ADDRESSING THE BURDEN OF CHRONIC COUGH

A Primary Care Primer to Proper Work-up & Management

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Chronic Cough: Current Unmet Needs

- High global prevalence, estimated at 10%
- Comorbidities are common
- Cough can persist for years
  - 20% of patients self-report coughing for ten years or more

Zeiger RS, et al. *Perm J.* 2020;24:20.022.
Morice A, et al. *Eur Respir Rev.* 2021;30:210127.
Kuzniar TJ, et al. *Mayo Clin Proc.* 2007;82:56-60.
Mazzone SB, McGarvey L. *Clin Pharmacol Ther.* 2021;109:619-636.

Chronic Cough is Common and Impairs Quality of Life

- Significant impact on quality of life
  - Physical
    - Sleep disturbance, stress urinary incontinence, chest pain, syncope, vomiting
  - Social
    - Isolation, inability to enjoy leisure activities
  - Economic
    - Healthcare cost
    - Impact on career

Kuzniar TJ, et al. *Mayo Clin Proc.* 2007;82:56-60.
Mazzone SB, McGarvey L. *Clin Pharmacol Ther.* 2021;109:619-636.

The Psychological Burden of Cough

- Fear, anxiety, frustration, depression, anger are common
  - Baseline depression predicts more severe cough
  - Symptoms of depression, stress, and anxiety predict a worse quality of life
  - Improve if the cough gets better
- Social isolation is nearly universal
  - Helplessness, embarrassment
- Patients often comment about feeling dismissed by healthcare providers
  - Cough is viewed as a symptom, not a condition or disease

Kuzniar TJ, et al. *Mayo Clin Proc.* 2007;82:56-60.
Mazzone SB, McGarvey L. *Clin Pharmacol Ther.* 2021;109:619-636.

Chronic Cough: High Healthcare Utilization

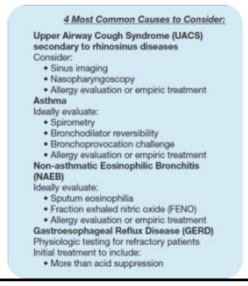
- Multiple visits to primary care office
- Specialty referral is not uncommon
  - Pulmonary, Allergy, ENT, Gastroenterology
- Chronic cough patients undergo more testing and have higher frequency of healthcare utilization
  - Outpatient visits
  - Emergency department visits and hospitalizations as well

Weiner M, et al. *CHEST.* 2021;159:2346-2355.

Cough: General Guidelines

- Timing is key:
  - Acute: <3 weeks
  - Subacute: 3 to 8 weeks
  - Chronic: >8 weeks
- Duration of cough is the first step in narrowing the list of differential diagnoses
- Assess for red flags
- Ensure follow-up if the cough persists

Chronic Cough: Most Common Causes



- *Non-smoker*
- *Not on ACEI*
- *Not on Sitagliptin*
- *Cough is typically <u>not</u> productive*
- *Normal chest x-ray*

Chronic Cough: Red Flags

- Hemoptysis
- Smoker >45 years with new cough, change in cough, or coexisting voice disturbance
- Adults 55-80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years
- Prominent dysnea, especially at rest or at night
- Hoarseness
- Systemic symptoms
  - Fever
  - Weight loss
  - Peripheral edema w/ weight gain
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- History of abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration

Chronic Cough due to Airway Inflammation

- Most common diagnoses:
  - Cough variant asthma
  - Non-asthmatic Eosinophilic Bronchitis (NAEB)
- Making the distinction is important, particularly when determining length of treatment
  - NAEB more likely to be limited in duration

Asthma = Variable Airflow Limitation

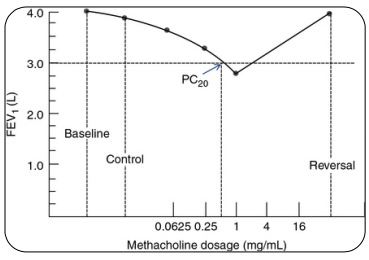
- Diagnosis requires compatible history AND evidence of variable airflow limitation
  - Spirometry or peak flow monitoring, ideally done off all inhaled therapy

