Chronic Cough in Children

Alan Goldsobel, M.D. FACAAI
Allergy and Asthma Associates of Northern California
Adjunct Clinical Associate Professor Pediatrics
Stanford University Medical Center
Clinical Professor Medicine
UCSF

Educational Objectives

- Understand and describe current cough guidelines
- Describe pitfalls in cough management
- Describe practical and cost-effective ways to manage chronic cough
- Apply and interpret common tests used to evaluate patients with chronic cough

Conflict of Interest

- Principal investigator for Cerecor-investigating new medication for chronic cough in adults.
Chronic Cough in Children is a Multi-Disciplinary Symptom

- Pediatrician
- Allergy/Immunology
- Pulmonary
- Otolaryngology
- Gastroenterology
- Speech therapy
- Behavior counseling
- Psychiatrist

Cough in Children

- Normal, protective defensive mechanism, necessary for effective airway clearance

Cough in Children

- Normal, protective defensive mechanism, necessary for effective airway clearance
  
  AND

- Common symptom of respiratory disease
Cough in Children

- Important protective defensive mechanism, necessary for effective airway clearance
- Common symptom of respiratory disease
- Most common symptom for visit to MD office in US (3.4%)
- < 16 y/o (1st care) cough with RTI lasts 20 days
- Parents report cough-22% preschool children w/out URI
  - 10% school-age children w/out URI
  - Parental reporting of cough correlates poorly w/ objective measures (frequency, duration, intensity)
- Cough known to cause anxiety and depression in parents

Traditional Recognizable Cough Characteristics in Children

<table>
<thead>
<tr>
<th>Cough Characteristic</th>
<th>Suggested Underlying Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barking or brassy cough</td>
<td>Croup, tracheomalacia, habit/psychogenic</td>
</tr>
<tr>
<td>Honking or throat-clearing</td>
<td>Habit/psychogenic</td>
</tr>
<tr>
<td>Spasmodic/paroxysmal</td>
<td>Pertussis-like syndrome</td>
</tr>
<tr>
<td>(with or without whoop)</td>
<td></td>
</tr>
<tr>
<td>Dry, staccato</td>
<td>Chlamydia in infants</td>
</tr>
</tbody>
</table>

The Cough Reflex

- Vagal Airway Sensory Nerve
- Respiratory Motor Nerve
- Airway
- Respiratory Muscles
- Cough
Anatomy of the Afferent Limb of the Cough Reflex


\[ \text{↑ CRS vs. Airway Hyperreactivity (AHR)} \]

- ↑ CRS and AHR are independent physiologic responses
- ↑ CRS and AHR often co-exist
- ICS→ AHR; no ↑ CRS
- Inhibition Studies
  - Meds that affect bronchoconstriction (albuterol, atropine, cromolyn) reduce AHR, not CRS
  - Meds that affect CRS (lidocaine, oral codeine) have no effect on bronchoconstriction or AHR

Chang, MJA 2006; 184:398-403
Choudry, ERJ 1990; 3:579-83
Sheppard, ARRD 1983; 127:691-4

Cough Receptor Sensitivity in Acute Asthma

- 31 children with asthma, mean age 9 yrs; hosp w/ acute asthma
- Capsaicin test in hosp, 7-10 d, 4-6 wk
- Results: Some patients cough, some do not; no correlation CRS with FEV1

Chang, Thorax 1997
Cough Receptor Sensitivity in Children with Recurrent Cough, Asthma, and Cystic Fibrosis

Classification of Cough

ADULT
- Acute Cough- up to 3 weeks
- Sub-Acute Cough- 3 to 8 weeks
- Chronic Cough- > 8 weeks

ACCP Guidelines 2006

CHILDREN < 14 yrs
- Acute Cough- up to 4 weeks
- Chronic Cough- > 4 weeks

ACCP Guidelines 2006

Conditions Associated with Chronic Cough

Asthma Syndromes

Rhino-sinusitis (UACS)

