Chronic Cough

UWI/BAMP
CME Meeting

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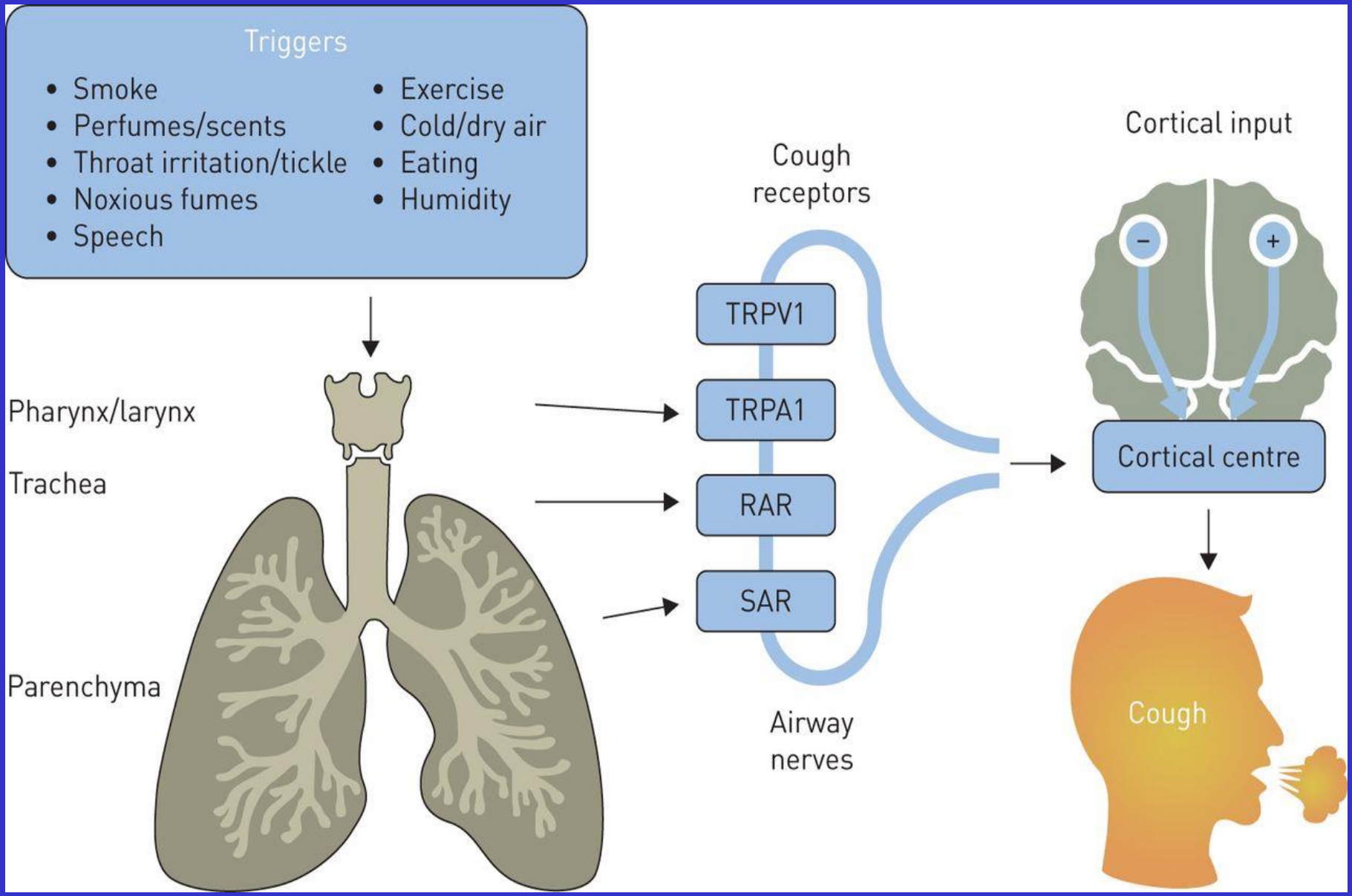
Cough

Cough

- **A normal protective mechanism of the respiratory tract as well as a common symptom of respiratory disease**
- **The most common cause for Primary Care visits in both adults and children**
- **Majority of cases resolves within a few days or weeks and usually due to an acute viral infection**

Irwin RS, Curley FJ et al. Chronic cough. The spectrum and frequency, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis 1990;**141**:640

Pathophysiology of cough



Mirjam J.G. van Manen et al. Eur Respir Rev 2016;25:278-286

ACCP evidence-base clinical practice Guidelines-chronic cough.

In adults cough is classified by duration into:

- **Acute cough < 3 weeks**
- **Subacute cough 3-8weeks**
- **Chronic cough > 8 weeks**

1. Irwin RS, Bauman MH, et al. Diagnosis and management of cough executive summary. ACCP evidence-based clinical practice guidelines. ***Chest*** 2006;129:1S

ACCP evidence-base clinical practice Guidelines-chronic cough.

- **This is a useful classification because post- infectious cough is estimated to last for up to 8 weeks.**
- **Therefore evaluation for patients with chronic cough should be reserved for those with cough > 8 weeks**

1. Irwin RS, Bauman MH, et al. Diagnosis and management of cough executive summary. ACCP evidence-based clinical practice guidelines. ***Chest*** 2006;129:1S

