Approach to a patient with cough: linking evidence with practice

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It’s just a cough…who cares?

- Cough is a very common symptom for which patients seek ambulatory care.
- Cough results in more than 30 million office visits per year.
- Americans spend more than $1 billion annually on medications for cough.

National ambulatory medical survey
Why are is an otolaryngologist talking about cough?

Cough is a multidisciplinary symptom and requires collaboration of:

- Allergy
- Otolaryngology
- Pulmonology
- Gastroenterology
- Speech therapy and behavioral counseling
- Psychiatrist
Why do we cough?

- Cough is an important defense mechanism of the body that serves to clear the airway of excessive secretions and foreign matter.
- It can be activated by:
  1. Mechanical stimuli: foreign body, dust, talking
  2. Chemical stimuli: smoke, perfumes
  3. Thermal stimuli: cold air, hot air, cold water ingestion
Why do people seek treatment for cough?

- Nuisance that affects quality of life
- Subjective perceptions of exhaustion and self-consciousness
- Symptoms of insomnia
- Hoarseness
- Musculoskeletal pain, rib fractures, sweating
- Urinary incontinence
- Pneumothorax, pneumomediastinum, subcutaneous emphysema
What’s the success rate?

• Cause of cough can be determined in 88 to 100% of cases

• Success rates with specific therapies range from 84 to 98%

Chest 1998;114(2):133s-181s
Thorax 1998;53:738-743
Classification based on duration of cough

Proposals:

• **Acute** cough lasting < 3 weeks (peds <2)
• **Sub-acute** cough lasting 3-8 weeks (peds 2-4)
• **Chronic** cough lasting > 8 weeks (peds >4)

*Chest 1998;114(2):133s-181s*
Causes of acute cough

- Common cold
- Acute bronchitis
- Allergic rhinitis
- Acute bacterial sinusitis
- COPD exacerbation
- Pertussis in some communities

*NEJM 2000;343(23):1715-1721*
*JAMA 2003;289(20):2701-2707*
Pertussis

When to suspect & whom to treat?

- Suspect and treat if a clear cut history of exposure
- Suspect and treat if cough and vomiting (?)
- Erythromycin is the drug of choice; however, unless administered early, it does not alter the course of the disease
- Bactrim, Zithromax

*NEJM* 2000;343(23):1715-1721
*JAMA* 1995;273:1044-1046
Common cold-induced cough

Which of the following is effective?

(A) Dextromethorphan
(B) Pseudoephedrine
(C) Ipratropium nasal spray (0.06%)
(D) Claritin, Allegra, Zyrtec, Clarinex
(E) Intranasal or systemic steroids
(F) Zinc lozenges

*NEJM 2000;343(23):1715-1721*
Causes of sub-acute cough

Sub-acute cough: 3-8 weeks duration
- Post-infectious
- Pertussis
- Sub-acute bacterial sinusitis
- Asthma
- Allergic rhinitis

*NEJM 2000;343(23):1715-1721*
Post-infectious Cough

• This is not asthma
• Cough after a respiratory tract infection with a normal CXR
• Usually resolves in 3-4 weeks
• Diagnosis is clinical, and one of exclusion
• Treatment: steroids, either inhaled or oral, ipratropium inhaler

NEJM 2000;343(23):1715-1721
Chronic Cough

- Specific causes
- Diagnosis and Treatment
- “Zebras”
Why do patients seek care for chronic cough

<table>
<thead>
<tr>
<th>REASON</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needs reassurance nothing serious</td>
<td>77</td>
</tr>
<tr>
<td>Concerned something is wrong</td>
<td>72</td>
</tr>
<tr>
<td>Frequent retching</td>
<td>56</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>54</td>
</tr>
<tr>
<td>Others think something is wrong</td>
<td>53</td>
</tr>
<tr>
<td>Difficulty speaking on phone, singing in church</td>
<td>39</td>
</tr>
</tbody>
</table>
Causes of chronic cough

