Taming Chronic Cough

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Potential Conflicts:

• Consulting:
  – AZ, Glaxo, Mylan, and Sanofi

• Clinical Research:
  – Glaxo, Medimmune, BI, and Novartis

• Organization
  – ABAI Board
Cough Guidelines

Diagnosis and Management of Cough
Executive Summary

ACCP Evidence-Based Clinical Practice Guidelines

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Guidelines for Evaluating Chronic Cough in Pediatrics

ACCP Evidence-Based Clinical Practice Guidelines

Anne B. Chang, MBBS, PhD; and William R. Clough, MD, FCCP

ERS TASK FORCE

The diagnosis and management of chronic cough

A.H. Morice and committee members

Cough

• defense mechanism
• spread infection
• one of the most common causes to see an MD*

## Reasons Why Pts with Chronic Cough Seek MD Attention

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Something’s wrong</td>
<td>98%</td>
<td>108 consecutive unselected pts</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Self conscious</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Life-style change</td>
<td>45%</td>
<td></td>
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<tr>
<td>Musculoskel pain *</td>
<td>44%</td>
<td>* MS pain in 1 pt rib fx</td>
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<tr>
<td>Hoarseness</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Excessive perspiration</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Fear of Ca</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Fear of Aids or TB</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Retching</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Syncope or Near Syncope</td>
<td>5%</td>
<td>Chest 1991;99:1477-84</td>
</tr>
</tbody>
</table>
Cough the basics

• **In healthy patients:**
  – mucociliary clearance is the major method to clear airway lumen.
  – cough is a reserve mechanism.
  – mucociliary clearance is 2 times that of pts with CB

• **With cough:**
  – healthy pts can increase clearance by 2.5%
  – CB pts can increase clearance by 20%.
Cough the basics

- Involuntary cough appears to be entirely vagally mediated
- Stimulation of structures vagally innervated can result in cough.
  - oropharynx
  - larynx
  - respiratory tract
  - tympanic membrane
  - external auditory meatus
Cough the basics

- Most sensitive sites to induce cough:
  - larynx
  - tracheobronchial tree especially corina and bronchial branching points

- Note: experimentally one can’t induce cough in smaller airways and the alveoli.
Cough the basics

• Larynx and pharynx: cough receptors appear to belong to group of rapidly adapting irritant receptors.
  • Usually silent, but when stimulated result in rapid adapting discharge with irregular pattern
    – conducted by fast velocity vagal myelinated fibers.

  – Triggers: cigarette smoke, ammonia, ether vapor, alkaline and acid solutions, hypo and hypertonic saline solutions, inflammatory mediators (histamine, bradykinin, PG) and mechanic stimuli (mucus, dust or a foreign body such as a catheter).
Cough the basics

• Central cough receptor:
  – Theoretical has never been established anatomically integrated by medulla oblongata (brainstem)
  • afferent fibers near nucleus of the tractus solitarius
  • motor outputs in ventral receptor group.
  • Nucleus retroambiguoualis sending motoneurons to respiratory muscles
  • nucleus ambiguous to larynx and bronchial tree.
• *most anti-tussive Rx acts centrally
  – don’t know how
Cough the basics

- Tracheobronchial tree
  - similar rapid adapting irritant receptors in trachea and large bronchi.

- Receptors within epithelium concentrated at airway branching points
  - enhanced by pulmonary congestion, atelectasis and bronchoconstriction.
Cough the basics

- Mucus secretion:
  - Afferent receptor that causes cough also result in reflex secretion of mucus from airway submucosal glands.

- Mucus:
  - entraps inhaled particles/chemicals and allows clearance via mucociliary transport as well as cough itself
  - results in narrowing of the airway which results in increase in linear velocity of airflow which yields increase in turbulence and central implication of pollutants
  - acts as a physiochemical barrier between lamina irritants and airway wall
Cough the basics

- **Respiratory muscles and cough:**
  - inspiratory phase – deep inspiration
  - compressive phase - forceful expiration against a closed glottis
  - explosive phase – glottis opens and expiration accelerates (200 m/sec)
    - expiratory respiratory muscles are the most important component of expiration of cough, as even without glottis can be effective (even with ET tube can clear secretions)
Cough the basics

• Ineffective cough results in:
  – Atelectasis
  – Pneumonia
  – Gas exchange abnormalities
Cough the basics

