Chronic Cough:  
Role of the Otolaryngologist

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“Paul, that’s a talk you never, ever want to give at a meeting... Trust me, you do not want to be the cough guy”

Pete Andersen

Chronic Cough:
Role of the Otolaryngologist

Joshua Schindler, MD
Oregon Health & Science University
Scope of the Problem

Estimated 28 million outpatient visits annually (2002)
- Most common condition for which patients seek medical treatment


US Retail sales of OTC medications was $15.1 billion in 2004 (excluding Wal-Mart)
- $3.6 billion in cough and cold medication

Outline of Discussion

• Basic science of cough reflex and pathways
• Review of common causes of cough and work-up
  – Otolaryngologist perspective
• Presentation of unusual upper airway causes of cough and management

Take Home Points

• The causes of cough are as myriad as the nerves that meditate them
• Asthma and GERD/LPR probably account for the majority of chronic cough
• Post-nasal drip/UACS is not likely real
• GERD/LPR is difficult to diagnoses and expensive to treat
• An otolaryngologist may be helpful in evaluating and managing chronic cough
Why We Cough

**Adaptive**
- Defensive mechanism
  - Protection from aspiration
  - Clearance of particulate debris

**Maladaptive**
- Upper and lower airway irritation
  - Inflammation
  - Hyperreflexia
- Habit?
Mechanism of Cough

Vagal Afferents

- Lung parenchyma
- Bronchioles
- Bronchi
- Trachea
- Larynx
- Supraglottis?

Rat Trachea

Vagal Afferents

3 Primary Types:

- Slowly Adapting Receptors (SARs)
- Rapidly Adapting Receptor (RARs)
- C-fibers
**Targets for Antitussives**

- Hypertonic saline
- Capsaicin
- Bradykinin
- Citric acid (H+)
- Histamine
- Adenosine
- 2-methyl-5-HT

Targets include: Jugular Aβ fibers, Nodose Aδ fibers, and Slowly Adapting Receptors (SARs).

**Cortic, BJ; AJP 2008**

**Vagal Afferents**

**Slowly Adapting Receptors (SARs)**

- Primarily intrapulmonary
- Responsible for reflexive exhalation at full lung volume
- May act centrally in cough
- Insensitive to irritants
- Limited role in clinical cough syndromes

**Ho et al., Respir Physiol 2001; 127:119-124**
Vagal Afferents

**Rapidly Adapting Receptors (RARs)**

- Terminate within epithelium and smooth muscle
- Rapidly adapt to increases in lung volume
- Not directly sensitive to chemical stimuli
- Dynamic response to:
  - Diameter
  - Length
  - Interstitial pressure

Ho et al., Respir Physiol (2001); 127:113-124

Vagal Afferents

**C-fibers**

- Defensive cough
- Chemoreflex
  - Apnea
  - Bradycardia
  - Hypotension
- Release neuropeptides (*Axon Reflex*)
  - Bronchoconstriction
  - Increase mucous
  - Edema
  - Inflammatory cell migration

Ho et al., Respir Physiol (2001); 127:113-124
**Vagal Afferents**

**C-fibers**
- Unmyelinated
- Majority of fibers
- Direct nociceptors
  - Chemical
    - Capsaicin, citric acid, vanilloids
  - Mechanical
    - High threshold

*Ho et al., Respir Physiol (2001); 127:113-124*

**Complicated Web**

*Widdicombe, J. Anat Record Pt A (2003) 270A: 2-10*
Vagal Afferents

C-fibers

- Unmyelinated
- Majority of fibers
- Direct nociceptors
  - Chemical
    - Capsaicin, acid, saline
  - Mechanical
    - High threshold
- Complicated modulation
  - ↓↓ to lung inflation
  - ↑↑ by bronchodilators
  - ↑ by histamine

Ho et al., Respir Physiol (2001); 127:113-124
Morice, AH & Geppetti, P; Thorax (2004); 59: 257-8

Transient Receptor Potential Vanilloid (TRPV)-1

Monice, AH & Geppetti, P; Thorax (2004); 59: 257-8
Vanilloid Receptors in Larynx

Vanilloid receptors in the larynx have been studied. Koike, S et al. Acta Otolaryngol (2004); 124: 515-519.