Gastro-esophageal Reflux
### Etiology of Chronic Cough

<table>
<thead>
<tr>
<th>Condition</th>
<th>Irwin 1990 (n=102)</th>
<th>Kastelk 2005 (n=131)</th>
<th>Marchant 2006 (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNDS/UACS</td>
<td>41%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Asthma</td>
<td>24%</td>
<td>24%</td>
<td>4%</td>
</tr>
<tr>
<td>GERD</td>
<td>21%</td>
<td>22%</td>
<td>3%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>4%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Chronic Bronchitis/ COPD</td>
<td>3%</td>
<td>5%</td>
<td>PBB 40%</td>
</tr>
<tr>
<td>Post Infectious</td>
<td>-</td>
<td>8%</td>
<td>NR 22%</td>
</tr>
<tr>
<td>Big 3</td>
<td>86%</td>
<td>82%</td>
<td>9%</td>
</tr>
<tr>
<td>Multiple causes</td>
<td>26%</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td>Dx made/Improved</td>
<td>99%</td>
<td>93%</td>
<td>91%</td>
</tr>
</tbody>
</table>
Chronic Cough in Children

Prospective, cohort study to evaluate algorithmic approach to dx and tx

All children (<18 y/o) with chronic cough >3 weeks consecutively referred to Respiratory Clinic at Royal Children’s Hospital-Brisbane (6/02-7/04)

Exclusions --<37-week preemie
--known lung disease, neurodevelopmental abnormality, cardiac abnormality

108 children enrolled (57 female)
Median age 2.6 years
Median duration of cough 6 months
62% onset in first in 1st year
50% wet cough
Households with ETS 43%
Pre-study diagnosis - asthma 50%, no dx 32%, bronchitis 2%

Results
CXR 63% abnl – most peribronchial thickening
Spirometry (<4 y/o)–12% abnormal –1 with reversible airway obstruction
Bronchoscopy–90% macroscopic abnormal
57/95 bronchitis
36/95 malacia
BAL cell count–48% abnormal (most neutrophilia; 3% eosinophilia)
CSF
H. flu 47%, M. cel 20%, E. pneumo 35%
Lab
3 IgA deficiency
5 IgG2 deficiency
3 IgG > 1000 IU/mL
3 single, 4 F508 CF gene mutation
Sweat cl normal
pHmetry 17% abnl
Results cont'd.

Final primary diagnosis achieved in 91% n = 108

- Protracted bacterial bronchitis 40%
- Natural resolution 22%
- Asthma 4%
- 1st GERD 3%
- 2nd GERD (tx–no Δ cough) 15%
- UACS 3%
- Habit cough 1%

Chronic Cough in Children

Protracted bacterial bronchitis 40%

a) chronic wet cough
b) +BAL C&S- H. flu 47%, M. cat 26%, S. pneumo 35%
   (many > 1 organism)
c) response to Augmentin (45 mg/kg/day) x 2 + wks

Etiology of Pediatric Chronic Cough

<table>
<thead>
<tr>
<th>Marchant 2006 (n=108)</th>
<th>Edell 2007 (n=40)</th>
<th>Astley 2008 (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6 yrs</td>
<td>9.2 yrs</td>
<td>8.4 yrs</td>
</tr>
<tr>
<td>PNDS/UACS 3%</td>
<td>38%</td>
<td>26%</td>
</tr>
<tr>
<td>Asthma 4%</td>
<td>33%</td>
<td>44%</td>
</tr>
<tr>
<td>GERD 3%</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>Bronchiectasis 6%</td>
<td>-</td>
<td>3%</td>
</tr>
<tr>
<td>Infection PBB 40%</td>
<td>5%</td>
<td>PBB 35%</td>
</tr>
<tr>
<td>Post infectious 22% (NR)</td>
<td>-</td>
<td>2% (NR)</td>
</tr>
<tr>
<td>Idiopathic 9%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Big 3</td>
<td>9%</td>
<td>83%</td>
</tr>
<tr>
<td>Multiple causes -</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Dx made/improved 91%</td>
<td>90%</td>
<td>94%</td>
</tr>
</tbody>
</table>
Malacia in PBB

1. Marchant, Chang 2004 — 33% tracheo or bronchomalacia (5% broncheclasia)
2. Douros, 2011 — no mention
3. Zgherea, 2012 — 30% (<3 yrs)
4. Kompare, Weinberger, 2012 — 74%
5. DeBaets, 2012 — 46%

Using the pathophysiological model, protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD) and radiological bronchiectasis likely represent different ends of a spectrum. This is however speculative and yet to be confirmed. Untreated, it is likely that some (but not all) children with PBB will progress to develop CSLD.