- Measure of cough: max expiratory mouth pressure:
  - $>60$ mmHg can result in peak flow transients
  - $<40$ mmHg associated with difficulty in raising secretions
Diagnostic Evaluation

- RECEPTORS
- "COUGH CENTER"
- GN GLOSSOPHARYNGEAL NERVE
- PN PHRENIC NERVE
- TN TRIGEMINAL NERVE
- VN VAGUS NERVE
- ?N CORTICAL INPUT
Diagnostic Evaluation

- Diagnostic evaluation
- via the anatomic diagnostic protocol
  - systematic evaluation through assessing locations of afferent limb of the cough reflex

*Irwin et al. Chest 2006;1-292s*
The Anatomic Diagnostic Protocol - Adults

- Chronic cough => 8 weeks
  - With use of protocol in studies cause can be determined 88-100% of the time.
  - Resultant therapy with success rate of 84-98%.
  - Single cause 73-82%, multiple causes up to 26% with 3 causes up to 8% of cases.
The Anatomic Diagnostic Protocol

• In 91-94% of time 4 different causes:
  – PND
  – Asthma
  – GER
  – Chronic Bronchitis.

Goldsobel JACI 2012;130:825
Usefulness of Components of Cough Dx Protocol

ARRD 141:640-7
Causes of Cough

ARRD 141:640-7
Causes of cough

ARRD 141:640-7
Cough the basics

• Cough timing and quality not useful*

• If cigarette or irritant exposure or use of ACE noted in history, 1st remove and follow x 4 weeks

* Attention peds

Rank Ann All 2007;98:305-13
Cough the basics

• Reversible extrathoracic upper airway obstruction arises from stimulation of cough reflex in the upper respiratory tract associated with PND, throat clearing or both.

Rank Ann All 2007;98:305-13
Chronic cough/PND

- most common cause
  \[ \Rightarrow \text{stim sensory nerves} \Rightarrow \text{cough reflex} \]
  - \( Hx \): patient describe PND with pharyngeal irr (occ sense of foreign body). Consider \( \propto \) AR, NARES, post infection, env irritant, VMR or sinusitis.
    - Important to remember pts may have no symptoms
  - PE: Posterior pharynx with mucoid secretions, cobblestone appearance of post pharynx (observe for throat clearing) Flow Volume loop with variable extrathoracic upper airway obstruction

*Rank Ann All 2007;98:305-13*
Chronic cough/ Asthma

• 2nd most common cause
  Inflammation ⇒ stimulation of sensory nerves ⇒ cough reflex

*Hx*: Wheeze, SOB, triggers
  – Spiro with obstruction with reversibility

*Rank Ann All 2007;98:305-13*
Chronic cough/ GERD

• 3rd most common cause
  – Stimulation of afferent limb of cough reflex at the distal esophagus

• Hx:
  – heartburn, sour brash or regurgitation
  – 2/3 patients without symptom of GERD

• Dx:
  – pH probe abnl (may be seen in assoc with cough) even in absence of pt sx or therapeutic trial of PPI BID

Rank Ann All 2007;98:305-13
Chronic cough/ ACE inhib

• ⇒accumulation bradykinin or substance P ⇒ ↑ sens of cough reflex (Bradykinin, ? Subs P inactivated by ACEI)

• **Hx:**
  - nonproductive/irritating/tickling cough +/- sensation of something in the throat
    - Class effect **not** dose related
    - Freq. 0.2%-33%
    - Overall ∝ 2%
    - May take wks to months and even yrs for onset

• **Dx:** confirm resolution with D/C (usu 1-2 mo)

*Rank Ann All 2007;98:305-13*
Chronic Cough/Misc.

- <6% causes
  - Bronchogenic CA
  - Metastatic CA
  - Sarcoid
  - Left Vent failure
  - Aspiration ∝ Zenkers Diverticulum

*Rank Ann All 2007;98:305-13*
Chronic Cough/Unusual Causes

- Irritation of tympanic membrane (hair, TE tubes)
- Gilles de la Tourette’s syn
- Neurolemmoma of vagus nerve in neck
- Endobronhial suture
- Esophageal cyst
- Pertusis
- Psychogenic cough

⇒ consider only after all other possibilities excluded

*Rank Ann All 2007;98:305-13*
Chronic Cough Rx

- Specific Anti-tussive therapy:
  PND/AR:
  - env control
  - drying H-1 antag
  - nasal steroids
  - IT

*Rank Ann All 2007;98:305-13*
Chronic Cough Rx

• Specific Anti-tussive therapy:

  PND/sinusitis:
  • antibiotics (consider 6-8 wks)
  • decongestant
  • nasal steroid

Rank Ann All 2007;98:305-13
Rx Asthma

- Controller Rx ICS/LTM etc.