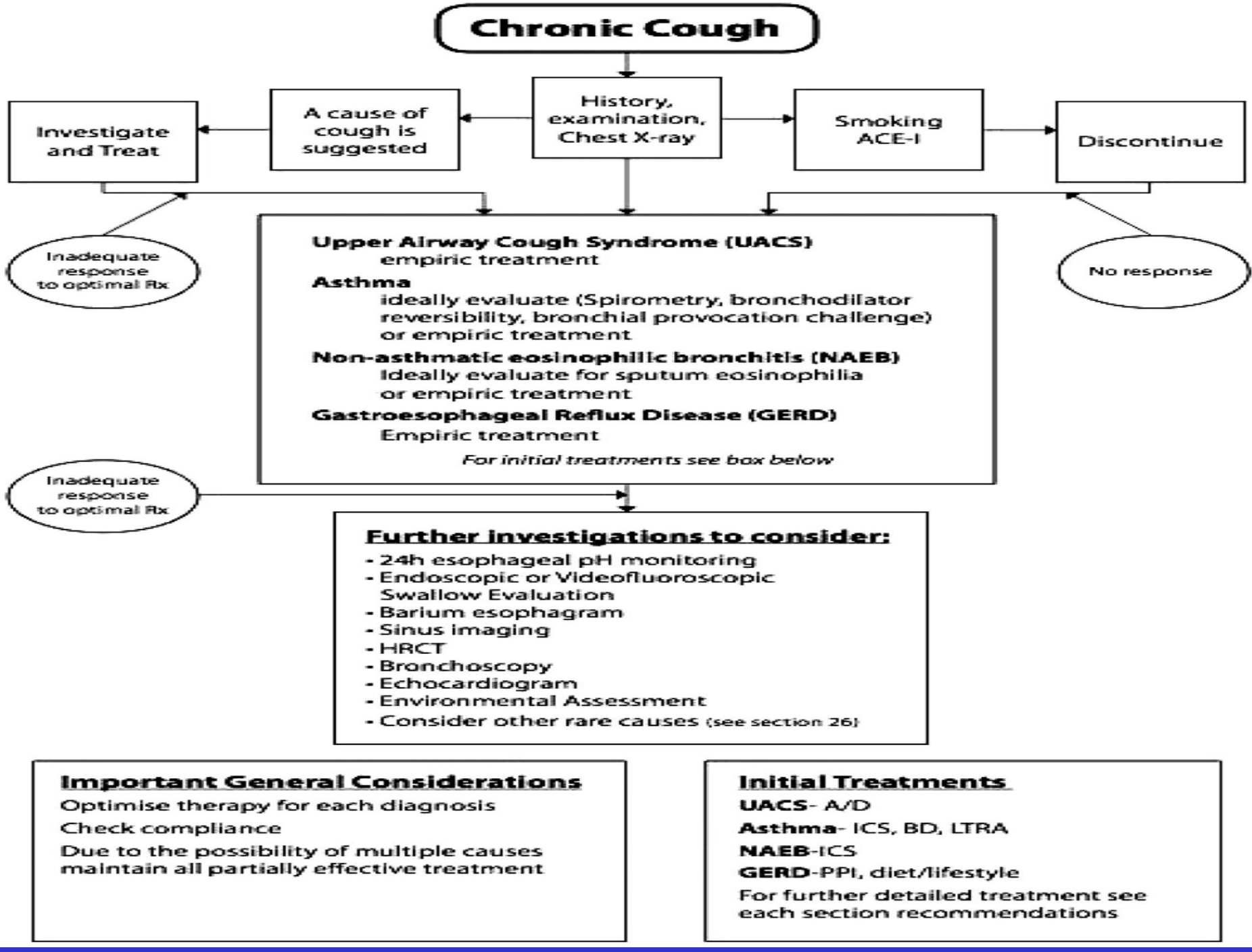
Chronic Cough

The major Guidelines for the treatment of chronic cough suggest an anatomic diagnostic paradigm which focuses on identifying the causes of the cough

2. Irwin RS, Corrao WM, et al. Chronic persistent cough in the adult: spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis* 1981:**123:**413-17.

Chest. 2006;129(1_suppl):1S-23S. doi:10.1378/chest.129.1_suppl.1S

Diagnosis and Management of Cough Executive Summary : ACCP Evidence-Based Clinical Practice Guidelines


Chronic Cough
History, examination, Chest X-ray
A cause of cough is suggested
Investigate and Treat
Smoking ACE-I
Discontinue
Inadequate response to optimal Rx
No response
Upper Airway Cough Syndrome (UACS)
empiric treatment
Asthma
ideally evaluate (Spirometry, bronchodilator reversibility, bronchial provocation challenge)
or empiric treatment
Non-asthmatic eosinophilic bronchitis (NAEB)
Ideally evaluate for sputum eosinophilia
or empiric treatment
Gastroesophageal Reflux Disease (GERD)
Empiric treatment
For initial treatments see box below
Inadequate response to optimal Rx
Further investigations to consider:
- 24h esophageal pH monitoring
- Endoscopic or Videofluoroscopic Swallow Evaluation
- Barium esophagram
- Sinus imaging
- HRCT
- Bronchoscopy
- Echocardiogram
- Environmental Assessment
- Consider other rare causes (see section 26)
Important General Considerations
Optimise therapy for each diagnosis
Check compliance
Due to the possibility of multiple causes maintain all partially effective treatment
Initial Treatments
UACS- A/D
Asthma- ICS, BD, LTRA
NAEB-ICS
GERD-PPI, diet/lifestyle
For further detailed treatment see each section recommendations

Chronic cough: causes

In 99.4% of immunocompetent, non smoking adult with normal chest x-ray , not taking a ACE inhibitor- the underlying cause of chronic cough is due to one or a combination of the following:

Mello CJ, Irwin RS, et al. Predictive values of the character, timing, and complications of chronic cough in diagnosing the cause. *Arch Intern Med* 1996;**156:**997

Chronic Cough- causes

Most common causes:

1. **Upper airway cough syndrome (postnasal drip)-** ***rhinosinusitis, Upper airway cough syndrome.***
2. **Asthma and Associated Eosinophilic Conditions**
3. **Gastroesophageal reflux**
4. **Post-infection-** ***following a URTI***

International Guidelines

Published Guidelines suggest diagnostic empiric trials of therapy in a sequential approach, targeting the three most common causes of cough in adults:

1. **Upper airway cough syndrome (postnasal drip)-** ***rhinosinusitis, Upper airway cough syndrome.***
2. **Asthma and Associated Eosinophilic Conditions**
3. **Gastroesophageal reflux**

Chronic Cough- Sequential, empiric approach

- Using a **sequential, empiric** approach to therapy is of **diagnostic** as well as **therapeutic** usefulness.
- It is best to follow **one avenue** of Rx at a time rather than multiple branches of treatment simultaneously.
- If there is partial or incomplete resolution of cough then the therapy for the **next** most likely cause can be added.

Chronic Cough- causes

- **Up to 25% of the time, > 1 diagnoses will be operative and these patients will need to be treated concurrently for the likely causes.**

Chronic Cough- causes

In adults the timing and the character of the cough (day vs night, wet vs dry) have not been shown to be predictive of the cause

Mello CJ, Irwin RS, et al. Predictive values of the character, timing, and complications of chronic cough in diagnosing the cause. *Arch Intern Med* 1996;**156:**997

Upper airway cough syndrome

The most common cause of chronic cough

Upper airway cough syndrome

Post nasal drip (PND) **is defined as the posterior drainage of secretions from the nose or paranasal sinuses into the nasopharyngeal area.**

Upper airway cough syndrome

Symptoms:

- **Frequent nasal discharge**
- **Sensation of liquid dripping in back of throat**
- **Frequent clearing of the throat**
- **“Silent”**
- **Examination:**

  Coble stone appearance and secretion in nasopharynx

Upper airway cough syndrome

In patients with chronic cough 20% to 40% found to be due to rhinosinus disease including:

- **Allergic rhinitis**
- **Non allergic rhinitis**
- **Vasomotor rhinitis**
- **Sinusitis**
- **Acute nasopharyngitis**

Upper airway cough syndrome

- **Tonsillar enlargement** in both children and adults have been reported to cause chronic cough
- **Obstructive Sleep Apnea (OSA)** as a cause of chronic cough can be considered part of UACS

Upper airway cough syndrome

- Signs and symptoms of UACS are **nonspecific**
- **No** clear diagnostic **criteria** for diagnosis of UACS
- The response to therapy **confirms** the diagnosis

Upper airway cough syndrome -treatment

Treatment is based on the underlying upper airway disorder.

