Husten: häufige (COPD) bis seltene (IPF) Differentialdiagnose

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Pathophysiology of cough.

Triggers:
- Smoke
- Perfumes/scents
- Throat irritation/tickle
- Noxious fumes
- Speech
- Exercise
- Cold/dry air
- Eating
- Humidity

Pharynx/larynx

Trachea

Parenchyma

Cough receptors

Cortical input

Cortical centre

Airway nerves

TRPV1: transient receptor potential vanilloid 1;
TRPA1: transient receptor potential ankyrin 1;
RAR: rapidly adapting receptor;
SAR: slowly adapting receptor
Possible peripheral cough response pathway

**A,** hyperstimulation: productive cough, endobronchial foreign body; increased response (cough reflex hypersensitivity): atopic cough, GERD, ACE-I-induced cough;

**B,** kypersimulation: bronchial asthma; increased response: cough variant asthma.

Because a carefully taken history with detailed questioning of the character, timing, and complications of chronic cough in adults had not been shown to be useful in diagnosing the cause of the cough


The world’s first cough guideline developed by the first American College of Chest Physicians (CHEST) Expert Cough Panel suggested in 1998 that cough be classified according to its duration

Although all coughs are **acute at the outset**, the panel believed that it was the **duration of the cough at the time of patient presentation** to health-care providers that helped narrow the list of possible diagnoses in adults.

The **first expert cough panel** classified cough duration into

- **Acute** (ie, lasting < 3 weeks) and
- **Chronic** (ie, lasting 3-8 weeks) categories
The **second ACCP Expert Cough Panel** suggested in **2006** that cough continue to be classified according to its duration but that there **should be three not two categories**

the second ACCP Expert Cough Panel suggested in 2006 that cough continue to be classified according to its duration but that there should be three not two categories.


Based on literature that had accumulated between 1998 and 2006, the panel believed that cough should be reclassified into

**Acute** (< 3 weeks),

**Subacute** (3-8 weeks), and

**Chronic** (> 8 weeks) categories

and suggested management algorithms for these categories that suggested the likeliest and most common diagnostic possibilities in each category.

For adult patients seeking medical care complaining of cough, we suggest that estimating the duration of cough is the first step in narrowing the list of potential diagnoses.

For adult patients around the globe complaining of cough, we suggest that the cough be managed using evidence-based guidelines that are based upon duration of cough.
The Causes Of Acute Cough: A Single-Center Study In Japan

374 patients (195 females, mean age 60.3 years) who visited the clinic complaining of cough

129 patients (35%): 63 females, mean age 61.5 years: suffered from acute cough

All acute cases were stratified into two groups based on the presence (n=43) or absence (n=86) of abnormal findings on the chest X-ray
The main causes of acute cough with abnormal findings were

Pneumonia (46.5%),
Interstitial pneumonia (18.6%)
Lung cancer (16.3%)
The main causes of acute cough without abnormal findings were:

- **Respiratory tract infection** (39.5%),
- **Post infectious cough** (18.6%) and
- **Bronchial asthma** (17.4%).

Acute cough was the primary complaint in **29.5%** and **19.6%** of all patients diagnosed with **bronchial asthma** and **cough variant asthma**, respectively.
The Causes Of Acute Cough: A Single-Center Study In Japan


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abnormal findings on the chest X-ray

Non-infectious diseases including asthma as well as infectious diseases could be the causes in acute cough without abnormal findings on the chest X-ray
One hundred coughs Family practice case series.
Worrall GJ. Can Fam Physician 2008;54:236-7.e1-3

To record the presentation, diagnosis, management, and outcome of acute coughs presenting in family practice.
A case series of consecutive patients with **acute cough as their main symptom**

**One hundred** consecutive patients with cough, ages 1 to 90
One hundred coughs Family practice case series.
Worrall GJ. Can Fam Physician 2008;54:236-7.e1-3

73 patients had viral respiratory tract infections; 15 had asthma; 6 had influenza; 4 had pneumonia; 2 had croup

81 patients needed no prescription medication; 13 were prescribed steroids or bronchodilators for asthma 6 were prescribed antibiotics
No prescriptions for cough suppressants or decongestants were written
One hundred coughs Family practice case series.
Worrall GJ. Can Fam Physician 2008;54:236-7.e1-3

To record the presentation, diagnosis, management, and outcome of acute coughs presenting in family practice.
A case series of consecutive patients with acute cough as their main symptom

One hundred consecutive patients with cough, ages 1 to 90. MAIN

CONCLUSION

Most patients with cough require reassurance rather than medications, as their cough is selflimiting.