• ACE-inhibitor induced cough
• Upper Airway Cough Syndrome (formerly called Postnasal Drip Syndrome)
  (1) Allergic rhinitis
  (2) Nonallergic rhinitis
  (3) Chronic bacterial sinusitis
• Asthma
• Eosinophilic bronchitis
• Chronic bronchitis
• GERD/LPR
• “Neurogenic” cough
• “Zebras”

Chest 1999;116(2):279-84
History

• Triggers: Talking, laughter, walking, running, strong smells, perfumes
• Timing: Daytime vs. nighttime
• Relationship with meals
• Preceding Events:
• Viral URI, Recent Immigration from a developing country, foreign travel
• Review of systems is very important
Physical Examination

- Thick, yellow postnasal drip visible in oropharynx: think chronic sinusitis
- Look into ears to rule out wax impaction and other causes such as a foreign body (Arnold’s Nerve)
- Look at nails for clubbing (CF, COPD, etc.)
- Check for thyroid masses
- Look for signs of atopy
What are the most common diagnoses?

The following account for >90% of causes in a non-smoker who is not taking an ACE-inhibitor

• Upper Airway Cough Syndrome
• Asthma
• Reflux Disease
• Non-asthmatic Eosinophilic Bronchitis/NAEB (? Uncommon in the US)

Ayik SO. Respir Med 2003;97:695-701
Causes of cough:
single or multiple?

- Multiple causes were found in more than 60% when a large number of diagnostic tests are performed (US experience)
The “Silent” Syndromes

• Silent Postnasal Drip (Upper Airway Cough) syndrome (20%)
• Cough-variant Asthma (25-57%)
• Silent Reflux (50-75%)
Four basic steps for evaluating chronic cough

• Stop ACE-inhibitor (1-3 months)
• Stop Smoking (1 month)
• Chest X-ray
• Spirometry/PFT
  – (Pre- and Post bronchodilator)
Common Pitfalls

- Failure to consider common extrapulmonary causes
- Insufficient dose of medication or duration of therapy
- Failure to consider multiple concomitant etiologies
Upper Airway Cough Syndrome
(formerly Postnasal Drip Syndrome)

When to suspect

- History: Typical “drip” sensation, frequent throat clearing
- Physical Exam: Cobblestone appearance, excessive mucus seen
- (?)Silent UACS: Small group (10-20%) may have no symptoms or signs

This is described mainly in internal medicine literature.

NEJM 2000;343(23):1715-1721
Upper Airway Cough Syndrome
(formerly Postnasal Drip Syndrome)

How to treat

- **Treat the cause:** allergic rhinitis, sinusitis, idiopathic (?)

- **Dry up / stop the mucus:**
  1. (Dex)brompheniramine* (Brovex, Drixoral)
  2. Decongestants (be cautious in elderly)
  3. Nasal Steroid Sprays
  4. Nasal Antihistamine sprays
  5. Ipratropium (0.06%) nasal spray

- **Liquefy the mucus:**
  1. Saline nasal rinse
  2. Guaifenesin

*The only antihistamine shown to inhibit the cough reflex
NEJM 2000;343(23):1715-1721
Asthma

- Definition: chronic inflammation, variable airflow obstruction, airway hyper-responsiveness, reversibility
- Cough-variant asthma in 57% cases
- Wheezing: low sensitivity
- FEV1 is the most reliable measurement of airway caliber
Spirometry

- Extremely valuable
- Must be obtained in a pt. with suspected asthma
- Pre- and Post-bronchodilator spirometry
  FEV1: A difference of 12% and >200 mL is diagnostic of airway hyper-responsiveness
- Normal spirometry does not rule out asthma
Methacholine Challenge Test

In a setting of adult chronic cough patients:

• Positive predictive value: 60-88%
• Negative predictive value: 100%

*Chest 1999;116(2):279-84*
Role of IgE Antibodies

• Cough-variant asthma is common and may not respond to usual treatments (Steroid-resistant asthma)
• Check IgE antibodies in difficult to control asthma and evaluate patient for potential use of omalizumab/Anti-IgE therapy
Asthma and Cough