	Pred	LLN	ULN	Pre	%	Post	%	% chg
Date				021417		021417		
Time				10:52AM		11:11AM		
Height				161		161		
Weight				64		64		
FVC	3.02	2.34	3.70	3.02	100	3.08	102	2
FEV 1	2.30	1.73	2.87	1.55	80	2.07	90	12
FEV1Af	76.97	66.78	86.37	61.28	80	66.95	87	9
FEV 2	2.34	1.60	3.08	2.30	98	2.53	108	10
FEV 3	2.65	2.03	3.27	2.50	94	2.73	103	9
FEV3Af	92.15	86.79	97.51	82.72	90	88.09	96	7
MEF 50	2.99	1.81	4.17	1.09	36	1.52	51	40
FIF 50				3.84		3.59		-7
FI5/75	2.00	0.79	3.22	0.86	43	1.18	59	37

Cough Variant Asthma

- Cough as the predominant or only symptom
- Diagnosis: reversible airflow obstruction
- Normal exam and spirometry → assess for bronchial responsiveness with methacholine challenge test
- What about empiric therapy?
  - Caution against doing this

Methacholine Challenge Test



Non-asthmatic Eosinophilic Bronchitis

- Eosinophilic inflammation *without* bronchospasm
- Classic diagnosis: sputum eosinophilia
  - This has been replaced with exhaled nitric oxide (eNO)
  - Exhaled NO is typically very elevated
- Typically resolves with therapy, patients have a sustained remission

Exhaled Nitric Oxide (eNO, FENO)

- >50 ppb: eosinophilic airway inflammation
- High eNO suggests steroid responsiveness
- Useful in monitoring inflammation
  - 20% reduction = steroid responsiveness
  - Assessment tool for adherence
- Not a good diagnostic test for asthma
  - Also elevated in rhinosinusitis/atopy, eosinophilic bronchitis, COPD, eczema

Cough due to Airway Inflammation: Treatment

- **Cough Variant Asthma**
  - May require prednisone burst
  - Start with moderate to high dose inhaled steroid/long-acting bronchodilator
- **Non-asthmatic eosinophilic bronchitis**
  - Majority of patients respond to high-dose inhaled steroids
  - Wait six months before de-escalating the dose

The Cough That Won't Stop

- 69-yo female referred for chronic cough
- Duration: six years
- Diagnosed with asthma, not responding to inhaled steroids; currently on moderate-dose fluticasone
- Cough is episodic, gets temporary relief with prednisone
  - History of severe flares characterized by productive cough, emesis, and incontinence

69-yo Female with Chronic Cough

- Minimal shortness of breath, no wheezing or chest tightness
- No childhood history of asthma
  - History of prolonged cough with colds
- Past Medical History: seasonal allergic rhinitis (fall), sleep apnea (adherent to CPAP), reflux (controlled)

69-yo Female with Chronic Cough

Has tried and failed the following medications:

Symbicort	Flovent	Dymista/Flonase
QVAR	Albuterol	Azelastine
Arnuity	Singulair	Zyrtec/Claritin
Asmanex	Gabapentin	Prilosec
Pulmicort	Amitriptyline	

Pulmonary Function Testing and Laboratory Data

	Pred	LLN	ULN	Pre	%	Post	%	% chg
Date				021417		021417		
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Mild airflow obstruction with significant bronchodilator response

Exhaled nitric oxide = 46

Bronchoscopy cell count/differential:

8% Macrophages

7% Lymphocytes

59% Neutrophils

25% Eosinophils

Absolute eosinophil = 300

IgE = 115

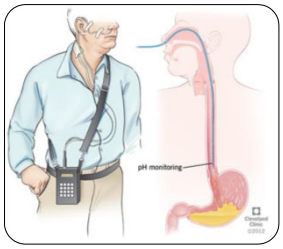
69-yo Female with Chronic Cough

- Diagnosis = Refractory Chronic Cough (RCC) due to cough variant asthma
- Stop inhaled steroids and start high-dose inhaled steroid/long-acting beta agonist (ICS/LABA) inhaler
  - Add long-acting muscarinic antagonist therapy (LAMA) if cough is not controlled with above
  - Consider anti-IL-5 therapy (biologic therapy)

