Chronic Cough

Michael Wert, MD
Assistant Professor - Clinical
Department of Internal Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

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Objectives

- Define chronic cough
- Identify the most common causes of chronic cough
- Learn the therapies for chronic cough
- Learn the therapies for refractory chronic cough
- Develop a stepwise approach for the management/treatment of chronic cough

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Chronic cough

- Cough present for > 8 weeks
  - Acute cough – present for up to 3 weeks
  - Subacute cough – 3-8 weeks
- Affects 10-12% of the population
- Female > male (2:1)
- Peak age of onset is 6th decade of life
- One of the more common reasons for outpatient pulmonary referrals
- Diagnosis is made in 60-90% of cases
  - Might be an overestimation!

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Why Do We Cough?

- The basics:
  - stimulus (irritant) → airway receptors → vagus nerve → brain cough centers → efferent motor nerves (phrenic, spinal, vagal) → coordinated cough
- Chemical cough receptors:
  - Stimulated by cold, heat, or other chemical irritants (stomach acid, fumes, perfumes, smoke, etc)
  - Chronic cough → may have cough reflex 'hypersensitivity'
    - Require much lower levels of irritant to trigger a cough

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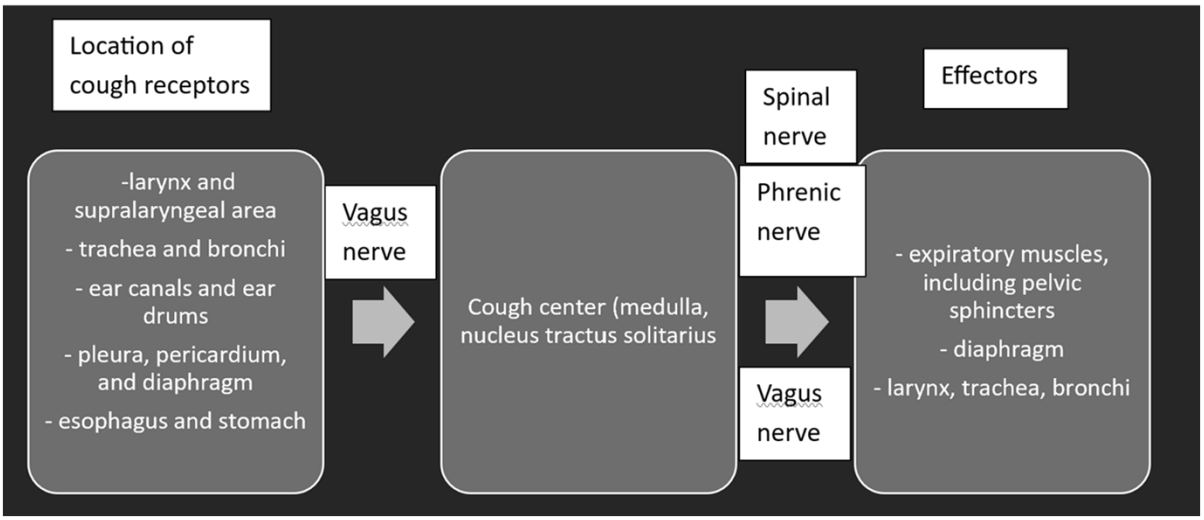
Why Do We Cough?



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Chronic Cough - Complications

- Why is diagnosing/treating chronic cough important?
  - Psychosocial ramifications
    - embarrassment, self-consciousness, self-isolation, irritation
  - Physical ramifications
    - Poor sleep
    - Voice hoarseness
    - Syncope
    - Urinary incontinence
    - Rib fractures
    - Pneumothoraces/pneumomediastinum

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Acute/subacute Cough vs Chronic Cough

- Acute/subacute cough:
  - Typically easier to diagnose and treat
  - Common etiologies:
    - Bacterial/viral upper respiratory tract infection/pneumonia, asthma/COPD exacerbation, lung mass, post-viral cough (cough tends to linger for a LONG time)
- Chronic cough:
  - Often much harder to pinpoint a diagnosis (the longer it has persisted, the harder it is to diagnose)
  - Common etiologies:

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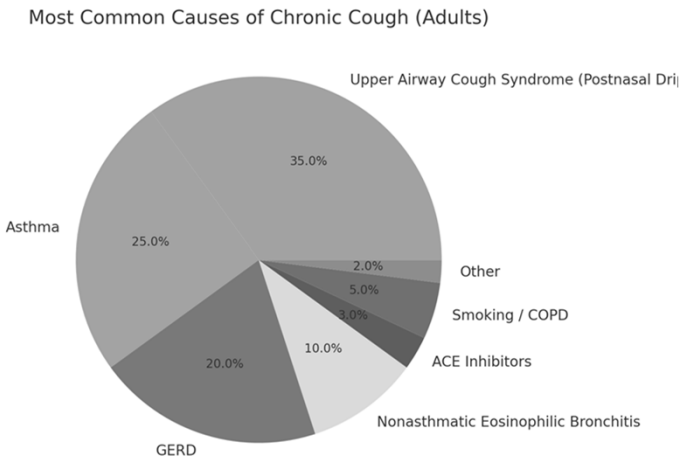
Chronic Cough



