsmoking patients of both genders who complained of cough for ≥ 3 weeks and had normal findings on plain chest radiographs were studied prospectively. Their histories were obtained, and physical examinations were performed. The diagnostic workup included pulmonary function tests, CT of the paranasal sinuses and chest, carbachol provocation test, fiberoptic rhinoscopy, fiberoptic bronchoscopy, and 24-h esophageal pH monitoring. The final diagnosis depended on clinical, radiologic, and laboratory findings; a successful response to therapy was required for confirmation.**
Results: **The causes of chronic cough were determined in all patients. Coughing was due to a single cause in 30 patients (38.5%) and multiple causes in 48 patients (61.5%). The five most important causative factors were asthma (46 patients; 58.9%), postnasal drip syndrome (PNDS; 45 patients; 57.6%), gastroesophageal reflux disease (GERD; 32 patients; 41.1%), bronchiectasis (14 patients; 17.9%), and tracheobronchial collapse (11 patients; 14.1%).**
Interpretation: **Asthma, PNDS, and GERD, alone or in combination, were responsible for 93.6% of the cases of chronic cough. The presence of these three conditions was so frequent that the expression "pathogenic triad of chronic cough" should be acknowledged in specialized literature. It is essential to consider pulmonary and extrapulmonary causes in order to prescribe a successful specific therapy for chronic cough.** ***(CHEST 1999; 116:279–284)***

Most common causes of chronic cough in patients investigated in specialist clinics

Most common causes of chronic cough in patients investigated in specialist clinics

	Number of patients studied	Asthma/eosinphilic syndrome	GOR	PNDS	Most common other (%)
Irwin et al. [1]	49	25	10	18	Chronic bronchitis (12)
Poe et al. [6]	139	33	3	20	Idiopathic (12)
Irwin et al. [2]	102	25	21	41	Chronic bronchitis
O'Connell et al. [7]	87	10	22	24	Idiopathic (22)
McGarvey et al. [8]	43	23	19	21	Idiopathic (18)
Brightling et al. [9]	91	31	8	22	Post-viral (13)

GOR, gastro-oesophageal reflux disease; PNDS, postnasal drip syndrome.

McGarvey *et al*. *Pulm Pharmacol Ther*

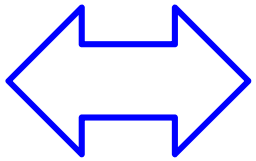
Chronic cough differential diagnosis

- Post Nasal Drip (Nose and Sinus Conditions)
- Gastroesophogeal reflux disease (GERD)
- Chronic Bronchitis from smoking
- COPD
- Left Ventricular Heart Failure
- Lung Cancer
- Tuberculosis
- Asthma

Chest X-ray and Differential Diagnosis

Normal X-ray

- **Post Nasal drip**
- **Reflux Disease**
- **Asthma**
- **Chronic Bronchitis**

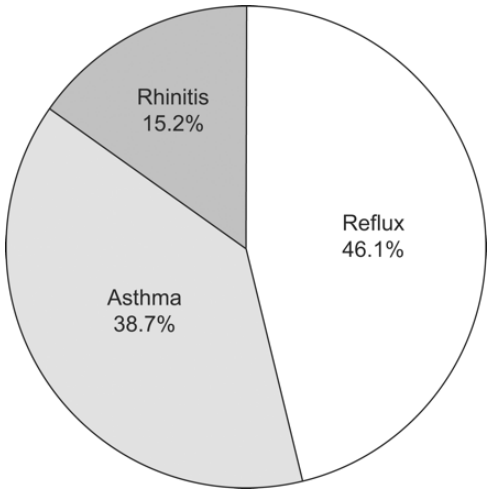


Abnormal X-ray

- **Tuberculosis**
- **COPD**
- **Heart Failure**
- **Lung Cancer**

Table 5 Causes of chronic cough in patients with a normal chest radiograph

- Reflux disease
  - Gastro-oesophageal reflux
  - Laryngopharyngeal reflux
  - Oesophageal dysmotility
- Asthma syndromes
  - Cough variant asthma
  - Eosinophilic bronchitis
- Rhinitis