TRPV1 Receptors in Cough

TRPV1 receptors have also been investigated in cough. Groneberg, DA, et al.; Am J Respir Crit Care Med (2004); 170: 1276-1280.
Targets for Antitussives

Vagal Afferents

C-fibers
- Defensive cough
- Chemoreflex
  - Apnea
  - Bradycardia
  - Hypotension
- Release neuropeptides (Axon Reflex)
  - Bronchoconstriction
  - Increase mucous
  - Edema
  - Inflammatory cell migration
- Many conflicting studies
New “Cough Receptor”?

Guinea Pig Trachea

- Concentrated in larynx, trachea and carina
- Action mediated by RLN
- No TRPV-1
- Exquisitely sensitive to
  - Mechanical stimuli
  - Acid
  - Distilled water
- Unresponsive to:
  - Lung volume/pressure
  - Capsaicin
  - Histamine
  - Methacholine

Targets for Antitussives

Canning, BJ; Chest (2006); 129(1): 33S-47S
Extrarespiratory Cough

- Ear canal
  - Mediated by “Arnold’s Nerve” to jugular ganglion and NTS

- Pharynx
  - Similar to acid/mechanoreceptors of larynx/trachea
  - Sensitive to water, not capsaicin
  - Presumed mediator of PND-associated cough

- Esophagus?
  - Not triggered by acid, capsaicin or distension
  - Gastric/esophageal stimulation increases tracheal mucous production (German, VF; J Appl Physiol (1982) 52:1153-55)

Otolaryngology Evaluation and Management of Chronic Cough
Definitions of Cough

**Acute Cough**
< 3 weeks

**Subacute Cough**
3 – 8 weeks

**Chronic Cough**
> 8 weeks

Nomenclature

Post Nasal Drip Syndrome (PNDS)
= **Upper Airway Cough Syndrome (UACS)**

Idiopathic Cough
= **Unexplained Cough**

Gastroesophageal reflux disease
= **Reflux disease**
Cough Freebies

- Smoking**
- ACE inhibitor therapy
  - Incidence 5-35%
  - Timing: hours-months after 1st dose
  - Resolution with cessation:
    - Typical 1-4 weeks
    - Range to 3 months

“In a patient with chronic cough, ACE inhibitors should be considered as wholly or partially causative, regardless of the temporal relation between initiation of ACE inhibitor therapy and the start of cough.”


“The Trifecta”

- Asthma
- UACS (PND)
- GERD

These 3 causes are said to cause 90% of all chronic cough
Cough and Asthma

Roughly 30% of all cough

Several variants:
- Classical asthma
- Cough-variant
- Eosinophilic bronchitis
- Atopic cough

Exhaled nitric oxide elevated in eosinophilic disease.

Unable to predict responsiveness to inhaled corticosteroids.
Cough and Asthma

• Evaluation
  – CXR
  – Spirometry +/- bronchodilator
  – Methacholine challenge
  – Allergy testing

• Management
  – Inhaled steroid (4 weeks)
  – Bronchodilator
  – Leukotriene inhibitor therapy
  – Antihistamine/desensitization

Fungal Laryngitis
what is post nasal drip?
- sensation something running down the back of the throat
- poor definition of syndrome
  - usually no physical findings

UACS (PND) and Cough

what is post nasal drip?
- 1 liter secretions/day
- ability to localize symptoms to OP/NP is poor
  - throat clearing
  - globus sensation
- association with cough is 8-56%
UACS (PND) and Cough

PND is a US perception
- Proctor & Gamble
  • 892 US telephone interviews
    - 50% suffer from “PND”
  • 1000 in UK
    - < 25%
  • Difference felt to be labeling/marketing

Our role is to consider the differential diagnosis:

- Allergic rhinitis
- Sinusitis
- Reflux related sx’s
- Dysphagia/Aspiration
- Post viral neuropathy
In patients with chronic cough, the diagnosis of upper airway cough syndrome should be determined by considering a combination of criteria, including symptoms, physical examination findings, radiographic findings, and, ultimately, the response to specific therapy. *Because it is a syndrome, no pathognomic findings exist.*
GERD and Cough