Chronic Cough and Gastroesophageal Reflux Disease (GERD)

- The mechanism of reflux-induced cough is unclear
  - Reflux triggers cough through vagal esophago-bronchial reflex
  - Microaspiration of gastric contents stimulates cough reflux

Diagnostic Testing Commonly Used



- Laryngoscopy
- Esophagogastroduodenoscopy (EGD)
- Catheter-based pH monitoring (Bravo) - capsule placed during EGD
- Impedance - transnasal catheter (data on pH and movement of reflux)
- Barium esophagram – helpful in dysphagia evaluation (not reliable for GERD)
- Modified barium swallow – for oropharyngeal dysphagia/concern for aspiration

Vaezi MF, et al. *Clin Gastroenterol Hepatol.* 2018;16:1018-1029.
Myclevelandclinic.org.

Cough and Reflux is a Complicated Relationship

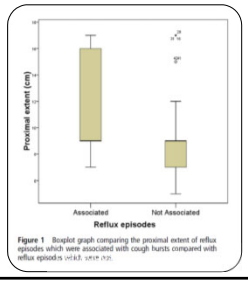
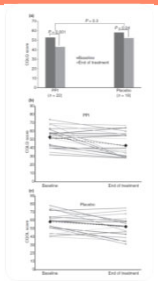


Figure 1 Boxplot graph comparing the proximal extent of reflux episodes which were associated with cough bursts compared with reflux episodes which were not.

- Acidity is not a major factor
  - Median exposure time 2.5%
  - Weakly acid reflux can cause cough
- Reflux episode → cough:
  - Volume clearance time (large volume for longer period of time)
  - Reflux burden → sensitization
  - Proximal extent of reflux (proximal reflux more likely to cause cough)

Herregods TVK, et al. *Gut.* 2017;66:2057-2062.

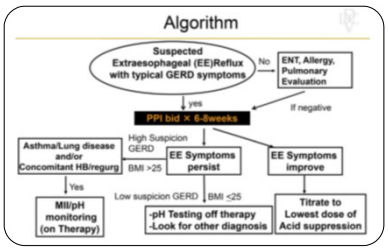
Empiric Proton Pump Inhibitor (PPI) Therapy and Chronic Cough



- Subjects with chronic cough and minimal to no heartburn
- All underwent 24-hr pH impedance monitoring and laryngoscopy
- Randomized to 40 mg PPI twice daily or placebo
- High-dose PPI therapy did not improve cough symptoms or quality of life
  - Subjects with + pH study and (-) MCT did not improve

Shaheen NJ, et al. *Aliment Pharmacol Ther.* 2011;33:225-34.

When Should I Prescribe a PPI?

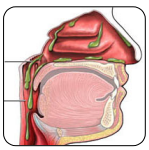


Vaezi MF, et al. *Clin Gastroenterol Hepatol.* 2018;16:1018-1029.

Treatment of GERD Should Not be Limited to Acid Suppression

- **Lifestyle Modifications**
  - Reduce weight
  - Elevate head of bed
  - Reduce offending food items
  - Avoid reflux-promoting drugs
  - Eat small meals
  - Avoid eating too close to bedtime
- **Endoscopic Antireflux Procedures**
  - Transoral incisionless fundoplication
  - Radiofrequency ablation
  - Endoluminal anterior fundoplication
- **Medical Therapy**
  - Antacids
  - Histamine-2 receptor antagonists
  - Proton pump inhibitors
  - Prokinetics
  - Baclofen
  - Alginates
- **Surgical**
  - Fundoplication
  - Linx magnetic ring

Rhinosinus Disease and Chronic Cough



- Mechanical stimulation of cough reflex
  - Nasal and throat symptoms
  - Hoarseness
- Terminology: Upper Airway Cough Syndrome (UACS)
  - Postnasal drip causing cough
- Includes: allergic rhinitis, nonallergic rhinitis (irritant and vasomotor), sinusitis
- Presence of allergy ≠ allergy is the cause of PND