*Rank Ann All 2007;98:305-13*
GERD and Cough

- Caused by irritation of the vagus fibers
  - Are sensitive to acid as well as nonacid volume reflux

- Dx is very challenging as no currently available tests are highly predictive
  - Barium swallow without aid
  - Nl endoscopy or pH probe does not exclude reflux
  - ACCP and BTS guidelines suggest empiric dietary manipulation and BID PPI
    - Diet changes, limit ETOH, elevation of HOB, wt loss, sleep apnea evaluation

*Rank Ann All 2007;98:305-13*
Chronic Cough Rx

- **Specific Anti-tussive therapy GER:**
  - H-2 antag alone may *not* be adequate
  - 90% efficacy: high protein low fat
    - 3 meals w/o snack
    - no eat/drink 2-3 hrs prior to recline
    - elevate HOB 30°
    - weight loss
  - H-2 antag +/- metoclorpramide with gradual resolution over 161 d (ave)

*ARRD 141:640-7*
GERD and Cough

• Utility of prokinetic agents:
  – 56 patients with GERD related cough treated with PPI BID
    • 24 responded
    • 18 others only responded with addition of prokinetic agent
      – Presumed to be a result of nonacid refluxate causing cough*

• This study also reinforces the utility of empiric Rx as 44 or 56 responded without endoscopy or pH probe

*Ours Am J Gastro 1999;94:3131-8

Poe Chest 2003;123:679-84
GERD and Cough

- In those that fail PPI and prokinetic agent consider:
  - RLG
  - pH probe
  - Impedance testing via GI consult

- Antireflux surgery should be considered in patients with continued sx and objective evidence of reflux – failing maximal medical Rx
  - Evidence regarding fundoplication for GERD induced cough is lacking

*Rank Ann All 2007;98:305-13*
Search methods
• We searched the Cochrane Airways Group Specialised Register, the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, review articles and reference lists of relevant articles. The date of last search was 8 April 2010.

Selection criteria
• All randomised controlled trials (RCTs) on GERD treatment for cough in children and adults without primary lung disease.
• Data collection and analysis
• Two review authors independently assessed trial quality and extracted data. We contacted study authors for further information.
Main results

We included 19 studies (six paediatric, 13 adults).

In adults, analysis of H2 antagonist, motility agents and conservative treatment for GERD was not possible (lack of data) and there were no controlled studies of fundoplication.

We analysed nine adult studies comparing PPI (two to three months) to placebo for various outcomes in the meta-analysis. Using intention-to-treat, pooled data from studies resulted in no significant difference between treatment and placebo in total resolution of cough (OR 0.46; 95% CI 0.19 to 1.15).

Pooled data revealed no overall significant improvement in cough outcomes (end of trial or change in cough scores).

We found a significant improvement in change of cough scores at end of intervention (two to three months) in those receiving PPI (standardised mean difference -0.41; 95% CI -0.75 to -0.07) using generic inverse variance analysis on cross-over trials.

Two studies reported improvement in cough after five days to two weeks of treatment.

Chang Cochrane 2010
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Chang Cochrane 2010
Figure 3. Forest plot of comparison: 2 PPI versus placebo (> 18 years), outcome: 2.1 Clinical failures (still coughing at end of trial or reporting period).