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Evaluation of Chronic Cough

- **History**
  - Character of cough, quality of the sound and the timing of cough (except the absence during sleep) have **not** shown to be useful
- **Physical**
  - Oropharyngeal mucous appearance suggests postnasal-drip syndrome
  - “silent” postnasal-drip syndrome

Evaluation of Chronic Cough

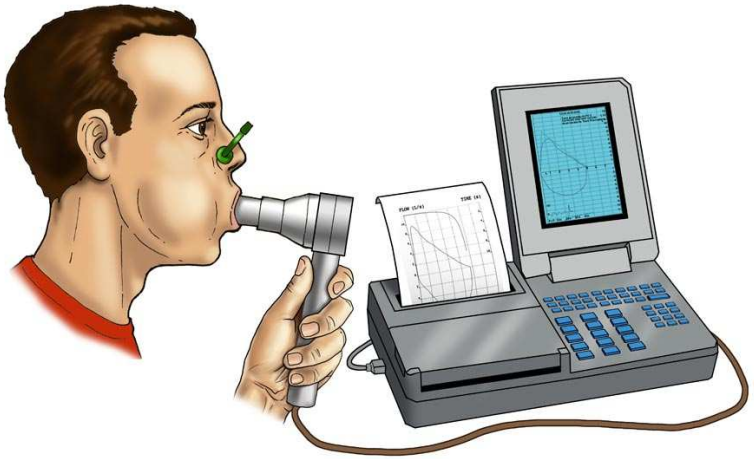
- ***Heartburn and regurgitation*** suggest Gastroesophageal reflux disease
  - *"silent" GERD* in up to 75% of patients
    - Irwin et al. Chest
- ***Wheezing*** suggests asthma
  - *"silent" asthma* (cough variant asthma) in up to 50% of cases
    - Irwin et al. Am Rev Respir Dis

Chronic Cough - PND

- PND is by far the most common cause of chronic cough
- Since the signs and symptoms are non-specific, the definitive diagnosis cannot be made by history and physical exam alone
- Therapy:
  - ***1st generation antihistamine and a decongestant***

Chronic Cough – Asthma

- Cough can be the only symptom of asthma in up to 50% of patients: cough-variant asthma
- +/- airflow obstruction on Pulmonary Function Test



Asthma Signs and Symptoms

Signs and Symptoms vary from patient to patient as well as being dynamic over time

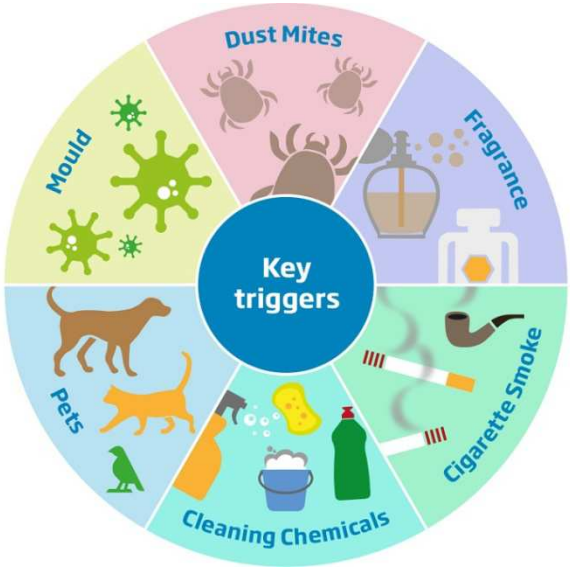
Classic symptoms include:

- Wheezing
- Shortness of Breath
- ***Cough***
- Chest Tightness

Asthma Precipitants

Many non-specific precipitants provoke Asthma symptoms and the need for medication:

- Respiratory Infections
- Exercise
- GI Reflux
- Stress
- Weather changes



Asthma treatment

Step 1 Mild Intermittent	No Daily Medications	Short Acting Bronchodilator B2 Agonist
	Long Term Control	Rapid Relief
Step 2 Mild Persistent	Low Dose Inhaled Steroids	Short Acting Bronchodilator B2 Agonist