Some authors have suggested that first generation anti-histamines are preferred for cough caused by UACS because they might directly inhibit cough reflex sensitivity (CRS).

However, successful treatment of allergic rhinitis with second-generation oral or topical antihistamines or topical nasal steroids have been shown to reduce cough.

Upper airway cough syndrome -treatment

In a pilot study of adult patients with PND and shown not to have asthma or GERD, 28 days of topical nasal therapy with *fluticasone*, *azelastine*, and *ipratropium bromide* was associated with significant improvement in cough, anterior nasal discharge and endoscopic nasal inspection.

Macedo P, wt al. Postnasal drip and chronic cough: an open intervential study. *Res Med* 2009;**103**:1700-5

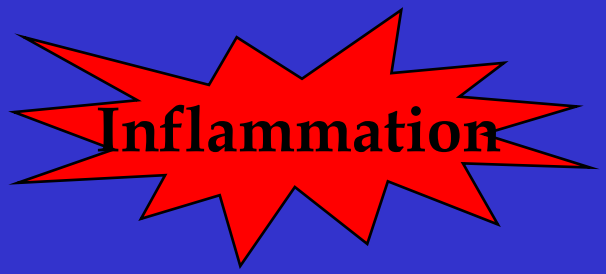
Allergic Rhinitis-Treatment

Allergen avoidance

Pharmacotherapy

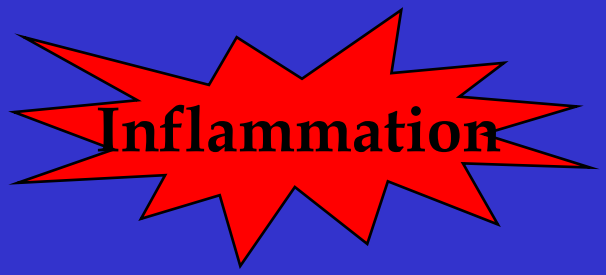
Anti-inflammatory **Antihistamines**

Pharmacotherapy



Intranasal Corticosteroids (INCS) are presently the most effective single maintenance therapy for allergic rhinitis and should be the first-line treatment for allergic rhinitis.

Pharmacotherapy



Intranasal Corticosteroids (INCS) are also effective for several types of non-allergic rhinitis including non-alergic rhinitis with eosinophilia and vasomotor rhinitis.

Antihistamine- Oral

Oral H1-antihistamines prevent and relieve:

- **Sneezing**
- **Itching**
- **Rhinorrhoea**
- **Cough**

F. Estelle R. Simons, Keith J. Simons. Histamines and H1 antihistamines: Celebrating a Century of Progress. J Allergy Clin Immunol.2011:128 Issue 6:1139-50

Antihistamine- Oral

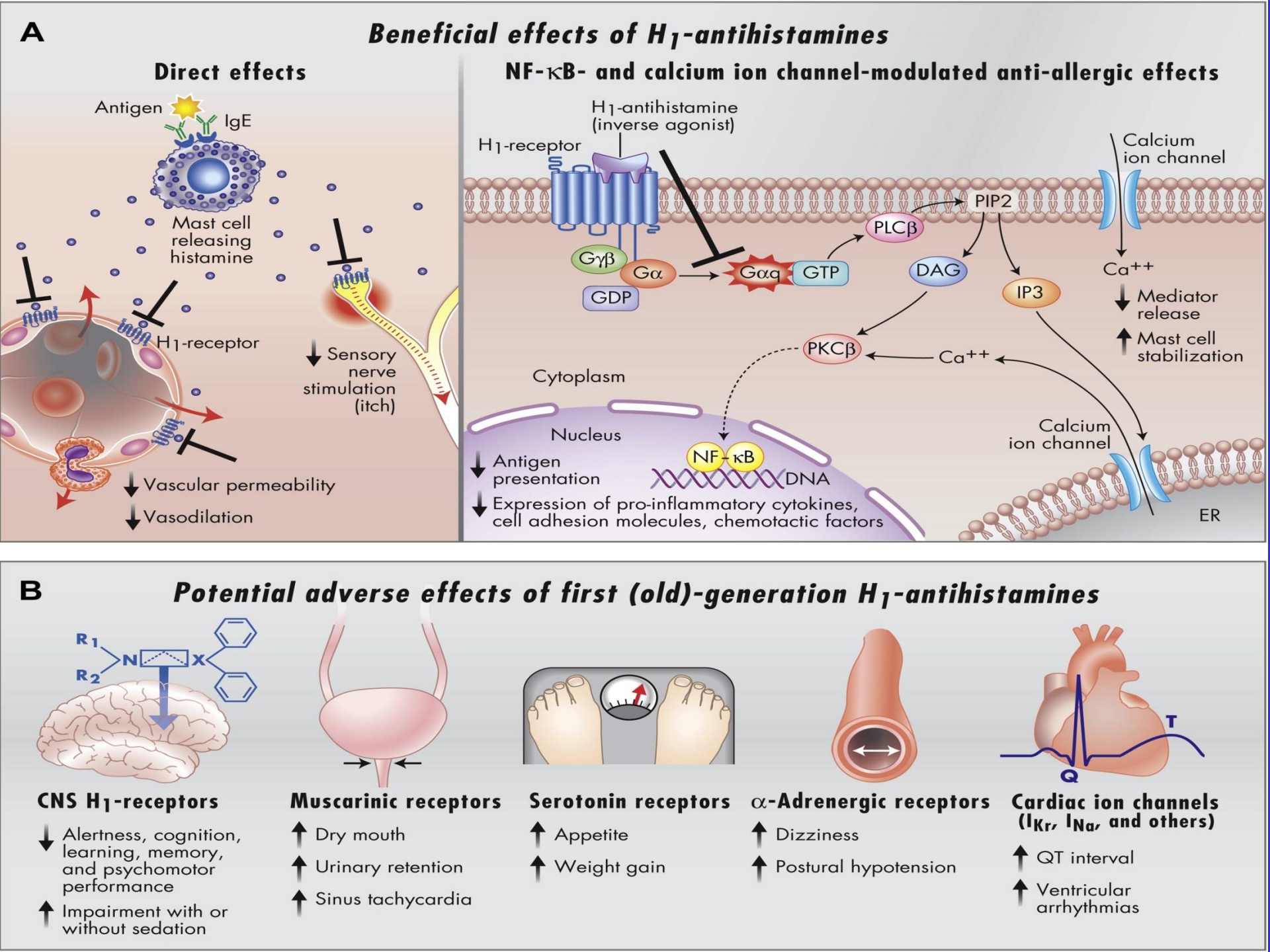
- **Oral H1-antihistamines are more effective than sodium chromoglycate and montelukast and all of these classes are less effective than INCS.**

- **First generation oral H1 antihistamines are generally more effective that second-generation antihistamines in non-allergic rhinitis**

Chronic cough-non-allergic rhinitis

For patients with suspected non-allergic rhinitis, use a diagnostic trial with:

- **Oral first generation anti-histamine (e.g. *chlorpheniramine, mequitazine)***
- **Or a combined anti-histamine-decongestant (*pseudoephedrine*)**


A
Beneficial effects of H1-antihistamines
Direct effects
Antigen
IgE
Mast cell releasing histamine
H1-receptor
Sensory nerve stimulation (itch)
Vascular permeability
Vasodilation
NF-κB- and calcium ion channel-modulated anti-allergic effects
H1-antihistamine (inverse agonist)
H1-receptor
Calcium ion channel
PIP2
PLCβ
Gγβ
Gα
GDP
Gαq
GTP
DAG
IP3
Ca++
Mediator release
Mast cell stabilization
PKCβ
Ca++
Cytoplasm
Nucleus
NF-κB
DNA
Antigen presentation
Expression of pro-inflammatory cytokines, cell adhesion molecules, chemotactic factors
Calcium ion channel
ER
B
Potential adverse effects of first (old)-generation H1-antihistamines
R1
R2
N
X
CNS H1-receptors
Alertness, cognition, learning, memory, and psychomotor performance
Impairment with or without sedation
Muscarinic receptors
Dry mouth
Urinary retention
Sinus tachycardia
Serotonin receptors
Appetite
Weight gain
α-Adrenergic receptors
Dizziness
Postural hypotension
T
Q
Cardiac ion channels (IKr, INa, and others)
QT interval
Ventricular arrhythmias

Antileukotriene-*Montelukast*

- **Nasal congestion correlates best LTC4 levels**
- *Montelulast* < effective INCS
- *Montelukast* = *loratadine* in systematic review of eight randomised trials
- *Montelukast* + 2nd generation oral antihistamine (e.g. loratadine or fexofenadine) > either alone
- *Montelukast* + *loratadine* = *fexofenadine* + *pseudoephedrine* (but insomnia).
- IN*Fluticasone* > *Montelukast* + oral antihistamine in 1 study, 2 studies showed comparable efficacy

Ipratropium bromide

- Congener of Atropine
- Acts by decreasing substance P
- Useful as it decreases rhinorrhoea and **cough**
- Less effective than INCS for sneezing, nasal obstruction or itching

Chronic cough- UACS

If the cough does not respond to empiric UACS therapy after two weeks:

UACS is unlikely to be the cause of the cough.

Chronic cough- Asthma

Asthma

The second most common cause of chronic cough

Chronic Cough-Asthma

- **Asthma is characterised by chronic or recurrent symptoms associated with airway inflammation and variable airway obstruction.**
- **In most patients symptoms include:**
  - **Wheeze**
  - **Dyspnoea**
  - **and/or Cough**

Diagnosis of asthma

There is no specific diagnostic test for asthma

Diagnosis of asthma

Symptom(episodic/variable)

- **wheeze**
- **shortness of breath**
- **chest tightness**
- **Cough**

Diagnosis based on the symptoms of asthma

Chronic Cough-Asthma

- In some patients determined to have asthma, cough is the **sole** or predominant symptom-

"Cough Variant Asthma"

- Because of possible pathophysiological differences, patients with cough variant asthma are thought to represent a **different** phenotype from those with classical asthma.

Diagnosis of asthma

The best way to confirm asthma as a cause of the cough is to demonstrate improvement in the cough with two to four weeks of appropriate therapy-inhaled corticosteroid.

Non Asthmatic Eosinophilic Bronchitis

A third cough-predominant eosinophilic airway disorder was first described by Gibson et al. as oesinophilic bronchitis and is now called Non Asthmatic Eosinophilic Bronchitis (NAEB). These patients are:

- **Nonsmokers**
- **Eosinophilic airway inflammation**
- **Normal chest x-ray and spirometry**
- **No evidence of variable airway obstruction**

Gibson PG, Dolovich J, et.al. Chronic Cough: eosinophilic bronchitis with cough. *Lancet* 1989:1:1346-48

Chronic Cough-Asthma, Cough-variant asthma and NAEB

- **In adult non-smokers with chronic cough, multiple prospective studies have shown that asthma or cough-variant asthma are among the most common causes (24%-29%)**
- **In other studies of adults with chronic cough, NAEB was found to be the cause in 13% of the cases.**

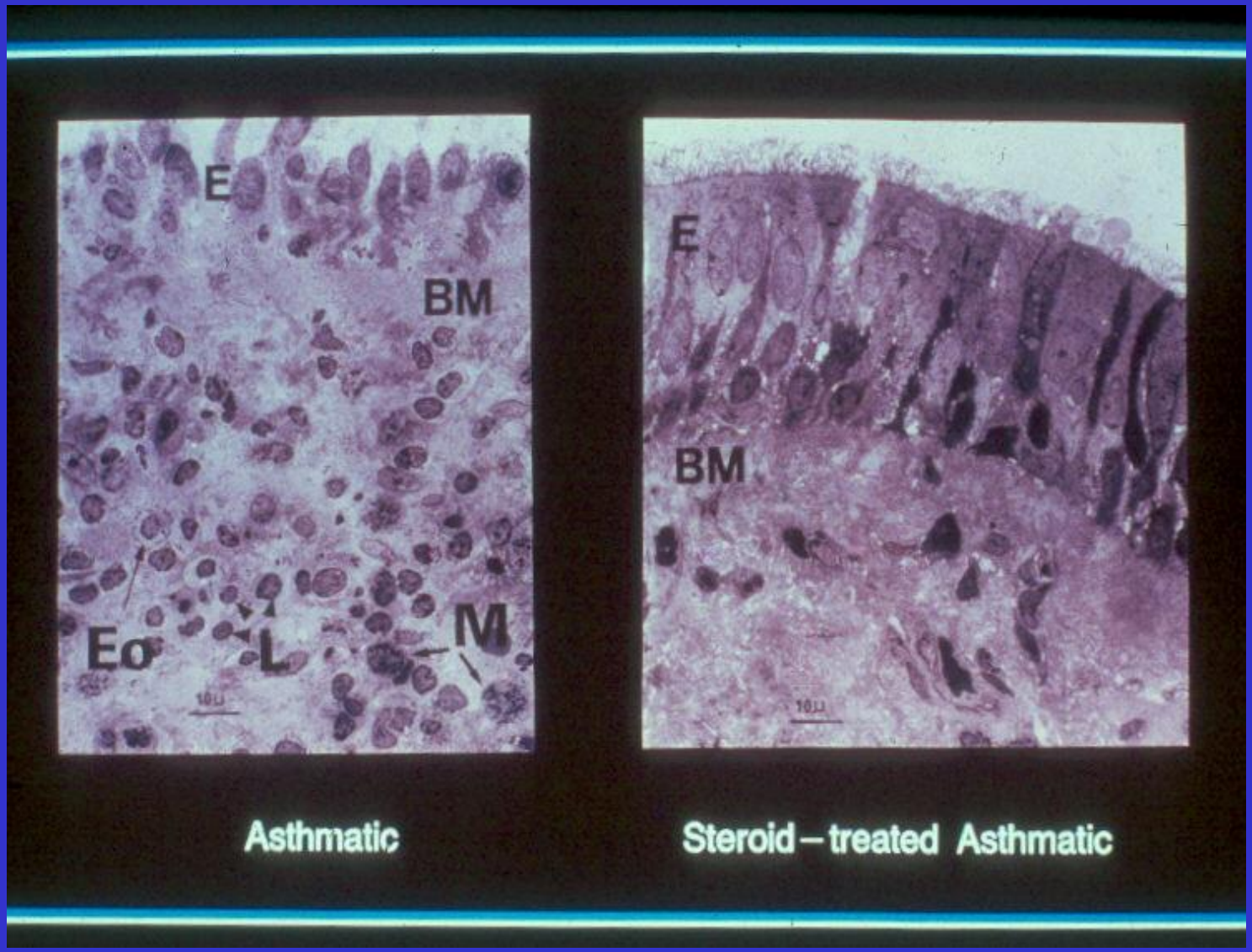
Irwin RS, Bauman MH, et al. Diagnosis and management of cough executive summary. ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:1S