Upper Airway Cough Syndrome

- Symptoms and exam are non-specific
  - Absence does not indicate non-responsiveness
- Acute bacterial rhinosinusitis is, by definition, not a cause of chronic cough
  - Chronic sinusitis → specialty referral
- Allergic rhinitis: nasal congestion, runny nose, itchy nose and or eyes, sneezing

UACS: Treatment

- Intranasal steroids and 2nd-generation antihistamines
  - Intranasal antihistamines
  - Intranasal anticholinergic (vasomotor rhinitis)
  - Chlorpheniramine

- Treatment response in days to weeks
- Allergy testing recommended when patients do not respond to empiric treatment
- Routine sinonasal imaging is not recommended

Seidman MD, et al. *Otolaryngol Head Neck urg.* 2015;152(1S):S1–S43.

Chronic Cough: Assess Treatment Response

- Treatment response can vary:
  - Asthma: days (systemic steroids) to weeks
  - NAEB: days to weeks
  - GERD: weeks to months
  - UACS: days to weeks
- Emphasize adherence and inhaler technique

Patient-Provider Communication

- Importance of setting expectations and goals
- Have a plan for follow-up and non-response
  - Optimize treatment duration (minimum of 4 to 6 weeks)
- Discuss plan for referral and additional testing options

The Cough That Won't Stop

- 73-yo male with chronic cough for over 15 years
- Was a public speaker, had to stop because of cough
- Counts his coughing episodes, had >70 in the week before his visit
- Triggers include talking and eating dairy
- Cough is occasional preceded by a tickle, has a feeling of upper chest congestion and feels like it gets stuck in his throat

73-yo Male with Chronic Cough

- Multiple treatment trials: nasal sprays, anti-histamine, Tessalon perles, PPI, sinus irrigations
- Coricidin HBP "takes the edge off"
- Multidisciplinary evaluation: pulmonary, ENT, allergy, GI; testing included pH probe (negative), allergy panel (+cockroach), PFTs (eNO = 22, spirometry normal with no significant bronchodilator response)

When the Cough Really Won't Stop

- Unexplained Chronic Cough (UCC)
- Refractory Chronic Cough (RCC)
  - Re-evaluate for most common causes
  - Specialty referral
- Think about Cough Hypersensitivity Syndrome
  - Also known as: Neurogenic Cough, Sensory Neuropathic Cough, Irritable Larynx
  - Diagnosis of exclusion (it is a real diagnosis)
  - Mechanism is poorly understood

UCC/RCC Patient Journey: Evaluation

Most of the time	Sometimes	Rarely
Chest x-ray	CT Chest (contrast is not needed)	Bronchoscopy
Pulmonary function testing (Spiro with BD, eNO)	Esophagogastroduodenoscopy (EGD)	
Laryngoscopy	Swallow testing/pH study	
Allergy testing	CT sinuses	
Direct laryngoscopy		

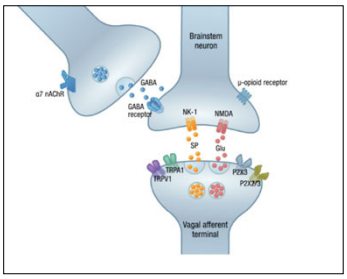
Cough Hypersensitivity Syndrome: History is Key to Diagnosis

- Tell me the story of your cough….
- Often preceded by viral infection/bronchitis
  - *I got better but the cough never went away*
- It is always a dry cough
  - Exception: 'bronchorrhea' after a severe episode
- Cough should be the only respiratory symptom
- Characterized by severe episodes or "jags"
- Post-tussive vomiting, cough syncope not uncommon

Cough Hypersensitivity Syndrome: History is Key to Diagnosis

- Can be unpredictable
- Often has common triggers:
  - Laughing, talking on the phone, singing
  - Change in position (sitting/standing to laying down)
  - Eating or drinking (cold liquids)
  - Strong odors or perfumes
  - Abrupt changes in temperature
- Laryngeal paresthesia is key feature

Patients with Chronic Cough Often Have Central Sensitization



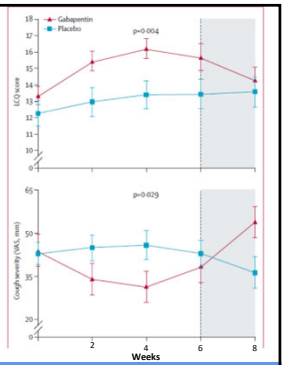
- Sensitivity of cough reflex is increased
- Both peripheral and central mechanisms
- Upregulation of neurotransmitters and receptors
- Shared qualities of neuropathic disorders

Mazzone SB, McGarvey L. *Clin Pharmacol Ther.* 2021;109:619-636.