Of the minority that requires medication, twice as many will benefit from adjustment of asthma medication as from antibiotics
Representative Punum ladders to assess (A) cough severity or (B) overall quality of life

Please check the rung on the ladder that best describes the severity of your cough taking timing, intensity, distress, and quality into account over the past week.

A

WORST POSSIBLE COUGH

VERY SEVERE COUGH

SEVERE COUGH

MODERATE COUGH

MILD COUGH

NO COUGH

B

WORST POSSIBLE PROBLEM

VERY SEVERE PROBLEM

SEVERE PROBLEM

MODERATE PROBLEM

MILD PROBLEM

NO PROBLEM
PE = pulmonary embolism; UACS = upper airway cough syndrome
LRTI = lower respiratory tract infection
URI = upper respiratory tract infection
Chronic cough is defined as a cough lasting more than 8 weeks (aged ≥ 15 years old) more than 4 weeks in children (aged < 15 years old).

It is a frequent cause of medical consultation and is associated with a large number of pulmonary and extrapulmonary disorders.

**Prevalence:** between 11 and 13% of the population

9.6% in a recent meta-analysis of 90 studies:
In this study, the prevalence of chronic cough was higher in Oceania (18.1%) America (11%) Europe (12.7%) Asia (4.4%) / Africa (2.3%)

Although **chronic cough in adults** can be caused by many etiologies, **four conditions account for most cases:**

- **Upper airway cough syndrome secondary to rhinosinus diseases**
- **Gastroesophageal reflux disease / Laryngopharyngeal reflux disease**
- **Asthma**
- **Nonasthmatic eosinophilic bronchitis**

*Chronic Cough: Evaluation and Management*  

Non-asthmatic eosinophilic bronchitis (NAEB) represents 10%–30% of chronic cough cases, is an important cause of chronic cough.

NAEB shares similar eosinophilic inflammation of airway (≥3% in induced sputum) and response to corticosteroids with asthma. However, in contrast to asthma, NAEB subjects have no airflow obstruction and airway hyperresponsiveness.

On the prognosis of NAEB, long term follow-up study suggested that **NAEB should be a distinct entity** rather than an early stage of asthma or COPD

There is no study on dose and duration of treatment

The **relapse rate is high after treatment**
Assessing sputum eosinophils after treatment is useful to identify those at risk of relapse.

**Treatment**

Low / medium doses of inhaled corticosteroid (ICS) for 4–8 weeks are usually efficient but long-term treatment can be necessary.

In patients with severe cough or refractory to ICS, oral prednisolone (10–30 mg/d) for 3–5 days might be proposed.

Up to 60% recurrence has been described after treatment cessation, and associated with sputum eosinophilia.
These patients are considered to have a specific asthma phenotype: **cough variant asthma**

Cough variant asthma (CVA)

**Cough alone** may sometimes be the **sole presenting symptom** of asthma

Patients experience cough **without wheeze or shortness of breath** and **with normal baseline pulmonary function test results**

These patients do, however, **demonstrate bronchial hyperreactivity** +

They also **respond** to specific traditional asthma therapy
Cough variant asthma (CVA)

In prospective studies of patients with chronic cough, an average of 25% have CVA.

 Patients have

- chronic cough:
  - diurnal variation of symptoms
  - recurrent episodes of symptoms
- normal baseline pulmonary function tests,
- positive bronchial inhalation challenge results [Metacholin Test]
- response to specific asthma therapy [response to inhalation of short acting β₂ agonist]
Cough variant asthma (CVA)

CVA was associated with high FeNO levels as well, and high FeNO levels were specific to CVA.

However, these useful characteristics were not significant in the patients who had been prescribed ICS before visiting our hospital.

Medical examination (SABA) and determination of FeNO levels are useful for the differential diagnosis of prolonged/chronic cough, before treatment with ICS.

Cough variant asthma (CVA)

**Treatment**

All therapies for typical bronchial asthma have been successful in controlling cough in patients with CVA.

The overall prognosis of CVA is excellent, with most patients requiring chronic inhaled corticosteroid therapy.
### Differential Diagnosis Between Various Diseases With Eosinophilic Inflammation of the Airways Associated With Chronic Cough

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Eosinophilic Bronchitis</th>
<th>Eosinophilic Asthma</th>
<th>Cough Equivalent Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Cough</td>
<td>Dyspnea, cough &amp; wheezing</td>
<td>Cough</td>
</tr>
<tr>
<td>Atopy</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bronchial hyperreactivity</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FEM viability</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Eosinophils in sputum</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Response to bronchodilators</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>Yes</td>
<td>Yes (if eosinophils in sputum)</td>
<td>Yes (if eosinophils in sputum)</td>
</tr>
</tbody>
</table>

Smoking is obviously a risk factor for chronic cough. A recent large study performed on 14,669 subjects in Copenhagen found a prevalence of chronic cough of

3% in never smokers,
4% in former smokers
8% in current smokers

The main risk factors of chronic cough could differ depending on smoking status, including

i) female sex, asthma and GORD in never smokers;
ii) obesity, asthma and GORD in ex-smokers
iii) airflow limitation in current smokers.

