Disclosures

No financial disclosures

I am a chronic cough (dys)enthusiast and have a love-hate relationship with chronic cough management
Guidelines

- American College of Chest Physicians Guidelines
  - Original Irwin et al. CHEST 2006
  - Updated Irwin et al. CHEST 2014, 2018
  - Cough and GERD Kahrilas et al. CHEST 2016
  - Unexplained Chronic Cough Gibson et al. CHEST 2016

- European Respiratory Society Guidelines
  - Morice et al. ERJ 2019

- British Thoracic Society Clinical Statement
  - Parker et al. BTS 2022

To cough or not to cough....

Cough
physiologically defined as a defensive respiratory response with a stereotypical motor pattern comprising of:

1) brief inspiration
2) expiration against a closed glottis (compression phase)
3) large expulsive airflow following glottis re-opening

Usually occurring through coordinated neural activity in the brainstem in response to an irritant stimulus within the airways (i.e. reflex cough)
Definitions

- Acute: <3 weeks
- Subacute: 3-8 weeks
- Chronic: >8 weeks


- Chronic Refractory Cough – Persistent cough despite treating known causes
- Unexplained Chronic Cough – >8 weeks with investigation + failed treatment

Gibson et al. Chest 2016

Epidemiology

- Prevalence
- Risk
- Burden

Prevalence in Pulmonary Clinic

Activities of Daily Living
Troublesome Symptoms
Social Isolation

Song et al. ERJ 2015

Anatomical Approach to Chronic Cough:

- Asthma
- Upper airway symptoms
- GERD

Treat 1 or ALL (sometimes regardless of symptoms)

Shift toward identification of treatable traits

- Cough Hypersensitivity
- Tobacco/irritants
- ACE-I
- Rhinosinusitis
- Type II airway inflammation
- Parenchymal lung disease
- Esophageal Symptoms
- Sleep apnea

Adapted Song et al. Asia Pac Allergy 2019, Parker et al. BTS 2022
Neural Regulation of Cough

Cough hypersensitivity: disordered neural state

**Allotussia**
Innocuous stimuli not sufficient to cause cough in normal circumstances can trigger
- E.g., the wind, laughing, change in ambient temperature, taking a deep breath, talking on the phone

**Hypertussia**
Smaller amounts of cough-inducing stimuli can trigger cough
- E.g., Smoke, irritants, allergens, fumes
Approach to Chronic Cough in 2023

History and Examination
- Quantify burden of cough
- Identify treatable traits* or risk factors (smoking, lung disease)
- Exclude red flags

Treatment
- Trait based therapy
- Limited therapeutic challenge (i.e., 4-6 wks)
- ?response -> continue, d/c if none

Address Cough Hypersensitivity
- Neuromodulators
- Speech language therapy

*predictability of certain traits for clinical response is not straightforward, few highly sensitive or specific tests/biomarkers to predict response to therapy

Cough with Eosinophilic/Type-2 inflammation

Type II Inflammation
- Inflammatory endotype best characterized in asthma
- Typically (not always) allergen associated
- Characterized phenotypically by elevated Eosinophils, FeNO, and IgE

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Cough Variant Asthma</th>
<th>Non-asthmatic Eosinophilic Bronchitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Cough, SOB, wheeze</td>
<td>Cough only</td>
<td>Cough only</td>
</tr>
<tr>
<td>Atopy</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Sputum Eosinophils</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Airway Hyper-responsive (i.e., Methacholine)</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ICS Response</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Cough with Eosinophilic/Type-2 inflammation

**DIAGNOSIS**
- Often defined by response to therapy
- Sputum eosinophils
  - >3% eosinophils in sputum,
  - Not available at Michigan Medicine
- FeNO >25 ppb or blood eosinophilia >0.3
  - FeNO has reasonable specificity (~85%) for Cough Variant Asthma (optimal cut-off not determined)
- Allergy testing – respiratory allergen panel, skin prick
  - IgE levels of common environmental allergens (RAST)
  - Total IgE level (RAST)
- Bronchial provocation testing – not routinely
  - Used in many centers, though opinions vary on utility
- Bronchodilator response – not routinely
  - Low negative predictive value, especially in those with normal lung function

**THERAPY**
- Medium to high dose ICS for 4 weeks
  - Assess response and continue for several months
  - If no response, discontinue
- Consider LTRA (e.g., montelukast, zafirlukast) for asthmatic cough/cough variant asthma for 4 weeks
  - If clinical asthma present or develops over time, treat per GINA guidelines
  - Consider advising trigger avoidance for clear allergies
  - In COPD with cough, eos >0.3 – consider LABA/ICS trial

Morice et al. ERJ 2019, Song et al. JACI 2017

Empirics ICS and Placebo Suppression

Placebo effect in chronic cough is real (and neurally mediated).