Immune Evaluation in PBB

Marchant, Chang CHEST 2006

108 children median age 2.6 yrs.
3 IgA deficiency
3 IgG2 deficiency
3 single ΔF508 (sweat chloride normal)

Marchant, Chang Pediatr Pulm 2008

100 children median age 2.58 yrs.
Airway neutrophil and endobronchial infection — innate immune activation defect?

BAL: IL8, active MMP-9, TLR-2 & 4 mRNA expression
Immune Evaluation in PBB

Lim, AJDC February 2012

Retrospective review — all child with chronic wet cough (>8 wks) at Pulm Clinic (UK) over 12 mo

96 children — all normal IgG, neg sweat chloride
24/96 (>2 y/o) — Pneumovax II
-14/24 abnormal response — specific ab deficiency (Paris, Sorenson, 2007)
-All nl response to T dependent antigens — tetanus, and/or H. flu type B
-5/24 given Prevnar — all normal response

Conditions Associated with Chronic Cough

Asthma Syndromes

Rhino-sinusitis (UACS)

Gastro-esophageal Reflux

Upper Airway Cough Syndrome
(Postnasal Drip Syndrome)

- most common cause of chronic cough (41% Irwin, 1990)
- stimulation of afferent limb of cough reflex in upper respiratory tract
- causes:
  - allergic rhinitis
  - nonallergic rhinitis
  - vasomotor rhinitis
  - postinfectious (postviral) rhinitis
  - environmental irritant rhinitis
  - chronic bacterial sinusitis
CVA in Children

- Uncommon cause of chronic cough in studies by Chang at al. Asthma-like conditions found in only 4% of children in Marchant cohort.

  "children with asthma can certainly present with cough alone, but in most children cough in the absence of wheeze and/or dyspnea is rarely asthma." Chang J Allergy 2008; 39 Suppl:22

- Over-diagnosis and over-treatment of asthma in children with chronic cough—Chang.

- In children with asthma who cough, multiple studies showing no correlation between cough frequency/severity and asthma severity (wheezing/sxs, airway caliber (FEV1), airway reactivity)

Marchant, Chest 2006; 129:1132-41

Over-diagnosis and over-treatment of asthma in children with chronic cough—Chang.

In children with asthma who cough, multiple studies showing no correlation between cough frequency/severity and asthma severity (wheezing/sxs, airway caliber (FEV1), airway reactivity) van Asperen, Pediatr Resp Rev 2006; 7:26-30

Use of eNO to predict ICS response in chronic cough

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>+LR</th>
<th>-LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>eNO &gt; 35 ppb</td>
<td>95</td>
<td>80</td>
<td>88</td>
<td>91</td>
<td>4.9</td>
<td>0.07</td>
</tr>
<tr>
<td>eNO &gt; 38 ppb</td>
<td>90</td>
<td>85</td>
<td>90</td>
<td>85</td>
<td>5.8</td>
<td>0.12</td>
</tr>
<tr>
<td>MCT</td>
<td>66</td>
<td>46</td>
<td>64</td>
<td>48</td>
<td>1.2</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Hahn, Mayo Clin Proc 2007

GERD and Chronic Cough (Children)

- Prospective study: 3% GERD (50% > 10 yr). Marchant, 2006

  "in contrast w/ adults, little convincing evidence GERD cause of isolated chronic cough in children." Chang ACCP 2006

- 150 children (mean age 8.2 yrs) w/ chronic cough and GERD sx

- Few studies have shown benefit of PPI tx in children w/ GERD and chronic cough (or asthma): Chang Cochrane Review, 2000

- 87 children w/ asthma and cough (mean age 7 yrs) not on GERD tx; combined pH and impedance monitoring – 38% of cough episodes occurred w/in 2 min of reflux event; equal proportion acid, weak acid, non-acid. Mehta J. Nemours Children Clinic, NASPIAN 2006.
Post-viral Cough—Post-infectious Cough

- Very common cause of nonspecific cough
- More common in children vs. adults.
- Dry cough; due to increased cough receptor sensitivity
- Lasts up to eight weeks by definition (pertussis)
- Is not CVA
  - No response to beta agonist
  - Response to ICS only if increased AHR
- Patients may have associated dyspnea, wheeze, reversible airflow obstruction and positive meth PC20 due to transient, viral-induced AHR.