A smoking history 20 pack-years or a modification of the cough in a smoker 45 years old should lead to further investigation.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and Dietary Measures</td>
<td><strong>Strong Recommendation</strong></td>
<td>Low Quality of Evidence</td>
</tr>
<tr>
<td>H2 antagonists</td>
<td><strong>Strong recommendation</strong></td>
<td>Low quality of evidence</td>
</tr>
<tr>
<td>PPIs</td>
<td><strong>Strong recommendation</strong></td>
<td>Moderate quality of evidence</td>
</tr>
<tr>
<td>Prokinetics</td>
<td><strong>Weak recommendation</strong></td>
<td>Very low quality of evidence</td>
</tr>
<tr>
<td>Antireflux surgery</td>
<td><strong>Weak recommendation</strong></td>
<td>Low quality of evidence</td>
</tr>
<tr>
<td>Disease</td>
<td>Symptoms and Parameters</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Asthma</td>
<td>Wheezing</td>
<td>94</td>
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<tr>
<td></td>
<td>Dyspnea</td>
<td>82</td>
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<tr>
<td></td>
<td>Airway obstruction</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Bronchial reversibility</td>
<td>11</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Acid taste in the mouth</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Retrosternal pyrosis</td>
<td>72</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Post-nasal drip</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Clearing of the throat</td>
<td>100</td>
</tr>
</tbody>
</table>
# Causes of chronic cough and warning symptoms.

### Causes of chronic cough

- Acute tracheobronchial infections including pertussis
- Chronic infections: bronchiectasis, tuberculosis, cystic fibrosis
- Airway problems: chronic bronchitis, osteoplastic tracheopathy, asthma, post-nasal drip
- Pulmonary parenchymal diseases: diffuse interstitial fibrosis, emphysema, sarcoidosis
- Tumors: lung cancer, bronchioloalveolar carcinoma, benign airway tumors, mediastinal tumors
- Foreign bodies in the airways
- Irritation of external auditory meatus
- Cardiovascular diseases: left ventricular dysfunction, pulmonary infarction, aortic aneurysm
- Other diseases: gastroesophageal reflux or bronchoesophageal reflux, Zenker's diverticulum, achalasia, recurrent aspiration, endobronchial sutures
- Drugs: angiotensin-converting enzyme inhibitors, covertine

### Warning symptoms

Hemoptysis, snoring, significant production of sputum, systemic symptoms, gastroesophageal reflux complicated with weight loss, anemia, hematemesis, dysphagia, or no response to specific treatment, choking or vomiting, recurrent pneumonia, or abnormal chest X-ray
GERD = gastroesophageal reflux disease
AECB = acute exacerbation of chronic bronchitis;
NAEB = nonasthmatic eosinophilic bronchitis
URI = upper respiratory tract infection pulmonary embolism;
UACS = upper airway cough syndrome; URI = upper respiratory tract infection
LRTI = lower respiratory tract infection

**Red Flags**
- Hemoptysis
- Smoker > 45 years of age with a new cough, change in cough, or coexisting voice disturbance
- Adults aged 55-60 years who have a 30 pack-year smoking history and currently smoke or who have quit within the past 15 years
- Prominent dyspnea, especially at rest or at night
- Hoarseness
- Systemic symptoms
  - Fever
  - Weight loss
  - Peripheral Edema with weight gain
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- History Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough
ACEI = angiotensin-converting enzyme inhibitor;
A/D = antihistamine/decongestant;
BD = bronchodilator;
HRCT = high-resolution CT;
ICS = inhaled corticosteroid;
LTRA = leukotriene antagonist;
PPI = proton pump inhibitor.
Overview of clinical approaches for the treatment of chronic cough in Korean patients

ACEi: angiotensin converting enzyme inhibitors
GERD, gastroesophageal reflux disease
Chronic cough in children

Non-specific chronic cough
- Empirical treatment
  - ICS*
  - HIRA*
- Diagnostic tests to predict steroid-responsive cough
  - FeNO*
  - Bronchial challenge test

Chronic wet cough
- Empirical antibiotics* based on local sensitivity pattern

Other specific cough is suggested
- Specific diagnostic test
- Specific treatment