Response to therapy may not be a reliable indicator of underlying pathophysiology.

Thus, short duration therapeutic trials with response to therapy assessments are best to prevent over treatment.

Lee et al. Allergy, Asthma, Immunol Res 2019
Neurally mediated suppression of urge-to-cough: Placebo Suppression

Leech et al. AJRCCM 2013

Cough with Esophageal Symptoms – GERD

DIAGNOSIS

- Heartburn and regurgitation – two most reliable symptoms for making diagnosis
- In the absence of peptic symptoms, 24-h pH monitoring unhelpful
- 24h pH/impedance monitoring
  - if peptic symptoms persist despite treatment and surgery is being considered
  - if GERD diagnosis is in question (near 100% NPV)
  - Should be performed with manometry for evaluation of dysmotility if surgery planned
- Barium swallow has poor sensitivity for GERD
- EGD has poor sensitivity for GERD
- Laryngoscopy findings are not helpful for the diagnosis of reflux

THERAPY

- Do not start empiric PPI in patients without acid reflux
- PPI (e.g., 20mg BID – up to 40mg BID) trial 4-8 weeks to improve GERD symptoms, may take up to 3 months to improve cough – if no response discontinue
- Life-style management
  - Weight loss
  - Avoidance of fatty food 3 hr before bed
  - HOB elevation
  - Food avoidance
- GI referral for:
  - Age >50, 5-10 years of symptoms, obese, male
  - Red flags – weight loss, dysphagia, bleeding
  - Refractory to therapy
  - Surgical referral for cough and proven GERD refractory to PPI therapy → pH-manometry

Kahrilas et al Chest 2016, Katz et al. AJG 2013, Morice et al. ERJ 2019
Cough with Esophageal Symptoms – Dysmotility/Aspiration

**DIAGNOSIS**
- Modified Barium Swallow/VFSS
  - Dysmotility may be detected with poor sensitivity
  - Will identify laryngeal aspiration
- Esophageal manometry
  - Best test for dysmotility

**THERAPY**
- Diet modification
- Speech therapy
- Promotility agents (baclofen, metoclopramide, domperidone) have not been evaluated by RCT
- Consider GI referral if considering promotility agents

Upper Airway Cough Syndrome

“Post-Nasal Drip Syndrome”: most patients with purulent nasal secretions do not complain of chronic cough*  

J. O’Hara, N.S. Jones

*Department of Otorhinolaryngology, Head and Neck Surgery, Freeman Hospital, Newcastle upon Tyne, United Kingdom

<table>
<thead>
<tr>
<th>Nasal Symptom</th>
<th>Percentage (no.) of patients with the symptom, with no history of coughing (n=45)</th>
<th>Percentage (no.) of patients with the symptom, with a history of coughing (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-nasal secretions</td>
<td>87% (39)</td>
<td>96% (22)</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>61% (27)</td>
<td>57% (12)</td>
</tr>
<tr>
<td>Anosmia or Hyposmia</td>
<td>74% (36)</td>
<td>91% (21)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>20% (17)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>67% (37)</td>
<td>57% (13)</td>
</tr>
</tbody>
</table>

Figure 2. Summary of nasal symptoms recorded for patients with purulent nasal secretions.

- The idea that nasal secretions cause cough is controversial
- Most patients with rhinitis (allergic or non-allergic) do not have cough as a symptom
- Emerging idea in the last 5-10 years that nose/throat symptoms may sensitize the cough reflex
  - Nasal histamine does not trigger cough in normal healthy adults, but does increase cough sensitivity to capsaicin
  - Cough reflex threshold is reduced in patients with allergic rhinitis.
  - Patients with UACS have increased cough sensitivity to capsaicin and increased lower airway inflammation compared to those with rhinosinusitis without cough

