5 & a Half Cases of Chronic Cough

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Disclaimers

• No conflict of interest

• I am not crazy

• Will mention medications not FDA approved for chronic cough
Goals

• Some clinical pearls on chronic cough

• Updates on chronic cough mechanisms

• Convince you cough is sexy
A Case of the Tough Mucus

- 60 yo woman P.S., RN, never smoked
- Cough x 15 years, following a LLL pneumonia
  - Severe paroxysms that persist until it results in 1 or 2 pieces of very dry, tenacious mucus, then she has a period of relief that can last half a day or more
- Mayo Manchester questionnaire
  - Day VAS 9/10, Night VAS 7/10
  - CSQLQ 80/112 ~ Miserable
    - Missing work, pre-syncopal, dry heaves, urine incontinence, hoarse voice, hurts to breathe, sleep disrupted, can't speak on the phone, socially disruptive, fatigued/exhausted
Prior Testing

• Bronchoscopy with some mild mucus (not casts)
• HRCT chest read as normal
• PFT with methacholine negative, negative exhaled NO
• CT sinus: mild inflammation
• Allergy testing positive: grass, cats, dogs, pollen, molds
• EGD with BRAVO probe negative
• CPET
• Cardiac MRI, ?sarcoid
• V/Q test, PA catheterization
• Autoimmune serologies (neg.), lip biopsy → Sjogren’s
• Immunoglobulins, HIV negative
• Therapeutic challenges:
  • Inhalers, steroids, antibiotics, immunotherapy, CPAP, chronic macrolide, flutter, VEST, gabapentin, TCA, roflumilast, speech therapy
What am I supposed to do now?
No diagnosis?

• Diagnosis: A cough that is trying to clear impacted mucus

• Treatment:
  • Counseling (lots…)
  • Secretion mobilization
    • Airway hydration: 7% hypertonic saline
    • Oscillatory PEP
    • +/- VEST
    • Future?: macrolides

• 3 months follow-up
  • 90% better.
  • CSQL 42
Non-CF Bronchiectasis

• Classic
  • Chronic cough with copious muco-purulent sputum
  • Recurrent pneumonias, Constitutional symptoms
• Non-classic ?
  • Cough +/- minimal sputum

• Radiographic criteria
  • Broncho-arterial ratio (Signet Ring)
    • Normal 0.65-1, Intermediate 1-1.5, Bronchiectasis >1.5
  • Airway within 1 cm of pleura
  • Non-tapering airways: Tram Track
  • Thickened walls, Air-trapping, Mucoid impaction, Atelectasis
Non-CF Bronchiectasis

• Treat underlying condition?
  • ?MAC
  • ?Obstructive lung disease
  • ?Aspiration

• Bronchial hygiene
  • Airway hydration: Saline nebs
  • Secretion mobilization: Oscillatory PEP, VEST/CPT, etc.

• +/- Reduce inflammation & mucus generation: mucolytics, inhalers, antibiotics
Sjogrens

• Chronic cough is leading symptom
  • ~41-50%

• Airway
  • Bronchiectasis, bronchiolitis

• Interstitial
  • NSIP, UIP, LIP

• Lymphoproliferative, +/- amyloid
  • LIP ~ Cystic lung disease with Nodules

• Xerotrachea
  • Dry cough, dry respiratory mucosa, no other physiologic or radiographic abnormality
  • ?Cevimeline/pilocarpine, airway hydration, biotene products...
“Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis”

- 7% saline vs Isotonic saline in Non-CF bronchiectasis
  - Randomized, cross-over design for 3 months, 1 month washout
- Significant improvements in
  - FEV1: 15.1% change vs 1.7% change (p<0.01)
  - FVC: 11.2% change vs 0.7% change (p<0.01)
  - Antibiotics /yr: 2.4 vs 5.4 (p<0.05)
  - Exacerbations /yr: 2.1 vs 4.9 (p<0.05)
  - QOL:

![Graph showing improvements in SCQS score](image)
Lesson’s (for me)

- Sometimes making a diagnosis doesn’t really matter
- Bronchiectasis is a spectrum of disease
- Invest in hypertonic saline?
- Sjogren’s commonly manifests with chronic cough
Proton pump inhibitors galore