• Bronchial inflammation causes vagal stimulation

• Asthma (and eosinophilic inflammation) are ruled out if:
  – MCT negative and
  – no response to prednisone 30 mg daily for 2 weeks (British Thoracic Society)

• Consider adding leukotriene modifiers if inadequate/no response to inhaled steroids

Chronic cough relieved by prednisone

Possibilities:
(1) Allergic rhinitis
(2) Asthma
(3) Eosinophilic bronchitis
<table>
<thead>
<tr>
<th>Eosinophilic bronchitis</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum eosinophilia</td>
<td>Sputum eosinophilia</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>No airway hyperresponsiveness</td>
</tr>
<tr>
<td>Treatment is inhaled or oral steroids</td>
<td>Treatment is inhaled or oral steroids</td>
</tr>
<tr>
<td>Natural history unclear</td>
<td></td>
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</tbody>
</table>
How can physiologic alterations in severe asthma promote GERD?

- Increase in transient LES relaxation
- LES hypotonia
- Esophageal dysmotility (due to autonomic dysfunction in asthma)
- Asthma meds can increase LES dysfunction (theophylline, oral beta agonists)
- Hyperinflation in asthma reduces crural diaphragmatic support to the LES
GERD/Laryngopharyngeal Reflux-- History

- Cough
- Hoarseness/vocal fatigue
- Throat clearing
- Excessive throat mucus
- Post-nasal drip
- Globus pharyngeus
- Tickle in the throat or sticky sensation
- Heartburn, sour taste and regurgitation are **unusual**.

- **Diurnal variation**
  - Cough on lying down - positional
  - Decreases when asleep
  - Wakes without cough
  - Cough on rising

- **Variation with food**
  - The act of eating
  - Types of food
  - Postprandial

- Silent reflux in 50-75% cases

*Am J Gastroenterol 2000;95(8 Suppl):S9-14
Chest 2002;121:1132-40
Ear, Nose, Throat J 2002;82 (9 Suppl 2): 10-13*
GERD—Grey areas

- Bravo probe vs 24-hour pH probe
- Role of Nissen fundoplication
- Is GI dysmotility the cause?
- 24-hour acid suppression with a pro-kinetic agent
- Non-acid reflux
- Normal EGD does NOT rule it out
- Do a pH probe while ON therapy to see if more intensive therapy needed
GERD

• In patients with chronic cough, it should not be assumed that GERD has been definitely ruled out as a cause of cough simply because there is a history of anti-reflux surgery

ACCP Guidelines 2006
GERD/Laryngopharyngeal Reflux

Pseudosulcus vocalis
Posterior commissure hypertrophy

Vocal fold edema
Ventricular obliteration

Ear, Nose, Throat J 2002;82 (9 Suppl 2): 10-13
Reflux Tests

- Laryngoscopy
- 24-hour Esophageal pH monitor
- Multichannel Intraluminal Impedance and manometry
- Bravo pH Probe
- EGD
- Barium Swallow
- Motility studies
24-hour esophageal pH monitoring

- Positive predictive value: 89%
- Negative predictive value: <100%
- Inconvenient for patients
- Controversy in interpretation of results in the diagnosis of cough
- Explore a temporal relationship between reflux and cough (keep a cough diary)
- Useful if therapeutic trial fails

Chest 1998;104:1511-7
Sleep apnea and GERD

- The phreno-esophageal ligament (PEL) connects the diaphragm to the Lower Esophageal Sphincter (LES.)
- During sleep apnea syndrome, there is increased respiratory effort by the diaphragm.
- This extra effort is transmitted to the LES by the PEL.
- This leads to further opening of the LES and possibly increases reflux.