Cough with Upper Airway Symptoms

**DIAGNOSIS**
- Rhinitis, post-nasal drainage, throat irritation, anosmia, nasal itching
- Allergy testing – respiratory allergen panel, skin prick via allergy
- Laryngoscopy – not routinely recommended
  - Erythema and inflammation have poor sensitivity/specificity for specific pathology
  - Recommended for prominent laryngeal symptoms (e.g., hoarseness, dysphonia, throat tightness)
- Rhinoscopy – not routinely recommended
  - Useful for polyps, pre-surgical evaluation for chronic rhinosinusitis refractory to treatment or anatomic issues suspected
- CT Sinus – not routinely recommended
  - Mucosal thickening often not directly associated with cough or response to therapy
  - Patients refractory to treatment or with concern for recurrent acute/chronic bacterial sinusitis

**THERAPY**
- Allergic rhinitis (IgE mediated)
  - ± Nasal saline irrigation
  - Intra-nasal corticosteroid or anti-histamine, both if severe
  - Second generation anti-histamine
  - LTRA second line
- Non-allergic rhinitis (non-IgE mediated)
  - ± Nasal saline irrigation
  - Intra-nasal corticosteroid or anti-histamine, both if severe
- Anterior rhinorrhea
  - Intra-nasal anticholinergic
- Trigger avoidance
- Consider referral to allergy and/or rhinologist if persistent nasal symptoms

---

Obstructive Sleep Apnea – a tertiary care center experience

<p>| Initial snoring: Combinations of diagnoses in patients with chronic refractory cough. |
|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
<th>OSA</th>
<th>BS</th>
<th>BPH</th>
<th>EEM</th>
<th>GER</th>
<th>AERF</th>
<th>Asthma</th>
<th>COPD</th>
<th>Bronchitis</th>
<th>VCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>54/64</td>
<td>64%</td>
<td>Obstructive Sleep Apnea</td>
<td>–</td>
<td>43</td>
<td>25</td>
<td>31</td>
<td>30</td>
<td>30</td>
<td>19</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>27/99</td>
<td>78%</td>
<td>Rhinitis</td>
<td>25</td>
<td>27</td>
<td>–</td>
<td>20</td>
<td>16</td>
<td>14</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/42</td>
<td>68%</td>
<td>Obstructive Sleep Apnea</td>
<td>31</td>
<td>20</td>
<td>–</td>
<td>20</td>
<td>18</td>
<td>10</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>57/86</td>
<td>68%</td>
<td>Sleep Apnea</td>
<td>31</td>
<td>20</td>
<td>–</td>
<td>20</td>
<td>18</td>
<td>10</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>54/64</td>
<td>63%</td>
<td>Rhinitis</td>
<td>31</td>
<td>20</td>
<td>32</td>
<td>–</td>
<td>20</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>68/85</td>
<td>75%</td>
<td>Rhinitis</td>
<td>30</td>
<td>20</td>
<td>18</td>
<td>25</td>
<td>–</td>
<td>21</td>
<td>0</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>28/99</td>
<td>28%</td>
<td>Obstructive Sleep Apnea</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20/99</td>
<td>20%</td>
<td>COPD</td>
<td>15</td>
<td>16</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>26/99</td>
<td>25%</td>
<td>Bronchitis</td>
<td>13</td>
<td>16</td>
<td>8</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>3/99</td>
<td>3%</td>
<td>Vocal Cord Dysfunction</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Good et al. Resp Med 2018
Speech Therapy – Cough Control/Mitigation

- Trial of cough control therapy recommended in all adults with Chronic Cough
- Two RCTs - UCC/CRC-type patients
  - Typical chronic cough traits with failure to respond to typical therapy
  - Intervention: Education, laryngeal hygiene, cough control over multiple sessions 4-wk to 2-mo
  - Improved cough scores in both studies
  - Unclear if improvements are durable/lasting
- SLP or Oto Vocal Health (Multi-D Clinic – laryngology and SLP) referral at MM


Neuromodulation

- Gabapentin 300mg daily titrated to max 1800mg in two divided doses over 6 days (Ryan et al. Lancet 2012)
  - Single RCT, n=62, randomized to placebo or gabapentin
    - Improved cough frequency, cough-related quality of life
    - NNT=3.58 for clinical benefit based on cough-related quality of life
    - SE nausea and fatigue
  - Most treatment course last 6 months, Goal highest tolerable dose with most efficacy/least SE
- Pregabalin 300mg daily + SLP (Vertigan et al. Chest 2016)
  - Single RCT, n=40, randomized to placebo or pregab – all received SLP
    - Improved cough-related quality of life, cough severity
    - No reduction in cough frequency.
- Low dose morphine 5-10mg BID (Morice et al. AJRCCM 2007)
  - Single RCT, n=27, 4 weeks – each patient placebo and morphine
    - Reduces cough severity by 1-2 points
    - Improved cough-related quality of life
    - SE constipation, drowsiness
- Superior Laryngeal Nerve Blockade (observational, small trials) – available at MM
  - TCA – amitryptiline, often discontinued due to SE profile in real world practice
  - SNRI – Duloxetine
  - Nebulized/Spray Lidocaine (Lim et. al Chest 2013, Abdulqawi et al. JACI 2020)
Chronic Cough Drugs in the Pipeline