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Case

- A 35 year old female presents with chronic cough for 6 months:
  - Non-smoker
  - Some shortness of breath with exertion
  - Cough worse with cold weather
  - Cough worse at night
  - Normal SpO2
  - Faint wheeze + cough with forced exhalation (ie 'blowing out birthday candles')

Next steps? Empiric treatment? What would be at the top of the differential?

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Case

- Her exhaled nitric oxide level is 45 ppb

FeNO Level (ppb)	Interpretation	Clinical Meaning	Typical Actions
< 25 ppb	**Low**	Low likelihood of eosinophilic airway inflammation; asthma less likely	Consider non-eosinophilic causes of symptoms; ICS may be less effective
25–50 ppb	**Intermediate**	Possible eosinophilic inflammation; context-dependent	Reassess symptoms, exposures, repeat test, or consider ICS trial
> 50 ppb	**High**	Strong evidence of type 2/eosinophilic inflammation; asthma likely	Start or increase ICS; evaluate adherence and allergen exposure

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Case

So, if PFTs are normal, this ISN'T asthma, right?

- Pulmonary function testing:

Plethysmograph Report

Spirometry

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	5.85	5.63	96	5.70	97	1
FEV1	Liters	4.37	4.01	92	4.22	96	5
FEV1/FVC	%	74	71		74		
FEF25-75%	L/sec	4.27	2.53	59	3.08	72	22
PEF	L/sec	10.50	14.53	138	12.77	122	-12
FET100%	Sec		9.99		9.90		-1
FIVC	Liters	5.85	5.31	91	5.10	87	-4
FIF50%	L/sec		5.71		3.66		-36

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Case

- Methacholine challenge test:

Dose (mg/mL)	FEV_1 (L)	% Change from Baseline
0 (saline)	3.48	–1%
0.125	3.40	–3%
0.25	3.30	–6%
1.0	3.05	–13%
2.0	2.78	–20% ❗ **Threshold reached**

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Case

ASTHMA!!

- Methacholine challenge test:

PC_{20} (mg/mL)	**Airway Hyperresponsiveness**	**Interpretation**
> 16 mg/mL	None/Normal	Asthma **very unlikely**
8–16 mg/mL	Borderline / Mild	Asthma **possible**
4–8 mg/mL	Mild to Moderate	Asthma **likely**
1–4 mg/mL	Moderate	Asthma **likely**
< 1 mg/mL	Marked / Severe	Asthma **very likely**

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Case

- Prescribed her a prn albuterol and scheduled inhaled corticosteroid
- Cough improved over the next 6-8 weeks!

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Asthma

- One of the most common causes of chronic cough in adults (25-30% of cases in non-smokers)
- Patients can present with wheezing, dyspnea, and cough
  - Or sometimes JUST cough → cough-variant asthma
  - Can often elicit a wheeze with *forced* exhalation (**ask them to breath out hard like blowing out birthday candles**)
- Spirometry:
  - *Can* have obstruction on spirometry with a bronchodilator response
  - Absence of obstruction does NOT rule out asthma
    - If high suspicion, can get a methacholine challenge test

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Asthma

- Exhaled nitric oxide (eNO) → surrogate marker for airway eosinophilia
  - If very low, asthma *probably* unlikely
  - If very high, asthma should be strongly considered
  - Correlation with responsiveness to inhaled steroids
- Chest imaging
  - Usually not helpful one way or the other
    - CXR could show hyperinflation
    - Chest CT typically obtained to look for alternative etiologies
- Blood work:
  - CBC to evaluate for peripheral eosinophilia
  - IgE levels may be elevated
  - Allergy panel

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Asthma

- Best way to confirm or rule out asthma?
  - Treat and monitor for response!
  - Initial/empiric treatment:
    - Inhaled glucocorticosteroids (ICS)
    - Leukotriene receptor antagonists (ie montelukast)
      - If an allergic component is suspected
    - As needed short-acting beta-agonists (SABAs, ie albuterol)
    - Allergen/irritant recognition/elimination
  - If ZERO improvement after 2-3 months of inhaler therapy, asthma is unlikely to be the cause of the chronic cough

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Asthma vs NAEB

- Non-asthmatic Eosinophilic Bronchitis
  - Increasingly recognized as a common cause of non-productive chronic cough (10-30%)
  - Some similarities with asthma:
    - Atopic tendencies (eczema)
    - Elevated sputum eosinophils
    - Active airway inflammation
  - BUT….
    - There is an **absence** of airway hyperresponsiveness
      - Would have normal PFTs and a negative methacholine challenge test