Primary/secondary care
Secondary/tertiary care

Referral to specialist center if cough persists

Consider further remaining possibilities for cough
- Diagnostic tests
- Therapeutic trials
Algorithm for the management of refractory chronic cough

Hypersensitive cough reflex

- Reversible chronic cough
  1. Rhinosinusitis
  2. Laryngeal neuropathy or CV dysfunction.
  3. GER/laryngopharyngeal reflux
  4. Central hypersensitivity
  5. Psychogenic

- Persistent or refractory chronic cough
  1. Antihistamines. Nasal corticosteroids
  2. Speech pathology. Neuromodulators
  3. Strict anti-GER measures. Alginate, high-dose PPIs, prokinetics, fundoplication?
  4. Neuromodulators
  5. Psychiatric evaluation
Effect of ion channels in cough in airway disease

AIRWAY DISEASE

COPD  ASTHMA  IPF  IDIOPATHIC CHRONIC COUGH

ATP  PROTEASES  PGE₂  OXIDATIVE STRESS

P2X3  TRPV4  TRPV1  TRPA1

Ca²⁺  Ca²⁺  Ca²⁺  Ca²⁺

Sensory nerve depolarisation → Action potential formation → REFLEXES

Bonvini SJ, Belvisi MG. Pulm Pharmacol Ther 2017 Dec;47:21-28
Vielen Dank Für Ihre Aufmerksamkeit
Eine gute Rede ist eine Ansprache, die das Thema erschöpft, aber keineswegs die Zuhörer

Winston Churchill
There are three phases of cough:

- An **inhalation phase** which generates enough volume for an effective cough,

- A **compression phase** with pressure against a closed larynx by the contraction of chest wall, diaphragm and abdominal muscles

- An **expiratory phase** when the glottis opens resulting in high air flow
Approach for non-specific chronic cough in Korean adults (age ≥ 15 years)

ICS: inhaled corticosteroid
PPI: proton-pump inhibitor

H1RA: histamine-1 receptor antagonist
Algorithm for the management of chronic cough in primary care

Chronic cough. Primary care management

Investigate and treat
A cause for cough is suggested
History, physical examination and chest X-ray
ACE enzyme
Discontinue

Inadequate response to optimal treatment

Upper airway cough syndrome (UACS)
Empirical treatment

Asthma
Ideally evaluate (spirometry, bronchodilator reversibility, bronchial challenge test or empirical treatment)

Non-asthmatic eosinophilic bronchitis
Evaluate eosinophils in sputum and/or FeNO, empirical treatment

Treatment for gastroesophageal reflux
Empirical treatment

No response (1 month)
Two possible access pathways of stimuli of chronic cough

1. Intrinsic abnormality of cough reflex/irreversible
   +
   GER
   Laryngeal neuropathy (Unknown)

2. Intrinsic abnormality of cough reflex/reversible
   +
   EAO/ACEI Infections
   Smoking

Chronic cough

Legend
GER: Gastroesophageal reflex
EAO: Eosinophilic airway inflammation
ACEI: Angiotensin-converting enzyme inhibitor

Adapted from Reference 2
Interactions among peripheral stimuli of cough reflex

Legend
LRT: lower respiratory tract
URT: upper respiratory tract
BER: bronchoesophageal reflux
LER: laryngoesophageal reflux
LPR: laryngopharyngeal reflux
Practical management of patients with chronic cough

Chronic cough > 2 months
Non-smoker

Clinical evaluation
Chest X-ray/Spirometry with BD test

Hypersensitive cough reflex

Reversible chronic cough

Cause
- ACE-1 inhibitors
- Post-infection
- Cough responding to steroids (Asthma/eosinophilic bronchitis)
- Non-eosinophilic bronchitis: macrolides?

Irreversible chronic cough

Sequential, combined therapy: asthma, rhinitis, GER

No response
Interactions between idiopathic pulmonary fibrosis (IPF), gastro-oesophageal reflux disease (GORD), obstructive sleep apnoea (OSA) and cough.

1: traction leading to a weaker lower oesophageal sphincter tonus;
2: microaspiration inducing epithelial damage
Management of chronic cough in specialized units

Chronic cough. Specialized Medical Management

Consider the following

Any investigation pending?
- Yes
- No

Were empirical therapies effective?
- Yes
- No

Request studies
- Fiberoptic bronchoscopy/laryngoscopy
- Computed tomography of chest and facial sinuses
- pH-metry/impedance

Cough resolved?
- Yes
- No

Patient adherence
- No
- Yes

Manage non-adherence

Diagnosis of refractory neutrophilic asthma

Consider the following

Speech pathology intervention
- Psychoeducational aspects
- Behavioral therapy

Empirical low-dose narcotics or gabapentin or similar