Herr J. Chest 2001;120(3):1036-7
### Koufman Score (Wake Forest University)

**Table I**

<table>
<thead>
<tr>
<th>Reflux Finding Score (RFS)</th>
<th>2 = present</th>
<th>0 = absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subglottic Edema</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventricular Obliteration</strong></td>
<td>2 = partial</td>
<td>4 = complete</td>
</tr>
<tr>
<td><strong>Erythema/Hyperemia</strong></td>
<td>2 = arytenoids only</td>
<td>4 = diffuse</td>
</tr>
<tr>
<td><strong>Vocal Fold Edema</strong></td>
<td>1 = mild</td>
<td>2 = moderate</td>
</tr>
<tr>
<td><strong>Diffuse Laryngeal Edema</strong></td>
<td>1 = mild</td>
<td>2 = moderate</td>
</tr>
<tr>
<td><strong>Posterior Commissure Hypertrophy</strong></td>
<td>1 = mild</td>
<td>2 = moderate</td>
</tr>
<tr>
<td><strong>Granuloma/Granulation</strong></td>
<td>2 = present</td>
<td>0 = absent</td>
</tr>
<tr>
<td><strong>Thick endolaryngeal mucus</strong></td>
<td>2 = present</td>
<td>0 = absent</td>
</tr>
</tbody>
</table>

**TOTAL**

If RFS >7, 95% PPV for LPR
Management of Non-acid Reflux

• **Pro-kinetic agents:**
  – Bethanechol (bronchoconstriction)
  – Metoclopramide (dizziness)

• **Reducing transient LES relaxation:**
  – Baclofen (dizziness, drowsiness)

• **Avoid medications that relax LES:**
  – Calcium-channel blockers, beta agonists

• **Weight reduction / avoid overeating**
Management of Acid Reflux

- Diet and Lifestyle
- Weight reduction
- Treating sleep apnea
- H2 blockers
- PPI
- Properistaltic agents
- Avoid excessive exercise
Always remember non-pharmacologic measures

- No alcohol, soda/pop/orange juice/grape juice/tomato juice/chocolate/mint/fatty foods/spicy foods
- Eat smaller meals
- Elevate the head of the bed
- No smoking
- No food and drink except water for 2-3 hours before bedtime, avoid recumbency after a meal
- No tea/coffee or avoid empty stomach
- Avoid meds that relax LES: theophylline, etc.
Vocal Cord Dysfunction

• Can manifest as chronic cough
• Reports of transient postviral vocal cord dysfunction that completely resolve over time. (Rhinovirus, Influenza A virus, hMPV)
• Pathophysiology unclear
• Can manifest in a patient with asthma
• Reported in the internal medicine literature

JACI 2004:1471-1472
Habit (Psychogenic) cough

- True incidence unknown
- ? Over-diagnosed by physicians
- Diagnosis of exclusion
- Patient education, Breathing exercises, Speech Therapy, Behavioral Counseling, Self-hypnosis

*J Commun Disord 1988 Sep;21(5):393-400*
*Am J Respir Crit Care Med 2002: 165: 1469-1474*
Neurogenic cough

• Mechanism unclear
• Uncontrollable paroxysms of cough
• May be diagnosed with therapeutic trials
  – Neurontin
  – Elavil
  – Xanax
Unexplained Cough: A distinct entity?

• Typical patient profile-
  – female, perimenopausal, viral URI as an initiating event

• Mechanisms-
  – Increase in tachykinin content in lungs
  – upregulation of NK1 and substance P receptors
  – qualitative change in airway sensory nerves
  – chronic lymphocytic airway inflammation
    (high CD4 in Broncho-alveolar lavage)

• Exact incidence unknown (12-42%)
Refractory Unexplained Cough

Rule out all the possible causes first

Very challenging to treat

The following may be of value:

• Lidocaine nebulization
• Saline nasal irrigations
• Neurontin, Pamelor, Xanax, Baclofen
• Speech therapy evaluation and breathing exercises
• Patient and family education and counseling

Am J Respir Crit Care Med 1995;152:2068-75
How common is lung cancer in chronic cough?