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NAEB

- Non-asthmatic Eosinophilic Bronchitis
  - Diagnosis:
    - Clinical → symptoms + improvement with empiric therapy (inhaled steroids)
    - Can consider exhaled NO testing/sputum eosinophil evaluation
    - Bronchial biopsy?
      - Definitely not needed but would typically show eosinophilia
  - Treatment:
    - Very similar to asthma
    - Low to medium strength ICS
    - Leukotriene receptor antagonists (ie montelukast)

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Inhaled Corticosteroids

American Lung Association

Single Agent Inhaler (In alphabetical order) (Active Ingredient) Dosage Strength Frequency	Low DAILY Dose (Total)			Medium DAILY Dose (Total)			High DAILY Dose (Total)		
	Child 0-4	Child 5-11	>12 & Adults	Child 0-4	Child 5-11	>12 & Adults	Child 0-4	Child 5-11	>12 & adults
Alvesco (Ciclesonide HFA) 80 or 160 mcg Dosed twice daily	N/A	80mcg once daily†	160mcg	N/A	160mcg once daily†	320mcg	N/A	N/A	640mcg
ArmonAir Digihaler (Fluticasone proprionate DPI) 55, 113, 232 mcg Dosed twice daily	N/A	N/A	110mcg	N/A	N/A	226mcg	N/A	N/A	464mcg
Arnuity Ellipta (Fluticasone furoate DPI) 50, 100, 200 mcg Dose once daily	N/A	50 mcg	100mcg	N/A	N/A	100mcg	N/A	N/A	200mcg
Asmanex HFA (Mometasone furoate) 50mcg, 100mcg, 200mg Dose twice daily	N/A	N/A	200mcg	N/A	200mcg*	400mcg	N/A	N/A	800mcg
Asmanex Twisthaler (Mometasone furoate DPI) 110 or 220 mcg Dosed once or twice daily	N/A	110mcg once daily	110mcg once daily	N/A	N/A	440mcg once daily or divided twice daily	N/A	N/A	880mcg divided twice daily
Flovent Diskus[δ] (Fluticasone propionate DPI) 50mcg, 100mcg, 250mcg Dosed twice daily	N/A	100mcg or 200mcg	200mcg	N/A	N/A	400mcg or 500mcg	N/A	N/A	1000mcg
Flovent HFA (Fluticasone propionate HFA) 44mcg, 110, 220 mcg Dosed twice daily	176mcg*	176mcg‡	176mcg	N/A	N/A	220mcg or 440mcg	N/A	N/A	880mcg or 1,760mcg
Pulmicort Flexhaler (Budesonide DPI) 90mcg or 180mcg Dosed twice daily	N/A	180mcg or 360mcg¶	180mcg or 360mg‡	N/A	720mcg¶	720mcg§	N/A	N/A	1440mcg§
Pulmicort Respules[Δ] (Budesonide nebulizer) 0.25mg, 0.5mg, 1mg Dosed once or twice daily	0.25mg once daily	0.25mg once daily	N/A	0.5mg divided twice daily	0.5mg divided twice daily	N/A	1mg divided twice daily	1mg divided twice daily	N/A
QVAR Redihaler (Beclomethasone HFA) 40mcg or 80mcg Dosed twice daily	N/A	80mcg‡	80mcg or 160mg	N/A	160mcg‡	320mcg or 480mcg	N/A	N/A	640mcg

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Case

- 55 year old male presents with 9 months of chronic, dry cough:
  - Worse at night (actually awakens him from sleep)
  - Worse with laying flat
  - Cough worse after large meals
  - Wakes up with a sour taste in his mouth
  - Endorses dysphagia
  - Never smoker
  - No weight loss
  - Is obese
  - Top of differential? Next steps?

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GERD

- Recommended lifestyle modifications
  - Weight loss
  - Elevation of head of bed
  - Avoidance of reflux-inducing foods (chocolate, caffeine, alcohol, fatty foods)
  - Avoidance of meals 2-3 hours before bedtime
- Started him on a moderate strength proton pump inhibitor (PPI)
  - Omeprazole 40 mg daily
- Cough improved somewhat after 2 months of therapy
- Dysphagia persisted
- Now what?