- 69 yo F (DM), Cough for 15 years
  - Minimal occasional white mucus
  - Severe and disruptive with CSQL 80/112
  - No reflux symptoms: i.e. heartburn, regurgitation

- Prior Testing
  - CXR, allergy test (cats), EGD (gastritis), ENT, sinus CT

- Treatments
  - High dose BID PPI’s +H2, systemic steroids, inhalers, allergy shots, nasal sprays & rinses

- Testing
  - HRCT chest (h/o melanoma) ⇒ Incidental micronodules, proving stable
  - Normal PFT (negative methacholine at 25mg/mL)
  - Impedance-pH study
Impedance-pH (off meds)

- DeMeester 18.6
- Reflux events: 115 episodes/24hr:
  - Acid 85, Non-acid 30
- Symptoms
  - 9 Heartburn or regurgitation, all of which 4 were acid reflux related
  - 276 coughs
    - 178 were reflux related (Symptom index of 64%)
      - 147 acid reflux related
      - 51 non-acid reflux related
  - SAP (Symptom association probability)
    - All reflux, 100%
      - Acid reflux, 100%
      - Non-acid reflux, 100%
MII-pH (multichannel intraluminal impedance-pH)
**GERD pathophysiology**

- **Gastric juices reflux into the esophagus**
  - Transient lower esophageal sphincter relaxations (TLESR)
  - Increased gastric-esophageal pressure gradient
  - EGJ: LES/Crural diaphragm

- **Diagnosis?**

- **Treating with PPI’s…**
  - Non-acid reflux matters…

(DeMeester. GI Surg 2004;8:888–96)
Is the **apparent relationship** between reflux and cough occurring more than just by **chance** alone?
SAP: symptom association probability

• 2x2 contingency table of reflux to cough relationships
  • Fisher’s exact test on the contingency (i.e. p value)
  • SAP is the 1-p value x100.

• SAP >95% is considered temporally associated more than by chance alone

• Fallacies
  • The “window”
  • The patient underestimates cough episodes
  • Impedance-pH catheter can suppress cough
  • The mathematics & the algorithmic calculation of the SAP is actually not quite as mathematical as sold
So what to do after high dose PPI/H2?

- Reduce gastric-esophageal pressure gradient
  - Lifestyle/behavioral
  - Weight loss, Non-constraining clothes, Head of bed, meal size/type, ...
  - Possibly drugs in future (pro-motility)
- TLESR
  - Baclofen (off-label), centrally acting, observational studies only
  - Baclofen analogues (clinical trial)
- Liquid alginate suspension?
  - Small RCT for LPR shows benefit (McGlashan, Eur Arch Oto. 2009 Feb)
  - Hydrocolloid polymer barrier
  - Reflux barrier to acid & can bind pepsin/bile
Lessons (for me)

- Reflux can truly be asymptomatic
- Reflux is not a problem of excess acid
- PPI’s are not the end-all of reflux
- Impedance based testing with temporal association studies may give you better logic or the value of interventions or not
Out there treatment for cough

- 40 yo F (JE), spouse of a physician, never smoked, h/o IBD
- 2 years of chronic cough with copious green sputum, day & night, severe & disruptive (CSQL 84/112)
- Severe reflux symptoms with regurgitation episodes at night, with confirmed reflux by BRAVO and MII-pH study
  - 60% proximal, 33% non-acid
- CT chest with mild airway dilation with borderline thickening, but prominent air-trapping on expiratory views
- PFT normal, with negative methacholine, normal ENO
- Multiple sputum negative, 3 bronchoscopies
- ENT exams neg., Allergy test neg., CT sinuses normal
- P-ANCA positive, but no evidence clinical CSS, MPA, etc. Attributed to her IBD
Failed and Tried

- OTC meds
- Decongestants, antihistamines
- Steroids
- Antibiotics, macrolides
- Steroids
- Inhalers
- Lidocaine nebulizers
- PPI, hi doses
- Tussionex does give some relief to allow sleep
Reflux surgery?