Gabapentin as Treatment for Refractory Cough

Treatment group:

- Greater improvement in LCQ score compared to placebo
- Significant improvement in cough severity score compared to placebo
- Well tolerated, adverse effects included nausea and fatigue



Ryan NM, et al. *Lancet.* 2012:380:1583-9.

73-yo Male with Chronic Cough

- Agreed to off-label use of neuromodulator therapy: Gabapentin 300 mg QHS with slow titration up as tolerated
- 6-week virtual visit: cough is reduced by 50%
- “I haven’t felt this good in years”
- No longer having severe coughing jags, choking and gagging has resolved
- Currently on 300 mg TID of Gabapentin

73-yo Male with Chronic Cough

- Still having cough attacks around 10 AM
  - Dose increased to 600-300-300 mg
- 4 months later: cough is 80% reduced
  - No side effects
  - Dose increased to 600-300-600 mg, timing of dosage adjusted
- With 80% or greater cough reduction, continue this dose for six months then taper off

Cough Hypersensitivity Treatment

- Behavioral cough suppression therapy
- Acupuncture, lozenges (avoid menthol, eucaplyptus)
- All current medical therapies are off-label
- Primarily use neuromodulators
  - Gabapentin, Pregabalin
  - Amitriptyline, Nortriptyline
- When all else fails: Tramadol, Baclofen, Laryngeal botox, superior laryngeal nerve block

RCC/UCC: Role of Behavioral Cough Suppression Therapy

Table 2 Different interventions included in studies investigating nonpharmacological interventions in refractory chronic cough

Interventions	Vertigan et al. [7]	Ryan et al. [21]	Murry et al. [22]	Ryan et al. [20]	Patel et al. [9]
Education on chronic cough	✔	✔		✔	✔
Education on identifying cough triggers	✔	✔		✔	✔
Cough suppression techniques	✔	✔		✔	✔
Breathing exercises					
Pursed lip breathing	✔	✔	✔	✔	✔
Relaxed throat breathing	✔	✔	✔	✔	✔
Breathing control/diaphragmatic breathing					✔
Vocal hygiene and hydration strategies	✔	✔		✔	✔
Counselling	✔	✔		✔	✔
Throat massage					✔

Chamberlain S, et al. *Lung.* 2014;192:75-85.

New Drugs in the Research Pipeline for RCC/UCC

- P2X3 antagonists
- NK1 antagonists
- TRPV1/TRPA1 antagonists
- TRPM8 agonists
- Voltage-gated sodium-channel (NaV) blockers
- Opioid mu-antagonist/kappa agonist (nalbuphine)

Chronic Cough Drug Development

- Gefipixant: oral P2X3 receptor antagonist
- COUGH-1 and COUGH-2: randomized, double-blind, placebo-controlled, phase 3 trials
- RCC/UCC of ≥1 year
- Treatment group (45 mg twice daily) showed significant reductions in cough frequency compared to placebo
- Most common adverse events: taste disturbance

McGarvey LP, et al. *Lancet.* 2022:339:909-923.

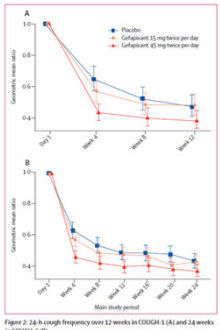


Figure 2: 24-h cough frequency over 12 weeks in COUGH-1 (A) and 24 weeks in COUGH-2 (B)
Error bars are 95% CIs.

Key Takeaways

- Detailed clinical history often key to diagnosis
  - Review testing and prior treatment trials
- Set expectations: it can take several weeks to months to see (full) improvement
- Chronic cough is often multifactorial
  - Lack of symptom response: re-evaluate for common causes
- Importance of validation in the management of chronic refractory cough