Chang Cochrane 2010
Chronic Cough Rx

• **Bronchiectasis:**
  - Theo/β-2 ⇒ stim mucocil cl
  - Chest physiotherapy + postural drainage

*Rank Ann All 2007;98:305-13*
Chronic Cough RX

**non-specific anti-tussive**

- *Narcotics* phenanthrene alkaloid group: codeine/morphine
  \[\Rightarrow \uparrow\text{threshold or latency of cough center}\]

  Recently AAP recommends avoidance

- *Non-narcotic*: benzonatate, dextromethroaphan, diphenhydramine, caramiphen, viminal and levopropizine
  - \[\uparrow\text{threshold/latency efferent arm}\]

- *Ipratropium bromide* – act efferent limb or at mucociliary factors

*Rank Ann All 2007;98:305-13*
Association of $\beta_2$-adrenoreceptor polymorphisms with nocturnal cough among atopic subjects but not with atopy and nonspecific bronchial hyperresponsiveness

**Objective**

- Evaluated the association between asthma phenotypes and $\beta_2AR$ polymorphisms at 2 sites (Arg16-Gly16 and Gln27-Glu27) in the general population.

**Methods:**

- Four hundred forty unrelated Korean adults were randomly selected, and asthma phenotypes were determined with a questionnaire, immunoassay, skin prick testing, and methacholine bronchial provocation testing.
- Genotypes of $B2AR$ polymorphisms were determined with PCR-based methods.

*Kim S-H et al. JACI 2002;109:630-5*
Association of β²-adrenoreceptor polymorphisms with nocturnal cough among atopic subjects but not with atopy and nonspecific bronchial hyperresponsiveness

- **Results:**
  - No significant association was found between β²AR alleles and haplotypes and total IgE levels, skin test responses to aeroallergens, and bronchial responsiveness to methacholine.
  - Among the atopic subjects, however, Arg16-Gln27 haplotypes was negatively associated with nocturnal cough, and in contrast, Gly16-Gln27 was positively associated with it.

*Kim S-H et al. JACI 2002;109:630-5*
Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial

• Background
  – Similarities between central reflex sensitisation in refractory chronic cough and neuropathic pain suggest that neuromodulators such as gabapentin might be effective for refractory chronic cough.

• Methods
  – This randomised, double-blind, placebo-controlled trial was undertaken at an outpatient clinic in Australia.
  – Adults with refractory chronic cough (>8 weeks’ duration) without active respiratory disease or infection were randomly assigned to receive gabapentin (maximum tolerable daily dose of 1800 mg) or matching placebo for 10 weeks.
  – Block randomisation was done with randomisation generator software, stratified by sex.
  – Patients and investigators were masked to assigned treatment. The primary endpoint was change in cough-specific quality of life (Leicester cough questionnaire [LCQ] score) from baseline to 8 weeks of treatment, analysed by intention to treat.

Ryan Lancet 2012;380:1583-9
Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial

• Findings
  – 62 patients were randomly assigned to gabapentin (n=32) or placebo (n=30) and ten patients withdrew before the study end.
  – Gabapentin significantly improved cough-specific quality of life compared with placebo (between group difference in LCQ score during treatment period 1.80, 95% CI 0.56–3.04; p=0.004; number needed to treat of 3.58).
  – Side-effects occurred in ten patients (31%) given gabapentin (the most common being nausea and fatigue) and three (10%) given placebo.

• Interpretation
  – The treatment of refractory chronic cough with gabapentin is both effective and well tolerated.
  – These positive effects suggest that central reflex sensitisation is a relevant mechanism in refractory chronic cough.

Ryan Lancet 2012;380:1583-9
<table>
<thead>
<tr>
<th></th>
<th>Gabapentin (n=17)</th>
<th>Placebo (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blurred vision</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>1* (17%)</td>
</tr>
<tr>
<td>Disorientation, confusion</td>
<td>2 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (18%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Dry or very dry mouth</td>
<td>2 (12%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (18%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Memory loss</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea, stomach pain</td>
<td>4 (24%)</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

Data are number of events (%). n=total number of events associated with study drug. *Possible comorbidity (present before study).