- **Reflux?** Yes!
  - EGD, BRAVO DeMeester 40

- **GI Symptomatic Reflux?** Yes!
  - Heartburn, regurgitation

- **Resp. Reflux related?** Maybe…
  - 5 episode of cough… (SAP neg.)
  - But the CT’s c/w aspiration?
Nissen fundoplication

- Complete resolution of heartburn, regurgitation, nocturnal aspirations

- Complete resolution of cough....
  - For a couple weeks
  - Then returned...

- Now what?
**Post-fundoplication**

- Confirmed fundoplication intact
- Stepwise therapeutic challenges repeated
- Bronchoscopy performed of our own twice:
  - “Significant copious mucopurulence throughout airways, consistent with acute infection”
  - Repeated myself, with biopsies, including EM studies
  - BAL sterile, neutrophil predominant
- Treated as if primary bronchiectasis syndrome
  - Airway hydration, Secretion mobilization, anti-inflammatory
  - Treat primary disease? Post-aspiration?
Inflammatory Airways Disease?

- Hypersecretory airway disorders
  - COPD
  - Asthma
  - Bronchiectasis
  - Eosinophilic bronchitis
  - Ciliary disorders
  - Cystic fibrosis
  - ? Microaspiration
  - “Bronchoalveolar cell carcinoma”
IBD & the Lungs

- **Airway disease**
  - Most prevalent manifestation
    - HRCT series 22-89%: Airway thickening/dilation, TIB, Mosaicism, centrilobular (Independent of symptoms, PFT)
  - Accounts for 40-63% of clinically significant pulmonary complaints
  - Can follow IBD by many years or decades
  - Usually IBD inactive when respiratory symptoms active/activate
  - Can lead to irreversible stenoses if untreated

- **Airway Manifestations**
  - Chronic suppurative & nonsuppurative bronchitis, Bronchiectasis, Bronchiolitis (granulomatous, diffuse panbronchiolitis, bronchiolitis obliterans), Stenoses, Asthma
Treatment?

- Treat associated disorder (e.g. asthma, IBD)
- Avoid steroids per the reviewer
- Maybe she had a mild flare of IBD?

- Infliximab (IBD dosing)
  - Induction: 5 mg/kg at weeks 2 & 6
  - Maintenance: 5 (or 10) mg/kg every 8 weeks

- Cough nearly resolved after first infusions, running backup to 2 miles/day, but the cough partially rebounding at 4 weeks before getting knocked down at the 8 week infusion
Lessons learned

• Even when it is clear reflux is occurring pathologically, be skeptical as to whether reflux surgery will help

• Purulence ≠ Infection

• “Airway disease” is the most common manifestation of IBD, with HRCT being the most sensitive, independent of symptoms/PFT, and can occur decades after active IBD.
Reflux related cough that is not due to reflux

- 40 yo, never smoker, h/o asthma

- Chronic cough for 7 years, mostly nonproductive, seen by 3 of our pulmonologists, GI, allergy, ENT.
  - Globus sensation, coughs to smoke/dusty settings, coughs to perfumes/odors/cleaning agents

- HRCT showed questionable airway thickening.
- Impedance-pH the year before without pathologic reflux
- Sinus surgery and had relief of nasal obstructive symptoms
- Sputum eosinophils negative
Asthma

- PFT with obstruction, hyperinflation, air-trapping
  - FEV1 varies from 41% to 65%, Normal DLCO
  - 15 to 41% BD responsive
- Exhaled NO 33-72 ppb
- No sputum/blood eosinophils
- IgE 227
- Treatments – help, but never fully resolve
  - ICS/LABA, Tiotropium
  - Montelukast
  - Omalizumab
  - Steroids! (chronically 8-12 mg methylpred.)
Reflux testing (Impedance-pH)

- Off medications
- DeMeester 10.3 (<14.7)
- 49 reflux episodes/24 hours (<73)

- Symptom association
  - (No heartburn/regurgitation)
  - Symptom index: 75% of all cough related to reflux episode
  - SAP: 100%

Thus, no pathologic reflux, yet there is a temporal association between reflux and cough. Is this reflux-cough?
Reflux-Cough Temporal Association
Smith, Houghton. Gasto 2010, 139:754

- 78 chronic coughers
  - Impedance/pH
  - Acoustic ambulatory cough monitor

- Symptom associated probability (SAP)

- Cough reflex sensitivity
  - Citric acid inhalational challenge
## Reflux mediated Cough (>95% SAP)

