Mechanism of Cough Hypersensitivity Syndrome

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Chronic Cough Case

- 61 y/o non smoking, mildly obese female with ten years of continuous cough with onset after URI. Dry cough prompted by throat tickle and triggered by talking, scents/odors, and by changes in temperatures. Feels a post nasal drip but produces minimal mucus. Does not cough during exercise or at night unless awake.
- Cough can induce urinary incontinence. Feels socially isolated, anxious, and can be depressed. Family members and co-workers have expressed annoyance.
- Evaluated by primary care MD, two ENT’s, GI, Pulmonary and Allergy. Multiple diagnostic tests and unresponsive to multiple therapies including intranasal steroids, ipratropium bromide and antihistamines, inhalational steroids and bronchodilators, and courses of PPI’s.
- Finds throat lozenges and sipping on water helpful. Responds briefly to prednisone burst and codeine and hydrocodone.
Approach to Chronic Cough

- Looking for the etiology or “cause” of the cough
  - Paramount to identify conditions that are potentially life threatening
- Initial steps
  - Smoking, abnormal chest x-ray or ACE inhibitors
- Anatomic causation:
  - Upper airway, Lower airway, Gastro-esophageal, cardiac, Arnold’s reflex
- Intervention fidelity
  - extent to which an intervention was delivered as conceived and planned to arrive at valid conclusions concerning its effectiveness in achieving the target outcomes is important for reliably identifying or excluding potential conditions

Red Flags: Alarm Symptoms and Findings in Chronic Cough

- **Smoker** with >20 pack year smoking history
- Smoker over 45 years of age with a new cough, altered cough, or cough with voice disturbance
- Prominent dyspnea, especially at rest or at night
- Cough causing waking from sleep
- Substantial sputum production: more than one tablespoon a day
- Hoarseness and changes in phonation
- Gastroesophageal reflux disease symptoms other than throat symptoms
- Abnormal clinical respiratory examination
- Abnormal chest radiograph
- Systemic symptoms: fever, weight loss peripheral edema

The chronic cough that does not go away....

- **Refractory Chronic Cough** (RCC) is defined as a cough that persists despite guideline based treatment.
- **Unexplained Chronic Cough** (UCC) should be diagnosed if cough persists for longer than eight weeks with no etiology identified.
- Something else may be going on....
  - Many with GERD/Rhinitis/Asthma do not cough
  - Parameters and biomarkers do not identify those with GERD/Rhinitis/Asthma who cough from those who do not
  - GERD/Rhinitis/Asthma maybe a trigger rather that cause of some other process

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Cough Hypersensitivity Syndrome

- Common history of a cough triggered by low levels of thermal, mechanical, or chemical stimuli, including innocuous stimuli (allotussia)
- A sensation of itching or tickling in the throat (laryngeal paresthesia) accompanied by an urge to cough
- Increased responsiveness to tussive stimuli (hypertussia)
- This model is similar to neurogenic hypersensitivity seen in itch and pain and with cough and all share similar neurogenic pathways
- Evidence of central and peripheral neurogenic sensitization
- The mechanisms are most likely heterogeneous
The Cough Reflex/Response
Two overlapping pathways

- A-delta fiber rapid firing reflexes that are “primitive” protecting against mechanical and acid exposure that occurs awake and unconscious
- Type C fiber, slow firing afferents, triggered by chemical and sensory stimuli that disappears when unconscious. Produce inflammatory mediators (e.g., ATP) activating receptors (TRPV1, TRPA1 and P2X3) are located in upper and lower respiratory tracts, (esophagus and pericardium). These receptors can be sensitized
- Cough centers in mid-brain in with opioid, NK-1, P2X3 and NMDA receptors and can lead to reflexive cough. Will also communicate to higher cortex
- Higher cortical input
  - voluntary cough
  - urge-to-cough
  - cough suppression

Singh et al., Peripheral and central mechanisms of cough hypersensitivity
Thoracic Dis. 2020 Sep; 12(9): 5179–5193
Cough Suppression is decreased in Chronic Cough