Asthma treatment

Step 3 Moderate Persistent	Inhaled Steroid (Med Dose) Or Long Acting Bronchodilator **(B2 Agonist or Theophylline)** + Inhaled Steroids	Short Acting Bronchodilator **Inhaled B2 Agonist**
Step 3 Moderate Persistent	Inhaled Steroid (Med Dose) Or Long Acting Bronchodilator **(B2 Agonist or Theophylline)** + Inhaled Steroids	Short Acting Bronchodilator **Inhaled B2 Agonist**

Chronic Cough - GERD

- ***When GERD is the cause of chronic cough, up to 50-70% of patients may have NO GI symptoms !***

- 24h esophageal pH monitoring is best
  - Negative predictive value is less than 100%
    - Positive predictive value is 89%
    - ***But it is inconvenient for the patient !***

Chronic Cough - GERD

- GERD
  - 24h esophageal monitoring is not routinely recommended
- Empiric therapy can be tried if:
- GI complaints compatible with GERD or
- No GI complaints with normal CXR, no ACE-I, no smoke, PND and asthma excluded

Chronic Cough - GERD

Therapy should include:

- ***H_2 blockers, PPI***
- ***dietary***
- ***life style changes (weight reduction, no caffeine or smoking, no gas water)***
- Improvement may take 2-3 months to begin and the MEAN TIME TO RECOVERYIS 160-180 DAYS.

Chronic Cough - GERD

- **Avoidance of reflux-inducing foods** (fatty foods, chocolate, excess alcohol)
- **Cessation of smoking**
- **Eating three meals** a day without snacking
- Avoidance of meals for two to three hours before lying down
- **Elevation of the head of the bed**
- Average time for response 2 to 6 months

COPD: Terms

- Chronic Bronchitis: Cough for at least 3 months in any 2 successive years without other cause

- Emphysema: pathologic diagnosis describing airspace destruction associated with obstructive disease

COPD: Risk Factors

- TOBACCO SMOKING
- Environmental/occupational exposure
- Genetic alpha-1 antitrypsin deficiency (less than 3% of cases)

COPD: Patterns of Advanced Disease

Pink Puffer (Emphysema)

- Dyspnea
- Age > 50
- **Rare Cough**
- Thin/Weight Loss
- Quit Auscultory Exam
- No Peripheral edema

Blue Bloater (Bronchitis)

- **Chronic Cough/Productive**
- Age > 40
- Mild Dyspnea
- Over Weight
- Cyanotic
- Chest + Rhonchi/Wheezes

COPD: Management

- Mild variable symptoms:

  - Anticholinergic agent or B2-Agonist

- Mild/Moderate continued symptoms:

  - Anticholinergic agent + B2-Agonist

Chronic Cough – ACE-I

- Class effect of drug; not drug related
- Incidence of 0.2% to 33%; true incidence may be **≈ 10%**
- Cough may appear within a few hours up to months after taking the first dose
- Pathogenesis seems be an accumulation of inflammatory mediators: bradykinin, substance P, and/or prostaglandins

Chronic Cough – ACE-I

- A non-productive cough is a complication of treatment with ACE inhibitors, occurring in **3 to 20 percent** of patients treated with these agents
- ACE inhibitor-induced cough has the following general features :
    - usually begins **within 1 week** of instituting therapy, but the onset can be delayed up to 6 months
    - It typically resolves **within 1 to 4 days** of discontinuing therapy, but can take up to four weeks
    - It generally recurs with rechallenge, either with the same or a different ACE inhibitor
    - It is a more common complication in **women** than in men
    - It does not occur more frequently in **asthmatics** than in non-asthmatics
    - It is generally **not** accompanied by airflow obstruction

Cough and Lung Cancer

- Lung cancer is the etiology in less than **2% of cases** of chronic cough, but it is deadly → CT scan, when?
- Most cases of lung cancer that manifest with cough are due to neoplasms originating in the large central airways
- Bronchogenic cancer should be considered as a possible etiology of cough in any current or former smoker, and should be particularly suspected in those with:
    - *A new cough or a recent change in chronic "smoker's cough"*
    - *A cough that persists more than one month following smoking cessation*
    - *Hemoptysis that does not occur in the setting of an acute airway infection*