- **Purinergic 2X3 Receptor Antagonists**
  - Gefapixant  (Phase 3 – declined by FDA in 2022 for more data)
  - BLU-5937  (Phase 2-3 ongoing)
  - Sivopixant  (Phase 2 ongoing)
  - Eliapixant  (Phase 2 – development halted due to DILI)
- **SE - dysgeusia**
- **Extended release mixed κ- agonist/ μ- antagonist opioid receptor**
  - Nalbuphine – 77% reduction in cough events in IPF (CANAL Trial 2022, stopped early for efficacy)
- **Neurokinin-1 Receptor Antagonists**
  - Orvepitant  (Phase 2, not promising)
- **Voltage-gated Sodium Channel Blockers**
  - Phase 1 and early phase 2 studies

Chronic Cough Initial Evaluation

- History taking and physical examination on presentation
  - Cough duration
  - Cough impact and triggers
  - Family history
- Cough score using VAS or verbal out of 100
- HARG
  - Associated symptoms: throat, chest, gastrointestinal
  - Risk factors: ACE inhibitors, smoking, sleep apnoea
  - Physical examination: throat, chest, ear

Initial management!
- Stop modulators
- Include corticosteroids (oral or inhaler) or LTRA, particularly when \( F_{E_{NO}} \) or 
  - Inhaled high dose PPI only when persisting symptoms or evidence of acid reflux and present

Follow-up assessment for cough
- Cough score using VAS or 0-100
- Associated symptoms

No improvement
- Consider low-dose opioids
- Consider proinflammatory
- Consider gabapentin
- Consider cough control therapy

Improvement
- Continue for 3 months and attempt withdrawal
- Additional evaluation where indicated
  - High-resolution esophagogastroduodenoscopy
  - Indocyanine green camera
  - CT scan

Morie et al. ERJ 2019
### History taking

#### Examination

**Routine Investigation**

- **General assessment:**
  - **Duration**
  - **Severity 1-10 scale**
  - Complications – e.g., incontinence, loss of sleep/work, relationships
  - Triggers/degree of hypersensitivity
  - Prior treatments/efficacy/adherence

- **Ask specifically:**
  - Heartburn and Regurgitation
  - Nasal/laryngeal symptoms
  - Chest symptoms (SOB, wheeze)
  - Productive cough

- **Prior specialist evaluations**

- **Exclude:**
  - red flags
  - treatable lung disease, TB risk
  - risk factors (smoking, ACEi, OSA)
  - Other medications: bisphosphonates, CCB may worsen GERD, NCEAD, clonidine, methyldopa, PDE-5 inhibitors may worsen rhinitis

- Spiro, CXR

- Consider: FeNO, blood eos, IgE

- **Goal:** Categorize cough by duration

- **Identify treatable traits**

- **Identify UCC/CRC**

- **Triage urgency of treatment/suppression**

### Initial Visit Treatment

#### Guidelines:

- **Trial ICS – mod or high dose**
- **Trial PPI – mod or high dose**

### Follow-up

#### Assess:

- Response and Adherence

- **Specialists:**
  - Laryngology – prominent laryngeal/pharyngeal symptoms
  - Rhinology – prominent sinus symptoms, recurrent sinus infections

- **Diagnostic studies:**

- **Consider:**
  - ACEi cessation
  - Smoking cessation – warn re: increased cough in first mo
  - OSA tx or optimization
  - Nasal therapies – nasal rinses, nasal ICS/AH, oral AH
  - LTRA for asthmatic cough, CVA
  - Multi-modal therapy in UCC/CRC
  - Referral to specialist if UCC/CRC
  - Cough suppression: SLP or neuromodulation in hypersensitive* patients with UCC/CRC*

#### Goal:

- **Treat treatable traits**

- **Reduce delays in care by recognizing UCC/CRC**

**Questions?**