Cough Hypersensitivity Mechanisms

- Assessing chronic coughers for autonomic dysfunction
- 96 chronic coughers and 76 controls assessing autonomic dysfunction
  - Excluded those with chronic respiratory diseases, diagnosed dysautonomic or neurologic diseases and neuromodulators
- COMPASS 32 SCORE
  - orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor
- Significant increase in chronic coughers in all domains except vasomotor which solely sympathetic
- Mechanism may be cough induced autonomic dysfunction vs associated autonomic dysfunction
- Dockery et al. ERJ Open Res. 2021 Jul; 7(3): 00105-20216
Cough Hypersensitivity
Mechanism

• Increased sensory airway nerve density in chronic cough
  • Analysis of bronchoscopy derived bronchial tissue
  • Nerve length and the number of branch points were significantly increased in epithelium, but not subepithelium, in chronic cough compared with healthy airways
  • Indicates the possibility of neuroplasticity of nociceptive type C fibers and triggered by either shearing forces on bronchial epithelium or inflammation e.g. ATP
  
  • Shapiro et al, AJRCCM.2021 Feb 1;203(3):348-355

P2X3 Receptors and Airway Sensory Nerves
Gefapixant
COUGH-1 AND COUGH-2

• COUGH-1
  • 12 week -62% reduction in 24 hour cough frequency compared to baseline
  • 18.45% reduction relative to placebo, 95% CI -32.92, -0.86; p=0.041
• COUGH-2
  • 24 week trial- 63% reduction in cough frequency, compared with baseline
  • 14.64% reduction relative to placebo, 95% CI -26.07, -1.43; p=0.031
• Placebo 55% and 57%
• Taste effect
  • Cough-1 and -2 respectively 58% and 69% of patients experienced taste-related adverse events. 15% and 20% of subjects, respectively, discontinued therapy because of adverse events.

The clinical presentation of cough reflex/response hypersensitivity

• Older women, mild obesity and associated with autonomic dysfunction
• Increased “urge to cough” or lower throat/upper chest sensation
• Cough increased with talking, irritants, drafts and diminishes during sleep(unless already awake) and exercise
• Complaints of “postnasal drip” but no minimal mucus production
• Rhinitis symptoms and minimal mucus as result of coughing
• Dysphonia and breathlessness may due to vocal cord hyperfunction
• May respond to neuromodulators
Summary

- Imperative to search for identifiable “cause” of chronic cough
- Chronic cough may be due to increased cough reflex/response hypersensitivity
- Cough Hypersensitivity Syndrome has identifiable clinical presentation
- Evidence is building, supporting central and peripheral mechanisms of CHS
- Emergence of promising cough neuromodulators such as P2X3 antagonists

• Song and Morice Allergy, Asthma Immunol Res. 2017 September;9(5):394-402.
Diagnostic Workup & Treatment Options for Chronic Cough: A Pulmonologist’s Perspective

Presented by:
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Professor of Medicine
Univ. of Massachusetts Medical School

Disclosures

- I do not have any financial relationships linked in any way to the contents of this lecture.
- I am a co-developer of cough severity and cough quality of life patient reported outcome measures that I will be mentioning.
- I will be mentioning the potential off-label use of a few medications
What Are The Outcomes Of Managing Chronic Cough?

Summary of Results of the Diagnostic Evaluation of Chronic Cough

- Chronic cough is often simultaneously due to more than 1 condition (18-93% of the time).
  - It has been due to 3 diseases up to 42% of the time.
  - Up to 4% of the time, it can be due to 5 conditions.
- While smokers have a cough, they have not been the group of patients who most commonly seek medical attention complaining of cough.
Summary of Results of the Diagnostic Evaluation of Chronic Cough

- In the US, in adults of all ages, upper airway cough syndrome (UACS) (previously referred to as postnasal drip syndrome), asthma, & GERD are the 3 most common causes of chronic cough.
- Worldwide, in prospective studies in adults, chronic cough is most commonly due to 6 disorders:
  - UACS due to rhinosinus diseases
  - Asthma
  - GERD
  - Chronic bronchitis
  - Bronchiectasis
  - Non-asthmatic eosinophilic bronchitis (NAEB)