Habit Cough Syndrome

- Dry, repetitive cough; honking character (children)
- Irritative, disruptive-pt unperturbed
- Increases with attention; decreases with involvement in activity and with sleep
- tic disorders, Tourette syndrome
- Marchant 1%, Weinberger 4%; Irwin very rare, overdiagnosed
- Treatment
  - 15 minute suggestion-therapy session Weinberger, Pediatrics 2007
  - Self-hypnosis
  - Behavior modification Vertigan, Gibson, Chronic Respiratory Dis 2007

Algorithm for evaluating chronic cough in children
Algorithm for evaluating chronic cough in children (modified from Chang, 2006)

**SPECIFIC COUGH**

- Bronchiectasis or recurrent pneumonia
- Aspiration
- Chronic or less common infections
- Interstitial lung disease
- Airway abnormalities
- Other less common pulmonary conditions
- Cardiac disease

Assess risk factors for:

- Reversible airway obstruction?
  
  - Yes
  
  - No

Investigations as outlined

Or Consider referral to allergy or pulmonary specialists

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**Therapeutic Trials: When to Expect a Response**

- Smoking Cessation: up to 4 weeks
- ACEI Discontinuation: up to 4 weeks
- Postnasal Drip Syndromes: up to 2-4 weeks
- Asthma: up to 6-8 weeks
- GERD: up to 8-12 weeks
- Eosinophilic Bronchitis: up to 3-4 weeks

Don’t give up too soon!

*Original image reference: 11/2013 CSE1/10/21*
Other Concepts in Chronic Cough

- Obstructive sleep apnea
  - Cough can be the sole manifestation
  - CPAP can effectively resolve cough
  - Possible mechanism: upper airway inflammation
  - Epithelial injury or increase transdiaphragmatic pressure → LES insuff → GERD → cough
- Chronic tonsillar enlargement—upper airway inflam
- Hypothyroidism
- Vitamin B12 deficiency
- Iron deficiency

Chronic Cough Hypersensitivity Syndrome

1. Chronic cough duration > 2 months
2. Minimal or no sputum production
3. One or more cough reflex triggers (cold air, speech, eating, odors such as perfume)
4. Urge to cough (tickles or itch) located in throat area (laryngeal hypersensitivity)
5. Adverse impact of cough on QOL
6. Positive cough reflex challenge test (capsaicin)
7. Female predominance
Chronic Idiopathic Cough

Post-viral vagal neuropathy (PVVN) - laryngeal sensory neuropathy -
- Amin, Koulman, Belafsky
- Vagal nerve injury or dysfunction following an antecedent viral illness
- Post-viral neuropathy, i.e. Bell palsy, Guillain-Barré, post-herpetic neuralgia

Laryngeal dysfunction (VCD) in chronic cough - Vertigan, Gibson
- Chronic cough and throat clearing can cause chronic laryngeal irritation,
  which can predispose the larynx to be hypersensitive to external stimuli
  and trigger paradoxical vocal cord closure during inspiration (PVCM)

- Treatment - speech therapy

Irritable larynx syndrome - Bucca
- Laryngeal hyperreactivity (LHR) measurable via histamine inhalation challenge (PHIC)

Chronic Idiopathic Cough

Medical Treatment

- Pregabalin (Lyrica) - GABA analog - release of neurotransmitters
  75 mg b.i.d. over three to four weeks to 150 mg b.i.d. (familysynapse dose)
  Somnolence, dry mouth, blurred vision, dizziness.
- Gabapentin (Neurontin) - interacts with GABA receptors
  100 mg q.d. - 100 mg t.i.d. - 300 mg t.i.d. (slow increase over four weeks)
  Similar side effects as Pregabalin.
- Baclofen - weak GABA analog; decreased release of neurotransmitters
  10 mg q.d. x 1 week, b.i.d. x 1 week, t.i.d.
- Amitriptyline - TCA with sedative properties; serotonin, NE
  FDA approved - depression; used for atypical facial pain, IBS, pain/postherpetic neuralgia
  10-20 mg q.h.s.
- Duloxetine (Cymbalta) - also has anxiolytic effect and may interrupt neurotransmitters
  Start 30-60 mg/day
- Lidocaine 2-4% solution without ep. Nebulized 2 ml b.i.d.-q.i.d. with or without albuterol
  May be irritating to lower airways.
- Laryngeal anesthesia - supraglottic
- TRP antagonists