Screening for Lung Cancer

- ***A low-dose spiral CT scan*** may be used to look for early signs of lung cancer. If the test finds cancer, treatment can start early …
- The test is not helpful for light smokers or people who quitted smoking more than 15 years ago: it's not usually recommended for people younger than age 55 or older than 80
- Even heavy smokers get only a small benefit from the test
- Studies show a slight benefit from CT scans for People age 55 to 80 who smoked 2 packs or more a day for 15 years, or people who smoked 1 pack or more a day for 30 years
- If 1.000 high-risk smokers get the test, about 3 will find lung cancer early and not die; 13 others will also find lung cancer, and will die anyway

Choosing Wisely®
An initiative of the ABIM Foundation

Chronic Cough - Treatment

- **Post nasal drip:**
  - Older antihistamine-decongestant combinations may work best
  - Therapy directed at cause of the PND including antibiotics for sinusitis
  - Ipratroprium nasal spray
  - Nasal corticosteroids

Summary – chronic cough

Chronic cough

Key points

- Chronic cough is defined as one lasting more than 8 weeks.
- It is reported by 10–20% of adults, commoner in females and obese.
- Cough accounts for 10% of respiratory referrals to secondary care.
- Most patients present with a dry or minimally productive cough.
- Decrement in quality of life is comparable with severe COPD.
- The presence of significant sputum production usually indicates primary lung pathology.
- In chronic cough a heightened cough reflex is the primary abnormality.

Clinical evaluation of chronic cough

Recommendations

- A detailed history including a thorough occupational history should be performed in all patients.
- Physical examination should concentrate on the afferent sites identified as most commonly associated with cough.
- The evaluation of patients with chronic cough should include an assessment of health status and cough severity. Cough visual analogue scores are an alternative to cough specific quality of life questionnaires but are less well validated. (Audit)
- Chest radiograph and spirometry are mandatory. (Audit)
- Bronchial provocation testing should be performed in patients without a clinically obvious aetiology referred to a respiratory physician with chronic cough and normal spirometry.
- Bronchoscopy should be undertaken in all patients with chronic cough in whom inhalation of a foreign body is suspected.
- High resolution computed tomography may be of use in patients with chronic cough in whom other more targeted investigations are normal.
- Optimal management should comprise a combination of diagnostic testing and treatment trials based on the most probable aggravant(s).
- Treatment effects should be formally quantified. (Audit)

General Treatment of Cough

1) **Antitussives** (cough-centre suppressants)
2) **Expectorants (Mucokinetics)**
3) **Mucolytics**
4) **Antihistamines**
5) **Bronchodilators**
6) **Pharyngeal Demulcents**

1. Antitussives

(cough-centre suppressants)

Drugs that suppress cough and produces symptomatic relief

Mechanism of action:

- Mainly suppress cough-centre in medulla (both central & peripheral effects)

E.g.: Opioid drugs = ***codeine, paracodine, dextromethorphan***, ***cloperastine,*** pholcodeine, noscapine, …

Opioids are most effective for cough

a) Codeine

- Codeine: is a pro-drug $\Rightarrow$ metabolized to morphine
- It is an alkaloid found in Opium poppy plant
- Has much less addiction
- (Resp. center depressant = ???)
- Has useful antitussive action at low doses (<15 mg)
- Produce drowsiness, thickening of sputum, constipation

c) Dextromethorphan

Available in syrup, tablets, spray forms

Mechanism of action:

- NMDA receptor antagonist

Uses: Cough suppressant, temporary relief of cough caused by minor throat & bronchial irritation (accompanies with flu & cold), pain relief

Adverse effects: Nausea, vomiting, drowsiness, dizziness, blurred vision

2) Expectorants

(Mucokinetics)

Act peripherally by ***increasing bronchial secretion*** or ***decreasing its viscosity*** ⇒ facilitates its removal by coughing