GERD
- Prevalence as cause of cough 5-41%
  - Trend toward increasing association
- Common GI symptoms
  - Heartburn
  - Regurgitation
  - Dysphagia
- Wide spectrum of clinical manifestations
  - ? Distal acid exposure can cause cough
    (Ing, A; Am J Respir Crit Care Med (1994); 149: 160-7)

GERD vs. LPR
Koufman 1991 – “reflux laryngitis” and “laryngopharyngeal reflux”

<table>
<thead>
<tr>
<th>Reflex Finding Score (RFS)</th>
<th>2 = present</th>
<th>1 = mild</th>
<th>0 = absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subglottic Edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular Obliteration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema/Hyperemia</td>
<td>1 = mild</td>
<td></td>
<td>0 = absent</td>
</tr>
<tr>
<td>Vocal Fold Edema</td>
<td>1 = mild</td>
<td></td>
<td>0 = absent</td>
</tr>
<tr>
<td>Diffuse Laryngeal Edema</td>
<td>1 = mild</td>
<td></td>
<td>0 = absent</td>
</tr>
<tr>
<td>Posterior Commissure Hypertrophy</td>
<td>1 = mild</td>
<td></td>
<td>0 = absent</td>
</tr>
<tr>
<td>Granuloma/Granulation</td>
<td>1 = mild</td>
<td></td>
<td>0 = absent</td>
</tr>
<tr>
<td>Thick endolaryngeal mucus</td>
<td>1 = mild</td>
<td></td>
<td>0 = absent</td>
</tr>
</tbody>
</table>

TOTAL

Belafsky, PC, et al. Laryngoscope (2001); 111:1313-317
Profile of GERD/LPR

American College of Chest Physicians CPG

Chronic cough
Not exposed to chemical irritants
No ACE-I use
Normal chest radiograph
Failure asthma therapy/Normal Methacholine
Failure of antihistamine
Normal/stable sinus imaging
No eosinophilia of induced sputum/failure to respond to inhaled corticosteroids

Irwin, RS; Chest (2006); 129 (1): 80S-94S
LPR Evaluation and Management

- Empiric treatment before testing
  - Omeprazole 40 mg BID or equivalent
  - Treatment should continue for 3-6 months
  - No benefit expected for 3 months
  - Revisit diagnosis if no improvement at 6 months

- 24-hour pH probe is “gold standard”
  - Conventional indices (DeMeester score)
  - Reflux induced coughs

- Barium esophagography or impedance testing for non-acid reflux determination

- Esophagoscopy can be normal
Problems with LPR/GERD Diagnosis

- Definitions are unclear
- Symptoms are poorly defined
- Physical findings are vague
- Poor “gold standard”
- Poor correlation with histologic findings
- High treatment failure rate
- Very poor studies

Uncommon Causes of Cough

- Wegner’s granulomatosis

Pulmonary disorders
- Tracheobronchomalacia
- Airway stenosis/stenoses
- Tracheobronchial stenosis/obstruction
- Mucous cysts (tracheobronchial)
- Tracheobronchial amyloidosis
- Airway foreign bodies
- Bronchietasis
- Lymphangiectasias
- Pulmonary Langhans cell histiocytosis
- Pulmonary alveolar proteinosis
- Pulmonary alveolar microlithiasis
- High altitude
- Tracheal hyperplasia
- Mechanical trauma
- Pulmonary edema
- Pulmonary embolism
- Drug-induced cough
- Miscellaneous (e.g., vocal cord dysfunction, surgical sutures in airways)
- Nonpulmonary disorders
- Connective tissue disorders
- Vasculitides (e.g., Weg, GCA, and RPC)
- Emphysema disorders (tracheobronchial and bronchiectatic)
- Inflammatory bowel diseases (e.g., Crohn disease and ulcerative colitis)
- Thyroid disorders (gland, thyrotoxicosis)
- Others (e.g., Tietze syndrome)
Bordetella Pertussis