<table>
<thead>
<tr>
<th></th>
<th>SAP+ (R→C) N=34 (48%)</th>
<th>SAP- (R→C) N=37</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Reflux events</td>
<td>62</td>
<td>69.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Acid Reflux events</td>
<td>39</td>
<td>36</td>
<td>0.31</td>
</tr>
<tr>
<td>% time pH&lt;4</td>
<td>3.6%</td>
<td>2.9%</td>
<td>0.59</td>
</tr>
<tr>
<td>Non-acid Reflux events</td>
<td>23</td>
<td>20.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Citric acid cough sensitivity (Log C5)</td>
<td>-0.9M</td>
<td>-0.6M</td>
<td><strong>0.03</strong></td>
</tr>
</tbody>
</table>
Both acid and non-acid reflux can be associated with reflux mediated cough!

Acid suppression is not the panacea for reflux mediated cough.

Reflux (total, acid, non-acid) was no more common in those with reflux mediated cough!

Pathological levels of reflux is not necessary for reflux to mediate cough. Or, the absence of pathological reflux does not exclude reflux mediated cough.

However, the cough sensitivity was increased in those with reflux mediated cough!

So, supports that reflux isn’t necessarily the fundamental problem in reflux mediated cough, but more that reflux is triggering a heightened cough reflex sensitivity.
Cough hypersensitivity syndrome

- Women
- Peri-menopausal
- Autoimmune associations (hypothyroidism)
- Airway inflammation (lymphocytes, mast cells)
- Multiple non-allergic sensitivities
  - Odors, perfumes, cleansing agents, dusts, talking, speech, laughing, dry air, deep breath, etc.
Cough Challenge Tests

Capsaicin • TRPV1 → Vagal afferent → NTS → Motor efferent

Increasing log concentrations of capsaicin inhaled

C5 = log concentration required to cause 5 coughs

Citric acid • TRPV1 • Acid sensor
Chronic idiopathic cough, 42%
# Neuropathy Analogy

<table>
<thead>
<tr>
<th>Neuropathy</th>
<th>Cough hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Hyperalgesia</td>
<td>○ Hypertussia</td>
</tr>
<tr>
<td>○ Allodynia</td>
<td>○ Allotussia</td>
</tr>
<tr>
<td>○ Paresthesia</td>
<td>○ Laryngeal paresthesia</td>
</tr>
<tr>
<td>○ Central sensitization</td>
<td>○ Central / Peripheral sensitization</td>
</tr>
</tbody>
</table>

Ryan, Lancet 2012 Nov.
Paradox?
Amitriptyline in Post-Viral Chronic Cough

Jeyakumar, Laryngoscope 2006; 116:2108

- 28 patients
  - 10 days

- RCT, non-blinded
  - Amitriptyline 10mg
  - Codeine, Guaifenesin

Cough QOL
Gabapentin for refractory chronic cough: a RDBPCT.
Response according to Capsaicin Cough Reflex Hypersensitivity

<table>
<thead>
<tr>
<th></th>
<th>Gabapentin (n=32)</th>
<th>Placebo (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No CS (n=13)</td>
<td>CS (n=19)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.9 (9.5)</td>
<td>13.5 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>15.0 (9.5)</td>
<td>16.2 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>15.3 (8.7)</td>
<td>17.1 (10.6)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No CS (n=10)</td>
<td>CS (n=20)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.2 (9.9)</td>
<td>12.9 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>14.1 (11.5)</td>
<td>13.6 (10.7)</td>
<td>0.240</td>
</tr>
<tr>
<td>Week 8</td>
<td>13.7 (12.2)</td>
<td>14.2 (10.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are mean score (SD). Adjusted p value for significance=0.0042. LCQ= Leicester cough questionnaire. *Gabapentin without CS vs placebo without CS, p=0.0006. Gabapentin without CS vs placebo with CS, p=0.0003. Gabapentin without CS vs gabapentin with CS, p=0.021. CS=central sensitisation.