Loose cough ►less tiring and more productive

Classified into

- Directly acting

E.g. Na+ & K+ citrate or acetate, Guaifenesin (glyceryl guaiacolate)

- Reflexly acting

E.g. Ammonium salt

a) Sodium & potassium citrate or acetate

They act directly *by increasing bronchial secretion by salt action*

Guaifenesin

- Expectorant drug usually taken by mouth
- Available as single and also in combination

Mechanism of action: Increase the volume and reduce the viscosity of secretion in trachea and bronchi

b) Reflexly acting

Ammonium salts

- Bronchial mucosa irritants $\Rightarrow$ This causes the production of ***excess respiratory tract fluid*** which presumably is easier to cough up.

- Ammonium salts are an irritant to the gastric mucosa and may induce nausea and vomiting reflexly $\uparrow$ bronchial secretions

3) Mucolytics

Help in expectoration ***liquefying the viscous tracheobronchial secretions***

E.g. ***Bromhexine, Acetylcysteine***

a) Bromhexine: Synthetic derivative of **vasicine** (alkaloid= *Adhatoda vasica*)

Meccanism of Action of Bromhexine:

a) Thinning & fragmentation of mucopolysaccaride fibers

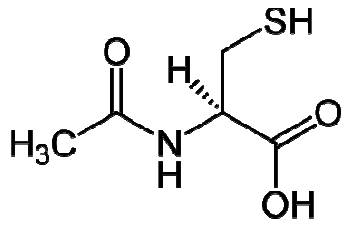
b) ↑ volume & ↓ viscosity of sputum

3) Mucolytics

b) Acetylcysteine

Mechanism of action of Acetylcycteine:

Opens disulfide bond in mucoproteins of sputum with ↓ of viscosity



Uses:

Cystic fibrosis (to ↓ viscosity of sputum)

Onset of action quick; used 2-8 hour

Adverse effects:

Nausea, vomiting, bronchospasm in bronchial asthma

NB: also used in the management of paracetamol (acetaminophen) overdose.

4) Antihistamines

- Added to antitussives/expectorant formulation
- Due to ***sedative and anticholinergic actions*** produce relief in cough but lack selectivity for cough-centre
- No expectorant action
- Reduce secretions (anticholinergic effect)
- Suitable for allergic cough (not for asthma)

E.g.: ***Chlorpheniramine, diphenhydramine, promethazine***

5) Bronchodilators

- Bronchospasm or stimulation of pulmonary receptors induce or aggravate cough + bronchoconstriction
- e.g. **β_2-agonist: salbutamol**
- Mechanism action of bronchodilators in cough:
- Increase surface velocity of air flow during cough → Clear secretions of airway
- Not used routinely for every type of cough but *only when bronchoconstriction is present*

6) Pharyngeal demulcents

Soothe the throat directly, and also by promoting salivation

Decrease afferent impulses from inflamed - irritated pharyngeal mucosa

Provide symptomatic relief in dry cough arising from throat

E.g.: **lozenges, cough drops, glycerine, liquorice, honey**


Bronchenolo
Sedativo e
Fluidificante
Flacone 150 ml


tusseval
FLU
SOLUZIONE ORALE
ADULTI
N-Acetil Cisteina 600 mg/20 ml
200 ml


Bisolvon
Linctus
4 mg/5 ml sciroppo
bromexina cloridrato
Senza zucchero
AROMA FRAGOLA
Mucolitico
Boehringer Ingelheim
2+ ANNI


FROBEN
TOSSE
GRASSA
4 mg/5 ml sciroppo
bromexina cloridrato
Mylan


MUCOSOLVAN
15mg/5ml sciroppo
Ambroxolo


ACTIGRIP
TOSSE SEDATIVO
15 mg, pastiglie, Droprapizina
PASTIGLIE
ACTIGRIP
TOSSE
SEDATIVO
15 mg/5 ml, sciroppo,
Droprapizina
SCIROPPO


LEVOtuss
LEVOtuss
30 mg / 5 ml
SCIROPPO