Chronic Cough-Asthma, Cough-variant asthma and NAEB

- **Classical asthma, cough-variant asthma and NAEB respond to inhaled corticosteroids.**
- **A response with decrement or resolution of cough can take up to 6-8 weeks with appropriate therapy.**

Inhaled Corticosteroids

Inhaled corticosteroids are the most effective drug available for the treatment of asthma


E
BM
Eo
L
M
10μ
Asthmatic
E
BM
10μ
Steroid – treated Asthmatic

Gastroesophageal reflux

The third most common cause of chronic cough

Gastroesophageal reflux

GERD is the third most common cause of chronic cough

- **Symptoms of GERD include:**
  - **heartburn**
  - **sour taste**
  - **regurgitation**
  - **chronic cough**
- **Up to 75% of patients with GERD-induced cough do not have symptoms of heart burn or acid indigestion**

Gastroesophageal reflux

Management include:

1. **Lifestyle Modification:**

- **Elevate the head of the bed- about 5-6 inches**
- **Stop smoking**
- **Sit up for 3 hours after a meal**
- **Avoid acid drinks, especially at suppertime**
- **Avoid tight restriction around waist e.g. tight belt**
- **Avoid food that aggravate reflux: fatty foods, excess alcohol, chocolate.**

Gastroesophageal reflux

Management include:

2. Acid suppression:

- **Proton pump inhibitor e.g. omeprazole 40 mg daily in the mornings**

- **it may take up to eight weeks or more for cough to improve.**

Gastroesophageal reflux

Management include:

3. Prokinetic drugs:

- ***Metoclopramide-*** **to treat oesophageal dysmotility. - beneficial in nonacid reflux and may add to the effectiveness of PPI. Note extrapyramidal side effects (e,g, rigidity, bradykinesia, tremor and restleness.**
- ***Domperidone*** **- to increase gastric emptying in GERD.**
-

Post-infection cough-

following a URTI

Post-infection cough- *following a URTI*

- **Postviral cough** is a **common** cause of subacute and chronic cough.

- **The symptoms typically persists for approx. three weeks but may prolong for greater than eight weeks.**

Post-infection cough- *following a URTI*

- **Lack of effective treatment prompts emphiric use of several courses of antibiotics.**
- **Although 90% of post-infectious cough are viral approx. two thirds are treated with antibiotics.**
- **These patients improve dramatically with use of oral corticosteroids.**

Post-infection cough- *following a URTI*

- **Infection due to Bordetella pertussis (whooping cough) may be responsible for prolonged cough.**
- **The diagnosis of pertussis should be considered in patients with postinfectious cough with inspiratory whoop and/or post-tussive emesis.**
- **These patients are treated with macrolide antibiotics or *trimethoprim-sulfamethoxazole*, if a macrolide cannot be given.**
- **However, there is limited evidence for the efficacy of Rx if administered beyond the first two weeks of treatment.**

Obstructive Sleep Apnea

Obstructive Sleep Apnea

- **Recent studies in adults have demonstrated that chronic cough can be a sole manifestation of obstructive sleep apnea and can be effectively treated with continuous positive airway pressure (CPAP)**

- **On presentation of these patients with chronic cough, OSA was not suspected and could not be identified from the clinical characteristics of the cough**

ACE Inhibitors

Angiotensin converting enzyme inhibitors – ACE inhibitors

- **ACE-inhibitors induce cough accounts for up to 2% of chronic cough**
- **The effect may be mediated by increased availability of kinins.**
- **The cough usually begins within 1 to 2 weeks of stating the medication but can be delayed for as long as 6 months.**
- **The cough usually resolves after 1 to 4 weeks after stopping the medication but can take up to 3 months.**

Angiotensin converting enzyme inhibitors –ACE inhibitors

- Angiotensin 11 receptor antagonists has **not** been associated with cough
- Their mechanism of action does not affect kinin metabolism

Lung Cancer

Lung Cancer

Lung cancer is the most feared diagnosis of anyone presenting with chronic cough.

However, it occurs in < 2% of cases of chronic cough

Neoplasms originating in the large, central airways where cough receptors are common can present with cough.

Hyde L et al. Clinical manifestations of lung cancer. *Chest* 1974;**65**:299.

Lung Cancer

Lung cancer should be considered in any current or past smoker especially in those with:

- **A new cough or recent change in chronic "smoker's cough.**
- **A cough that persists for > 4 weeks following smoking cessation**
- **Hemoptysis that does not occur in the setting of a lung infection**

Hyde L et al. Clinical manifestations of lung cancer. *Chest* 1974;**65**:299.

Clinical Case

Presented at AAAI meeting in 2012

A 64 year old man presenting with a history of chronic cough for 10 weeks. The cough was present day and night, with little mucus production and some associated feeling of shortness of breath and choking sensation especially at night. Additional complaints included postnasal drip, runny nose, sensation of mucus in the throat wheezing and snoring.