Summary of Results of the Diagnostic Evaluation of Chronic Cough

- Chronic cough is likely due to UACS, asthma, NAEB, &/or GERD ~ 92% of the time in patients with the following profile:
  - Nonsmoker
  - Not taking an ACE inhibitor or sitagliptin
  - Normal/near normal and stable chest x-ray.
- Chronic cough is likely due to GERD ~ 91% of the time if asthma, NAEB & UACS are also ruled out.
- Chronic cough can be the sole presenting manifestation of asthma and GERD up to 57% and 75% of the time respectively.
  - Methacholine inhalation challenge and 24-hour esophageal monitoring (pH-impedance), and, uncommonly, barium esophagography, have been singularly useful in diagnosing these conditions.

Summary of Results on the Outcomes of Managing Chronic Cough

• Based upon a systematic review of 23 studies published in 2015 that analyzed all articles in which the authors stated that they followed an evidence-based guideline, treatment failures (i.e., unresolved cough) averaged 10% (382/3636).
  – 17 uncontrolled, prospective, before and after observational studies
  – 2 RCTs
  – 4 retrospective, before and after observational studies

Possible Explanations for Treatment Failures

• Physician-related issues
  – Failure to use or faithfully follow the most recent validated protocol
    • Intervention infidelity
    • Treating GERD with acid suppression alone

• Patient-related issues
  – Failure to follow recommendations
    • Intervention infidelity

• The diagnosis is correct but cough is refractory to prescribed treatment regimen(s)
  – Treating GERD with acid suppression alone

• The patient has a truly unexplained cough
  – Cough Hypersensitivity Syndrome
The Chronic Cough Hypersensitivity Syndrome

• “A disorder characterized by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure.”
  ➢ An overactive cough reflex
  ➢ Sensory (vagal) neuropathic cough
• Most patients report abnormal sensations in the pharynx or larynx, such as a tickle or itch, or uncontrollable urge to cough.
• Consider it only when chronic cough is refractory to all treatments or unexplained after an evidence-based workup has been faithfully followed because assessing for its presence has been of limited value.
  • Only present in minority of patients
  • Seen in a variety of causes
  • In predicting outcome of treating the variety of causes


How Should Clinicians And Researchers Approach The Chronic Cough Problem?
Important Reminders in Managing Chronic Cough

**Important Reminders**
- Check for red flags and address them—see Red Flags box.
- Optimize therapy for each diagnosis.
- Check compliance during regularly scheduled and frequent follow-ups (assess for patient barriers to enrollment or receipt of instructions).
- Due to the possibility of multiple causes, maintain all partially effective treatment.
- Routinely assess for environmental and occupational factors.
- Routinely assess cough severity & quality of life with validated tools.
- Routinely follow up with patient in 4-6 weeks.
- Consider referral to a Cough Clinic for refractory cough.

**Red Flags**
- Hemoptysis
- Smokers > 40 years of age with a new cough, change in cough, or existing 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.
- Pruritus, especially at night.
- Hoarseness
- Systemic symptoms
  - Fever
  - Weight loss
  - Peripheral Edema with weight gain
  - Trouble swallowing when eating or drinking
  - Vomiting
  - Recurrent pneumonia
  - Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough.
Validated and Reliable Cough Severity and Cough QoL Instruments

French CL. [Link]

What Is The Next Step In Managing The Patient With A Chronic Cough That Appears To Be Refractory To All Treatments?

Consider Pitfalls in Management

• Upper Airway Cough Syndrome (UACS)
  – Failing to recognize that it can present as a cough-phlegm syndrome
    • Misdiagnosed as chronic bronchitis
  – Assuming that all H$_1$ antagonists are the same
    • Those without anticholinergic activity are not likely to be helpful in non-allergic rhinosinus conditions.
    • Those with anticholinergic activity may adversely affect memory, glaucoma, and prostate problems.
      – Consider ipratropium bromide nasal therapy
  – Failing to consider that this diagnosis can be “silent” up to 20% of the time

Consider Pitfalls in Management

• Upper Airway Cough Syndrome (UACS)
  – Failing to consider allergic rhinitis and failing to recommend the avoidance of allergens because symptoms are perennial
  – Failing to consider sinusitis because it is not obvious
  – Failing to consider aspirin-exacerbated disease
  – Failing to consider the usefulness of upper respiratory endoscopy
Consider Pitfalls in Management