- Presenting symptoms
  - mucus hypersecretion, conjunctival irritation, and slight cough
- Sx’s do not correlate well with the initial virulent stage of the infection
- Characteristic paroxysms of cough in B. pertussis begin appear 7–10 days after initial infection but persist for many weeks.
- Bradykinin mediated

Bordetella Pertussis

- Resurgence
  - Duration of the protection and waning immunity following infection and vaccination
  - Strain polymorphisms
  - Increased diagnosis and reporting as physicians become familiar with the infection and its
**Bordetella Pertussis**

- Immunization is key
  - Unless antibiotic therapy is initiated early during the infectious stage, drugs have no impact on transmission rates and little or no impact on disease duration and severity.
  - This discordance between the contagious and symptomatic periods of the illness has combined to produce outbreaks that can last for months.

**Sensory Neuropathy**

Lee & Woo (2005)
- 28 patients “cryptogenic” cough
- Duration of cough = 7 mo (range 2wk-20yr)
- 2/3 had “previous work-up”
- 20/28 felt to have RLN/SLN neuropathy
Lee & Woo (2005)

- Treated with gabapentin (Neurontin)
  - Started 100 mg/d– increased to ~900 mg/d
  - Dose titrated to effect/side effects

- Results:
  - 68% overall improvement
  - 80% of those with L-EMG neuropathy
Behavior Modification

• Cortical control is evident
  – Voluntary cough
  – Placebo-mediated cough suppression

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Medication</th>
<th>Dosing</th>
<th>Duration of study</th>
<th>Cough measure</th>
<th>Percentage of placebo response</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takkinen et al (1996)</td>
<td>Dextromethorphan</td>
<td>30mg three times daily</td>
<td>4 days</td>
<td>Subjective cough frequency</td>
<td>105</td>
<td>108 patients with acute cough</td>
</tr>
<tr>
<td>Adams et al (1993)</td>
<td>Meprobamate tablets</td>
<td>200mg twice a day</td>
<td>3.5 days</td>
<td>Subjective cough severity</td>
<td>88</td>
<td>108 patients with acute cough</td>
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<tr>
<td>Eccles et al (1992)</td>
<td>Codeine spray</td>
<td>30mg single dose</td>
<td>Laboratory study</td>
<td>Cough frequency</td>
<td>105</td>
<td>100 patients with cough</td>
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<tr>
<td>Pursen et al (1996)</td>
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<td>30mg single dose</td>
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<td>Cough frequency</td>
<td>105</td>
<td>100 patients with cough</td>
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<tr>
<td>study 1</td>
<td>capsules</td>
<td></td>
<td>on one day</td>
<td>Cough frequency</td>
<td>105</td>
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<td>study 2</td>
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<tr>
<td>capsule</td>
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<td>100 patients with cough</td>
</tr>
</tbody>
</table>

Eccles R; Pulm Pharmacol Ther (2002); 15: 303-8

Behavior Modification

• Cortical control is evident
  – Voluntary cough
  – Placebo-mediated cough suppression
  – Cough depressed/absent in:
    • Coma
    • Left cortical stroke
    • Sleep/anesthesia

• Cough Suppression
  – Capsaicin-induced cough can be suppressed in humans (Hutchings, et al.; Respir Med 1993; (87) 379-382.)
Complications of Cough

Acute Hemorrhage

Complications of Cough

Vascular Polyp
Complications of Cough

Chronic Cough Algorithm

- Stop tobacco and ACE-inhibitor
- Chest X-ray
- Trial benzonatate and cough suppression therapy
- Trial prednisone 30 mg daily for 14d or/
- Inhaled Steroid for 4 weeks
- CT sinus & chest
- Esophagoscopy +/- biopsy
- Trial proton pump inhibitor
- Trial amitriptyline
- Trial gabapentin
- Trial lyrica
- Trial acupuncture
Pearls

- Chronic cough is almost always multifactorial
  - Listen to patient’s symptoms
- Optimize therapy and testing for each suspected diagnosis
- Patience is critical
- Behavioral cough suppression can be tremendously useful
- Eliminate OTC medications/cough drops

Thank you