Clinical Case
Presented at AAAI meeting in 2012

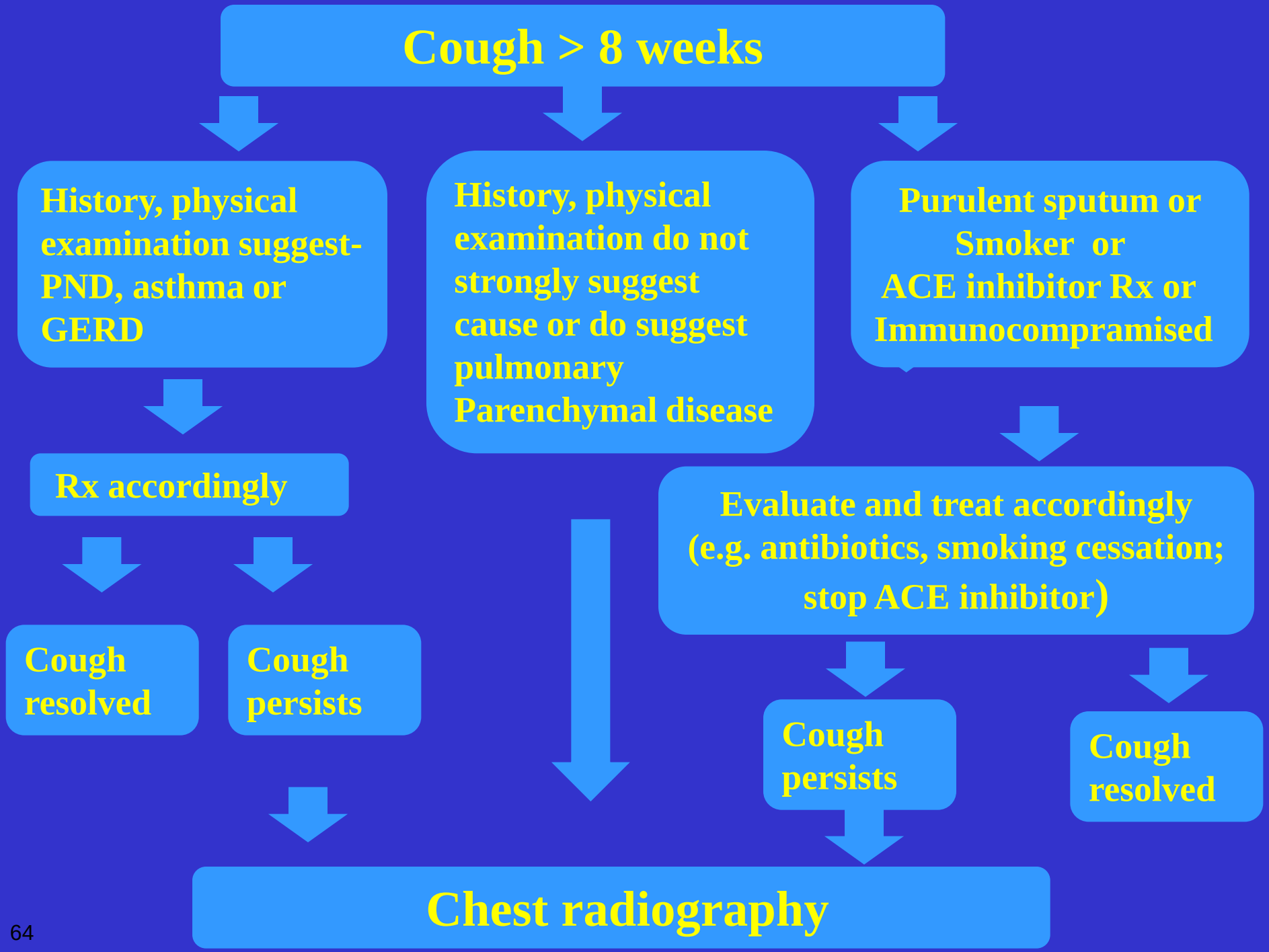
There was no history of smoking and he is not on any chronic medication.

Physical examination was unremarkable, with stable vital signs, including heart rate at 80 beats/min (regular) and blood pressure of 128/78. Height was 68.5 inches and weight 178 lbs.

Q: What investigations would you do and how would you manage patient.

Cough > 8 weeks

History
and
physical examination

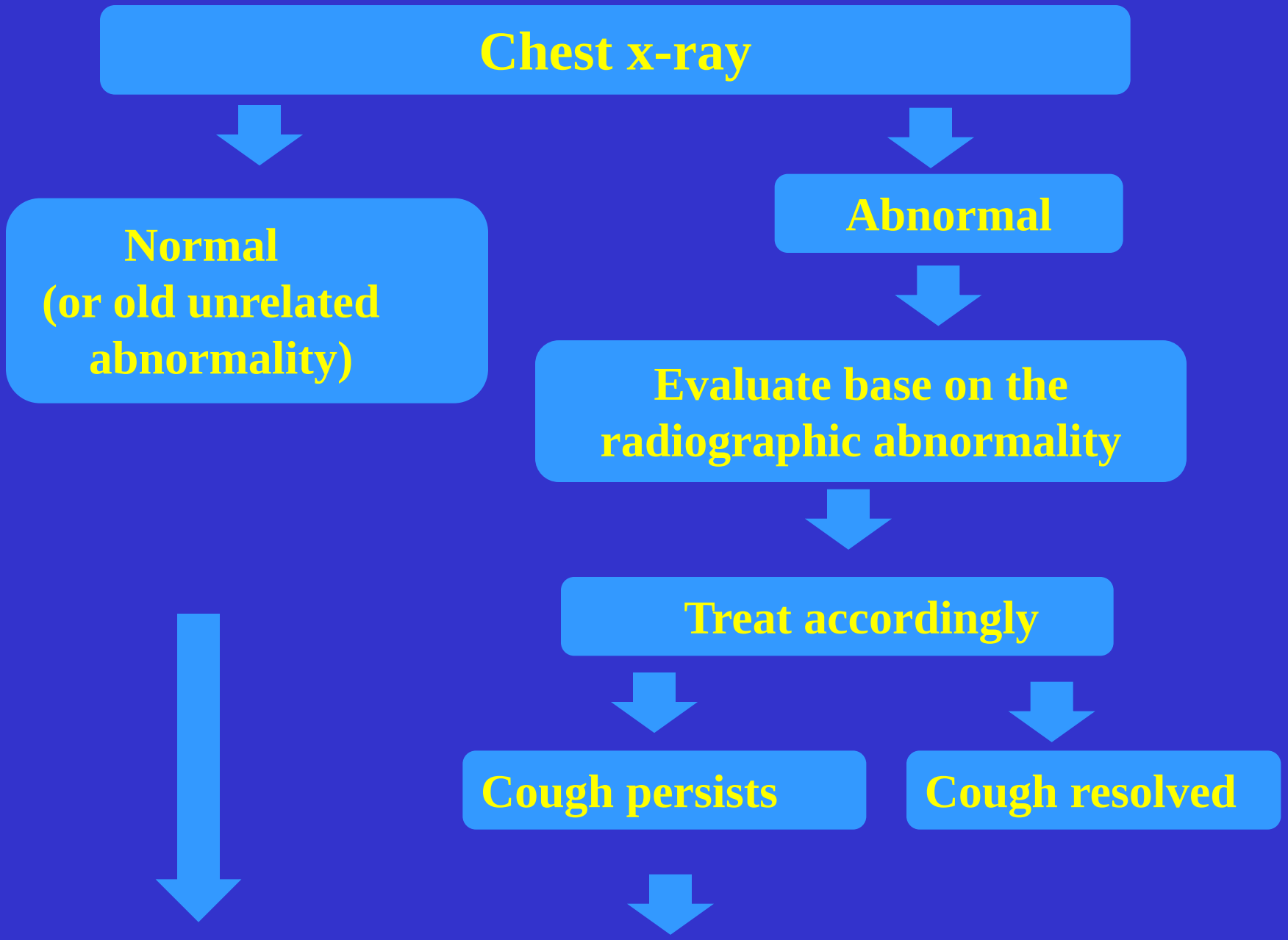

Cough > 8 weeks
History, physical examination suggest- PND, asthma or GERD
History, physical examination do not strongly suggest cause or do suggest pulmonary Parenchymal disease
Purulent sputum or Smoker or ACE inhibitor Rx or Immunocompramised
Rx accordingly
Evaluate and treat accordingly (e.g. antibiotics, smoking cessation; stop ACE inhibitor)
Cough resolved
Cough persists
Cough persists
Cough resolved
Chest radiography

Clinical Case
Presented at AAAI meeting in 2012

The patient was treated with:

- **Antibiotics**
- **Antihistamines**
- **Nasal steroid spray**
- **Oral steroids**
- **Proton pump inhibitors**

Treated with the above medications by four doctors over a period of six weeks with no improvement in the cough.