- Very rare (0 to 2%)
- CXR has a negative predictive value of >95%, and a positive predictive value of 30 to 40%

*Chest 1998;114(2):133s-181s*
Therapeutic trials: When to expect a response?

- Smoking cessation: up to 4 weeks
- ACE-inhibitor discontinuation: up to 12 weeks
- Postnasal drip syndromes: up to 2-3 weeks
- Asthma: up to 6-8 weeks
- GERD/LPR: up to 8-12 weeks
- Eosinophillic bronchitis: up to 3-4 weeks

Don’t give up too soon

*Chest 1998;114(2):133s-181s*
When to use antitussives and protussives?

• Very rarely
• Incurable lung cancer
• Only for a short period in habit cough
• Guaifenesin:
  – May decrease cough receptor sensitivity
  – Mucolytic

*Drugs, 1993;46(1):80-91*
Chronic cough can have multiple causes

- More than 1 cause: up to 93%
- More than 2 causes: up to 53%
- More than 3 causes: up to 35%
- More than 4 causes: up to 5%

If partial success, add on therapy (don’t substitute)

Am J Respir Crit Care Med 2002: 165: 1469-1474
Eur Respir J 2005; 235-243
Work-up for chronic cough

Individualize the approach
Be cost-effective

- CXR
- Limited sinus CT
- Spirometry
- Methacholine challenge test
- Allergy skin tests
- Environmental control
- R/O occupational exposures

- Chest CT
- Neck CT
- Nasolaryngoscopy
- Bronchoscopy
- 24-hour esophageal pH/impedance monitor
- Barium swallow, etc.
Tips about work-up

- Plain Sinus films can be false negative (consider limited sinus CT)
- CXR can be false negative in Interstitial Lung Disease (consider HRCT Chest)
- OK to get second opinion from another Radiologist
- May need to repeat/reinterpret the tests that were done previously
Detecting Unusual Causes

- Preceding Events: Recent Immigration from a developing country, foreign travel (Tuberculosis)
- Review of systems: Weight loss (Hodgkin’s)
- Check Family History (Cystic Fibrosis)
Strategies in Cough
suggested further reading

• Diagnosis and Management of Cough Executive Summary: ACCP Evidence-Based Clinical Practice Guidelines. Irwin, et al. Chest 2006


• The Anatomic Diagnostic Protocol
  – Offers framework for many of the published diagnostic algorithms
  – Success Rates of 84-98%
General Tips on Pediatric Chronic Cough

• The younger the child the greater the chance of foreign body aspiration
  – Even very young infants (FB supplied by toddler siblings)

• The younger the child the greater the chance of an anatomic abnormality (e.g. TEF, hemangioma, posterior laryngeal cleft)

• Under 6 months of age requires thorough workup

Irwin RS Chest 2006 ACCP Guidelines
Zebras to watch for

- “Clinically silent” suppurative airway disease
- Congestive heart failure
- Cancer: bronchogenic, esophageal, metastasis
- Cystic fibrosis
- Interstitial lung disease
- Foreign bodies
- Pneumonia, recurrent aspiration
- Sarcoidosis
Zebras to watch for, continued

- Pressure from an intrathoracic mass
- Primary ciliary dyskinesia (infertility)
- Lingual thyroid (hypothyroidism)
- Sleep apnea (as a cause for cough)
- Vocal cord dysfunction
- Pulmonary tuberculosis
- Bronchiectasis

Otolaryngol Head Neck Surg 2001;125:433-4
J Allergy Clin Immunol 2001;108(1):143
Take Home Points

- Upper Airway Cough Syndrome (PND), Asthma, and GERD/LPR are responsible for >95% cases of chronic cough
- More than one cause may be responsible
- Two Approaches: empiric treatment trials or diagnostic testing-directed trials
- INDIVIDUALIZE THE TREATMENT!

Kastelik JA, et al. ERJ 2005;235-243
Morice AH, et al. ERJ 2004;24:481-492