Table 4: LCQ score according to presence of central sensitisation of the cough reflex
Therapeutic plan

- Maximized asthma therapy, weaning steroids
- Treat reflux, behavioral as well as trial of PPI
- Started gabapentin, PRN lidocaine nebulizer
- Suppressive behavioral techniques, lozenges, sips
- Outcome @ 4 months: Down to 2 mg methylprednisolone so far, weaning slowly...
Lessons learned

• Reflux can cause cough even when there is no reflux. I.e. Cough hypersensitivity syndrome

• Some data exists showing that treating it as a “neuropathy” may have meaningful clinical benefit

• Hypertussia, allotussia, and laryngeal paresthesia might be new lingo to add to our characterization of chronic coughers

• Can co-exist with other diseases: e.g. reflux, asthma, etc.
A case of the too little cough

- 76 yo, former smoker, moderate COPD

- Main complaint of 30# weight loss over 2.5 years

- Tonsillar cancer in 2002, irradiated, very severe mucositis, required PEG for nutrition

- Diagnoses of pneumonia multiple times though didn’t think he had much fevers or sputum at those times

- Severe dryness of mouth, no apparent dysphagia, no cough, but some dyspnea
Swallow video
Bronchoscopy with biopsies

- Organizing pneumonia
- Bronchiolitis

- Review of outside specimens: Foreign body granulomas, apparent vegetable matter
Treatments

• PEG/J

• NPO

• Treat COPD

• Voodoo:
  • ACE-inhibitor
  • Secretion mobilization, airway hydration
**Lessons learned**

**Cough sensitivity**

- **Atussia**
  - Aspiration, pneumonia, ARDS

- **Hypotussia**
  - ?: bronchiectasis, fibrosis, rejection

- **Eutussia**
  - Physiologic/Protective
  - Habitual, Psychogenic, Functional

- **Hypertussia/Allotussia**
  - Cough hypersensitivety syndrome
I Surrender

• 47 yo F. Never smoked. Non-productive cough for 7 years.
  • Hypertussia, Allotussia, tickle in her throat
  • No exposures, meds, timing. Occurs just days.
  • Miserable, drives husband crazy day and night.

• Work-up
  • PFT with methacholine normal.
  • HRCT normal
  • Negative sputum eosinophils (& outside bronchoscopy)
  • CT sinus & nasal endoscopy normal
  • Impedance-pH normal
Chronic cough algorithm (ACCP 2006)

Irwin R S et al. Chest 2006;129:1S-23S

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Chronic cough algorithm (ACCP 2006)

Further investigations to consider:
- 24h esophageal pH monitoring
- Endoscopic or Videofluoroscopic Swallow Evaluation
- Barium esophagram
- Sinus imaging
- HRCT
- Bronchoscopy
- Echocardiogram
- Environmental Assessment
- Consider other rare causes (see section 26)

Important General Considerations
- Optimise therapy for each diagnosis
- Check compliance
- Due to the possibility of multiple causes maintain all partially effective treatment

Initial Treatments
- UACS- A/D
- Asthma- ICS, BD, LTRA
- NAEB-ICS
- GERD- PPI, diet/lifestyle

For further detailed treatment see each section recommendations

Irwin R S et al. Chest 2006;129:1S-23S
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“Diagnoses”

- Upper airway cough syndrome ~40%
- Asthma ~25%
- GERD ~20%
- Eosinophilic Bronchitis ~10-15%
Therapeutic challenges

- “Irwin protocol” was applied and failed
- Speech therapy
- Lozenges, sips
- Amitriptyline no effect
- Gabapentin trial tolerated up to 1800mg/day, but excessive dysphoria and leg edema, and no benefit on cough after 3 months
- Failed: OTC meds, benzonatate, steroids, antibiotics, inhalers, etc.

- Now what...
Treatment

- Lidocaine nebs with generous degree of “suggestive therapy”
  (Lim. Chest 2013; 143(4): 1060.)
- PRN Opiate based antitussives, with lots of warnings (& headaches for you)
- (Botox contemplated, threatened?)
- Cough persists, but 50% better, enough to live… (both patient and spouse)
Lessons learned

- Tailor expectations

- Huge placebo effect, take advantage of it
  - Some patients just want reassurance that there is no cancer

- Cough without a disease is still a problem for your patient…
  - Cough is no longer a symptom, but the disease itself

- Quality of life matters
  - Treat it symptomatically, balancing risks/benefits, with an informed discussion
Thanks!