• Asthma
  – Failing to recognize that it can just present as cough (cough-variant asthma) or as a cough-phlegm syndrome
  – Failing to recognize that inhaled medications may exacerbate cough
  – Assuming that a positive methacholine challenge alone is diagnostic of asthma

• Non-asthmatic eosinophilic bronchitis
  – Failing to consider the diagnosis, order the correct test, or consider occupational/environmental causes


Consider Pitfalls in Management

• Gastroesophageal Reflux Disease (GERD)
  – Failing to recognize that it can present as a cough-phlegm syndrome
  – Failing to recognize that “silent” reflux disease can be the cause, that it may take 2-3 months of intensive medical treatment before cough starts to improve, and, on average, 5-6 months before cough resolves
  – Assuming that cough cannot be due to GERD because cough remains unchanged when gastrointestinal symptoms improve
  – Assuming that one can reliably make the diagnosis of GERD based upon the appearance of the vocal cords
Consider Pitfalls in Management

- Gastroesophageal Reflux Disease (GERD)
  - Failing to recognize that co-existing diseases or their treatment may be making GERD worse
    - Obstructive Sleep Apnea
    - Rx for coronary artery disease or hormone replacement
  - Not being aware that acid suppression alone will not improve cough
  - Failing to consider non-acid reflux disease
  - Failing to consider the importance of diet, avoiding intense exercising, and prokinetic therapy
  - Failing to treat adequately co-existing causes of cough that perpetuate the cycle of cough and reflux

Consider Pitfalls in Management

• Triad of UACS, asthma, and GERD
  – Failing to consider that more than one of these conditions may be contributing simultaneously to cough
  – Failing to consider these common conditions because of another “obvious” cause (e.g., IPF)
  – Failing to appreciate that these chronic conditions cannot be cured at this time and will periodically flare especially with colds
    • When cough flares after a period of remission, re-evaluate the cough as if it is a new problem
    • Asthma may become a problem when it wasn’t before

• Unsuspected airway diseases
  – Failing to perform bronchoscopy when chest radiograph and CT are normal
    • Transnasal route allows inspection of upper and lower respiratory tracts
  – Failing to appreciate that IV therapy for suppurative airway disease for prolonged period of time may be successful when the same drug given orally failed

**What Management Options Are Available For The Truly Refractory Unexplained Cough?**

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<th>Management Options</th>
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<td>Referral to a cough clinic</td>
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<td>Speech pathology therapy</td>
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<tr>
<td>Opiates</td>
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<tr>
<td>? nebulized local anesthetics</td>
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<td>Off label use of drugs</td>
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</table>
  - Gabapentin. pregabalin |
  - ? Amitriptyline  
    - Blocks muscarinic cholinergic and H₁-histaminergic receptors |
| Consider treating symptoms of depression/anxiety |
Speech Language Pathology Intervention for Chronic Cough

Monica Shaffer, MA, CCC-SLP

Learning Objectives

1. Understand foundations of SLP intervention for refractory chronic cough

2. Understand appropriate referrals to SLP for refractory chronic cough

3. Be able to explain to a patient why you are referring them to speech therapy for their cough
Laryngeal hypersensitivity cough

Education & Counseling

Cough control techniques

Voice therapy

Home practice
Education & Counseling

- Nature of the cough
- Laryngeal hygiene
- Internalize control

Home practice

Education & Counseling

Laryngeal hypersensitivity cough

Voice therapy

Cough control techniques
Cough Control Techniques

- Cough control breathing
- Cough control swallowing
- Distraction

Home practice

Education & Counseling

Laryngeal hypersensitivity cough

Voice therapy

Cough control techniques
Voice Therapy

Resonant Voicing

Conversational Training Therapy

Laryngeal hypersensitivity cough

Home practice
Voice therapy
Education & Counseling
Cough control techniques
Home Practice

- Daily log
- Breathing practice
- Voice practice

- Frequency and severity
- Rating of success
- Urge to cough
- Leicester cough monitor