Chest x-ray
Normal
(or old unrelated
abnormality)
Abnormal
Evaluate base on the
radiographic abnormality
Treat accordingly
Cough persists
Cough resolved

Sequentially treat (or evaluate) for the most common causes of cough

1. UACS (allergy skin testing, sinus CT) 2. Asthma (PFTs) 3. GERD (oesophageal pH monitoring.) 4. Non-asthmatic eosinophilic bronchitis.

Treat accordingly

Cough persists

Cough resolved

Clinical Case
Presented at AAAI meeting in 2012

Chest x-ray, CT scans of the sinuses, computed tomographic scans of the sinuses and high-resolution computed tomographic scans of the chest were all normal.

Spirometry was performed: Forced vital capacity was 4.52 L (106% of predicted value). FEV1 was 3.45L (100% of predicted value). The FEV1/Forced vital capacity ratio was 76%. Forced expiratory flow at 25% to 75% of forced vital capacity was 2.24L/s (79% of predicted value.

Clinical Case
Presented at AAAI meeting in 2012

The patient underwent a metacholine inhalation challenge. The FEV1 was reduced by 9% at the highest concentration (25mg/ml).

Evaluate for less common conditions (e.g. sputum tests, HRCT scan, oeosphageal pH probe monitoring, oesophagoscopy, flexible bronchoscopy, cardiac studies)

Treat accordingly

Cough persists

Cough resolved

Always consider adequacy of treatment regimes before considering cough to be psychogenic

Clinical Case
Presented at AAAI meeting in 2012

Because the patient's symptoms did not improve with common therapeutic trials for common disorders causing chronic cough, history and review of the systems were revisited. On specific questioning, the patient noted that he has had snoring and restless sleep for many years. The patient's spouse reported that snoring was minimal and no apnea was observed.

Clinical Case
Presented at AAAI meeting in 2012

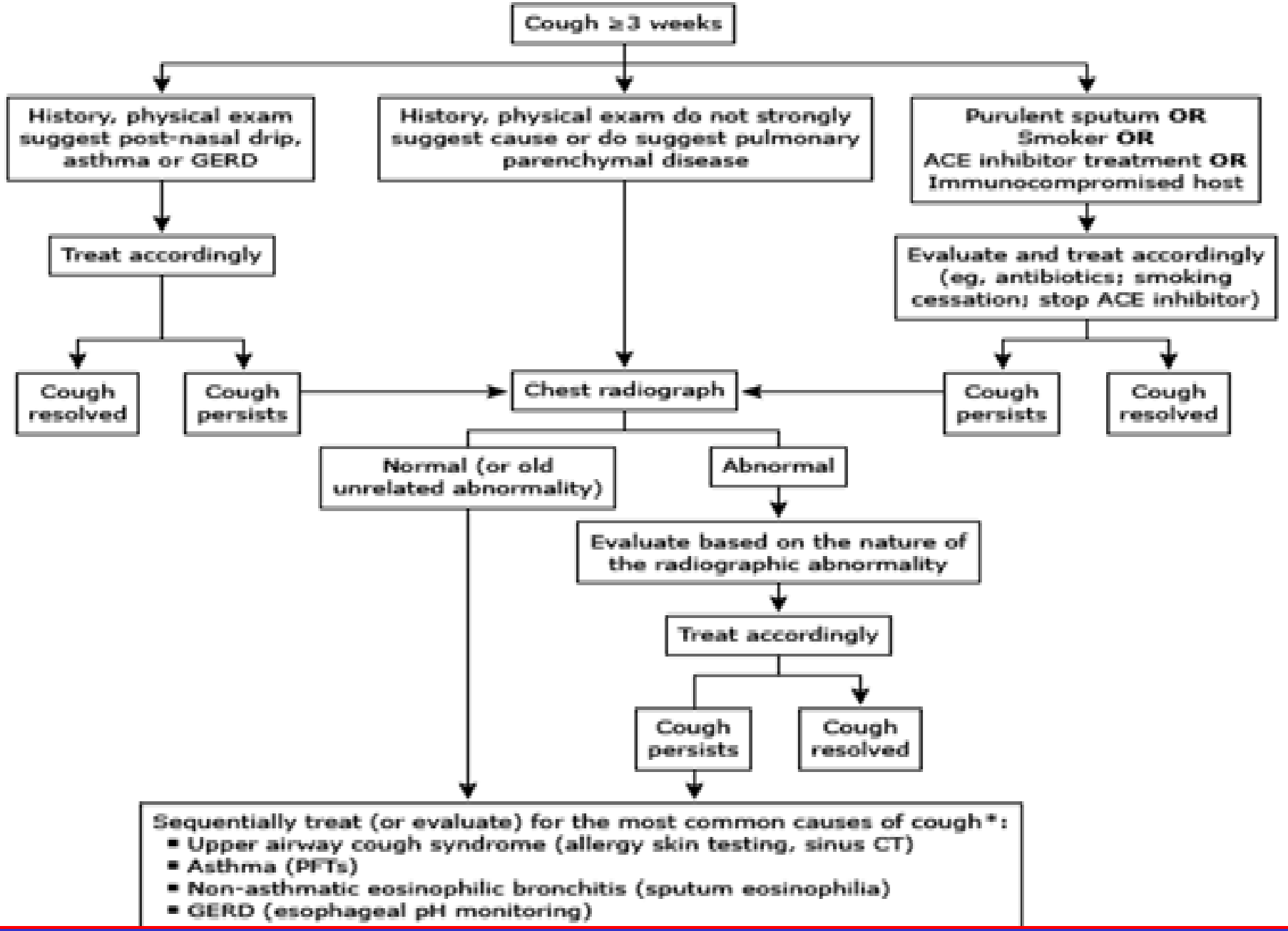
However, friends of the patient claimed that the patient sounded like "race tractor trailer" while asleep. The patient also noted daytime lethargy . The led to the consideration of obstructive sleep apnea (OSA) and he underwent a sleep study.