**Table 2: Adverse effects**
<table>
<thead>
<tr>
<th></th>
<th>Gabapentin Mean (95% CI)</th>
<th>Placebo Mean (95% CI)</th>
<th>Difference* (95% CI)</th>
<th>p value</th>
<th>Gabapentin Mean (95% CI)</th>
<th>Placebo Mean (95% CI)</th>
<th>Difference* (95% CI)</th>
<th>p value</th>
<th>Between-group difference in change from treatment period to post-treatment period* (95% CI)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LCQ score†</td>
<td>+2.5</td>
<td>+1.1</td>
<td>1.8 (0.56 to 3.04)</td>
<td>0.004</td>
<td>+1.7</td>
<td>+1.4</td>
<td>0.85 (-0.75 to 2.44)</td>
<td>0.30</td>
<td>-1.22 (-2.35 to -0.09)</td>
<td>0.034</td>
</tr>
<tr>
<td>Cough frequency (coughs/h)</td>
<td>-22.5</td>
<td>-4.3</td>
<td>-18.2 (-51.75 to -3.88)</td>
<td>0.028</td>
<td>-9.7</td>
<td>-8.9</td>
<td>-0.8 (-43.31 to 37.11)</td>
<td>0.88</td>
<td>26.49 (0.49 to 52.48)</td>
<td>0.046</td>
</tr>
<tr>
<td>Mean cough severity (VAS score, mm)</td>
<td>-11.1</td>
<td>+0.8</td>
<td>-12.23 (-23.22 to -1.25)</td>
<td>0.029</td>
<td>+2.0</td>
<td>-4.8</td>
<td>5.57 (-4.93 to 16.07)</td>
<td>0.29</td>
<td>18.92 (7.71 to 30.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cough reflex sensitivity at C5 (µM)</td>
<td>+15.1</td>
<td>+5.1</td>
<td>3.12 (-13.59 to 19.82)</td>
<td>0.72</td>
<td>+30.5</td>
<td>+8.6</td>
<td>13.3 (-14.67 to 40.97)</td>
<td>0.35</td>
<td>10.06 (12.35 to 32.46)</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean urge-to-cough score</td>
<td>-0.7</td>
<td>-1.4</td>
<td>0.59 (-0.52 to 1.70)</td>
<td>0.30</td>
<td>-0.9</td>
<td>-1.1</td>
<td>0.021 (-1.29 to 1.34)</td>
<td>0.98</td>
<td>-0.21 (-1.35 to 0.93)</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean LDQ score</td>
<td>-1.6</td>
<td>-1.5</td>
<td>0.048 (-0.82 to 0.92)</td>
<td>0.91</td>
<td>-1.6</td>
<td>-1.8</td>
<td>0.44 (-0.45 to 1.33)</td>
<td>0.33</td>
<td>0.27 (-0.62 to 1.15)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Baseline refers to visit 1 (before treatment). Treatment period refers to visit 2 and visit 3 (on treatment). To calculate mean change between baseline and treatment period, an average of the score at visit 2 and visit 3 was taken away from the score at baseline. Post-treatment period refers to visit 4 and visit 5 (off treatment). To calculate mean change between baseline and post-treatment period, an average of the score of visit 4 and visit 5 was taken away from the score at baseline. LCQ=Leicester cough questionnaire. VAS=visual analogue score. C5=concentration of capsaicin needed to induce five coughs. LDQ=laryngeal dysfunction questionnaire. *Baseline differences adjusted for. A higher score indicates a better health status.

Table 3: Efficacy analysis for gabapentin versus placebo in the treatment of refractory chronic cough
Figure 2: Mean efficacy variable scores for gabapentin versus placebo, during and after treatment. Dose was escalated from days 1-6 and reduced from days 7-8. Treatment was stopped completely by visit 4 (dotted line). p values represent the significance of the between-group difference in the change in efficacy outcomes from baseline to treatment period (average score from visits 2 and 3). LCQ: Leicester Cough Questionnaire; VA: visual analogue scale; CI: cough reflex sensitivity defined by quantity of capsaicin needed to induce five coughs. Error bars show SE.
How Do we put all of this Together
Chronic Cough non-smoker

CXR

- w/u

Hx to Guide

PND

Empiric Rx

Cont + taper

More aggressive w/u
Asthma + GERD

Rank Ann All 2007;98:305-13
(-) => Hx to Guide

Asthma

Cont + taper

More aggressive w/u Asthma + GERD

GERD

No

Cont + taper

More aggressive w/u Asthma + GERD

?Gabapentin

Rank Ann All 2007;98:305-13

Ryan Lancet 2012;380:1583-9
Cough w/o reflux Sx

24 hr pH Probe

- unrelated

+ clinically silent

step down maint Rx
H-2 blocker w/ diet manipulation

Cough w/ reflux Sx

3 mo. trial
PPI BID

no

Repeat 24 hr pH probe w/ reflux Rx

pH+

Rx
• Prokinetic
• Surg

cough not related

pH-

Rank Ann All 2007;98:305-13