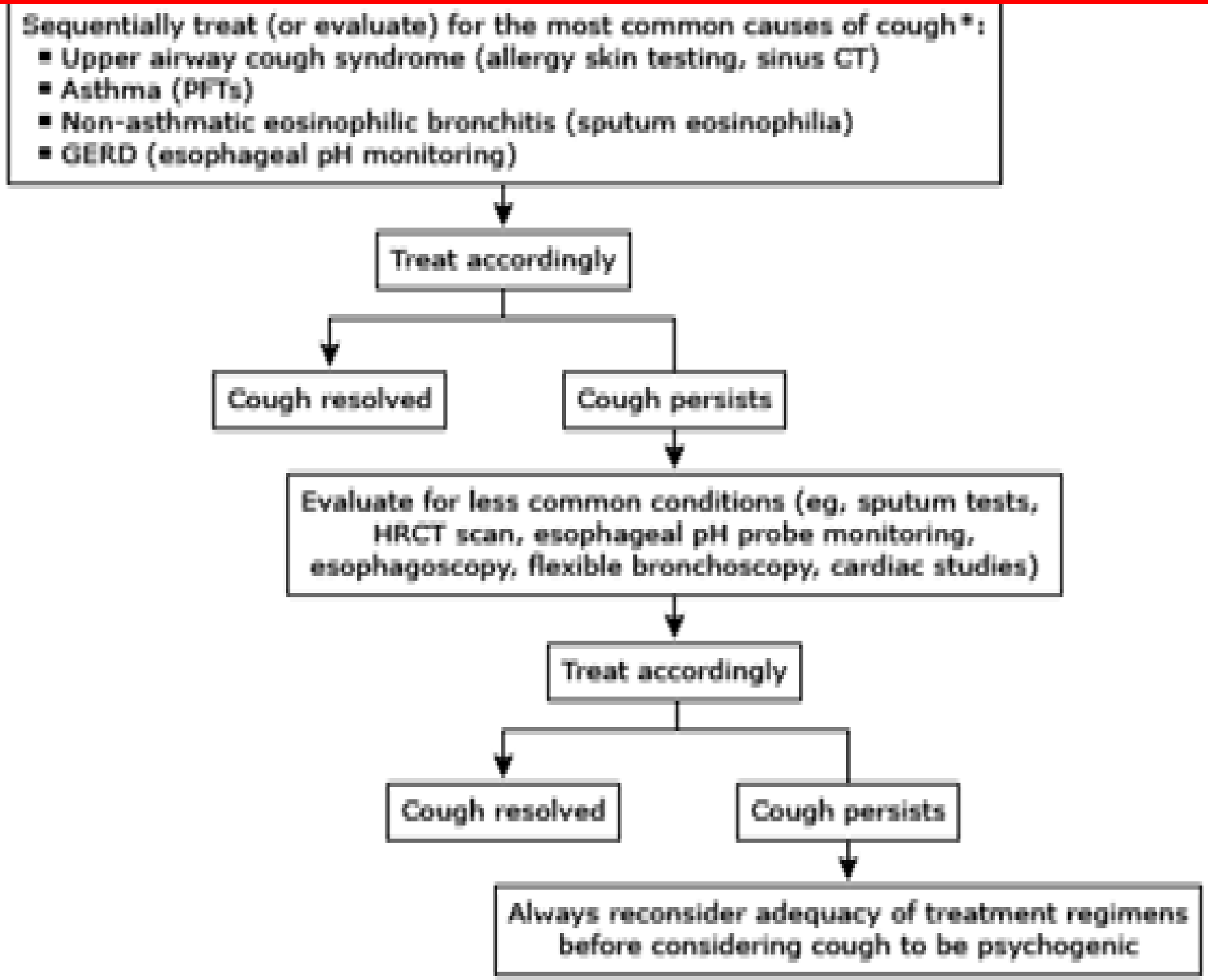
The study results were consistent with severe OSA syndrome and the patient was started on a trial of nasal CPAP at 12 mm of water pressure.

Clinical Case
Presented at AAAI meeting in 2012

The patient returned in 4 weeks, noting that when the nasal CPAP was used consistently, the cough resolved completely

Evaluation of subacute or chronic cough in adults




Sequentially treat (or evaluate) for the most common causes of cough*:
Upper airway cough syndrome (allergy skin testing, sinus CT)
Asthma (PFTs)
Non-asthmatic eosinophilic bronchitis (sputum eosinophilia)
GERD (esophageal pH monitoring)
Treat accordingly
Cough resolved
Cough persists
Evaluate for less common conditions (eg, sputum tests, HRCT scan, esophageal pH probe monitoring, esophagoscopy, flexible bronchoscopy, cardiac studies)
Treat accordingly
Cough resolved
Cough persists
Always reconsider adequacy of treatment regimens before considering cough to be psychogenic

Idiopathic or Refractory cough

Chronic Cough- Idiopathic or Refractory

- Although many investigators have used the paradigm with high success rate, there are a significant number who have **not**.
- Success rates as low as **58%** have been reported and the reasons for this is unclear.
- Some patients with chronic cough **do not respond** to therapy despite extensive evaluation.

Idiopathic or Refractory Cough

- **This has led to the suggestion that a new approach to chronic cough is necessary.**

The term“ Idiopathic” or “Refractory” cough has been suggested for these cases.

3. Haque RA, Barnes PJ, et al. Chronic idiopathic cough: a distinct clinical entity? *Chest* 2005;**127:**1710-1713.

Chronic Cough

Recently, a unifying hypothesis has been proposed- that chronic cough arises from a hypersensitivity of airway sensory nerve.

" Hypersensitivity cough syndrome"

Scientific Committee of ERS- task force to examine attitude and evidence behind our understanding of the aetiology and treatment of chronic cough

1. Morice AH, et.al. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. Eur Respir J 2014;**44**:1132-1148.

Cough hypersensitivity syndrome

- **Most patients with unexplained chronic cough have an abnormally sensitive cough reflex**
- **The sensitivity of the cough reflex can be assessed by the measuring the response to a variety of airway irritants e.g. capsaicin, citric acid.**

Birring SS. Controversies in the Evaluation and Management of Chronic cough. *Am J Respir Crit Care Med;* 2011:**183**:708-15.

Cough hypersensitivity syndrome

- **It has been hypothesised that chronic idiopathic cough may belong to a specific phenotype and share a common pathological mechanism- hypersensitivity of the cough reflex.**

Cough hypersensitivity syndrome

- As hypersensitivity is not restricted to idiopathic cough it has been proposed that chronic cough is the result of an interaction between intrinsic cough reflex abnormalities (i.e. hypersensitivity) and aggravating factor such as ACE-inhibitors, GERD, upper airway disorders, oesinophilic airway disease, cigarette smoke/COPD

Cough hypersensitivity syndrome

- **The term "Cough hypersensitivity syndrome" was coined to name the clinical entity characterised by enhanced cough reflex, comprising several phenotypes depending on which aggravating factor is involved.**

Birring SS. Controversies in the Evaluation and Management of Chronic cough. *Am J Respir Crit Care Med;* 2011:**183**:708-15.

Thank you for you attention