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GERD

- Esophageal pH monitor vs barium swallow vs GI referral
- Barium swallow:

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GERD

- GI referral for EGD…

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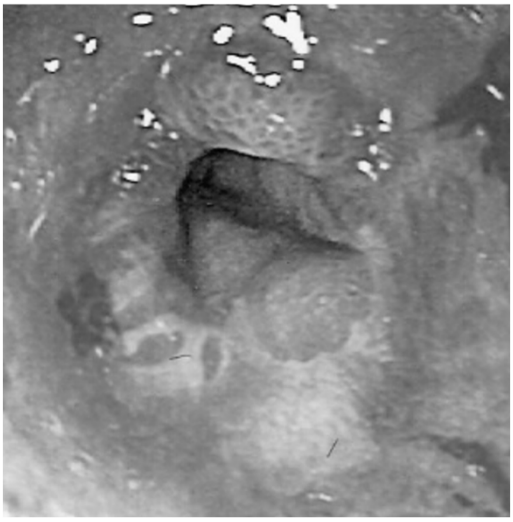
GERD



- EGD revealed esophageal stricture
- Stricture treated endoscopically
- Cough AND dysphagia resolved!

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GERD

- 2nd/3rd most common cause of chronic cough
- Induces cough by:
  - Stimulating receptors on the vagal afferent nerves in the larynx
  - Stimulating receptors in the lower airways via aspiration of gastric contents
  - Induces the tracheobronchial-esophageal cough reflex via the reflux of acid into the distal esophagus
- In addition to chronic cough, patients can have:
  - Dysphagia, sour taste in mouth, heartburn

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GERD

- Diagnosis:
  - Often clinical:
    - 'Classic' symptoms (heartburn/regurgitation) + response to empiric therapy
  - Barium swallow?
    - Not particularly useful for diagnosis of GERD *unless* warning sign like dysphagia
  - EGD?
    - Patients with 'red flag' symptoms or abnormal esophageal imaging
  - Esophageal manometry?
    - GERD symptoms + chest pain/dysphagia to rule out dysmotility, etc
  - Ambulatory pH monitoring?
    - Persistent GERD symptoms despite treatment
    - Confirmatory but often not necessary for the diagnosis of GERD

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GERD

- Treatment:
  - Lifestyle modifications
    - Weight loss (if necessary)
    - Elevation of head of bed
    - Smoking cessation
    - Avoid reflux-inducing foods/acidic beverages
    - Avoid eating 2-3 hours before bed
  - Acid-suppressing medications:
    - Empiric trial of a moderate dose PPI (ie omeprazole 40 mg once daily)
      - PPI therapy more effective that H_2 antagonist therapy
    - If only mild to modest improvement after 1-2 months?
      - GI referral (esophageal pH monitoring, EGD, etc)
      - Consider alternative cause of chronic cough

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Chronic Cough - GERD vs LPR

- **Laryngopharyngeal reflux disease (LPR)**
  - Retrograde reflux of esophageal/stomach contents into the laryngo-pharynx
  - Majority of patients do NOT have heartburn
  - Primarily have dysphonia/voice hoarseness, chronic cough, **frequent throat clearing**
  - Problem with the upper esophageal sphincter (vs lower ES in GERD)
  - Diagnosis?
    - Often need laryngoscopy (video/indirect vs direct) to confirm diagnosis
    - Gold standard → pH impedance testing
  - Treatment?
    - Similar to treatment for GERD (PPI, lifestyle modifications)
    - May need serial laryngoscopies to evaluate for improvement

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Chronic Cough - LPR

- Normal video laryngoscopy:

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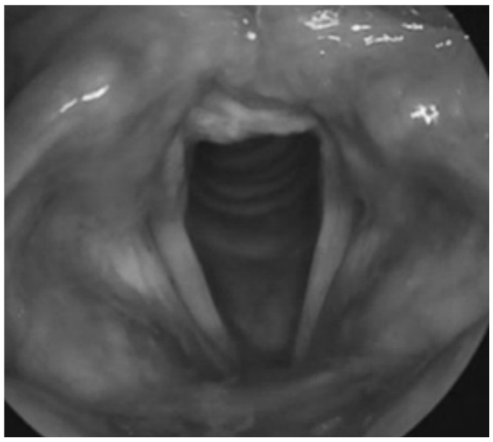
Chronic Cough - LPR

- Video laryngoscopy with LPR:



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Case

- 44 year old female presents with 5 months of mostly dry cough
  - Cough is worse in the morning and when laying flat
  - Describes a 'dripping' sensation in the back of her throat
  - Cough worse when around pollen and dust
  - Has to clear her throat often
  - Non-smoker
  - No heartburn symptoms
  - Not on an ACE inhibitor
  - Minimal improvement with OTC cough medicine
  - No change in symptoms with 3 month trial of inhaled corticosteroid

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Case

- 44 year old female presents with 5 months of mostly dry cough
  - Physical exam:
    - Boggy nasal turbinates
    - Cobblestoning of posterior pharynx
    - Lungs clear
  - Diagnostic work-up:
    - Normal CXR
    - Normal PFTs
    - Normal exhaled nitric oxide levels
- Diagnosis?

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Upper Airway Cough Syndrome (UACS)

- 44 year old female presents with 5 months of mostly dry cough
  - Treatment:
    - Started her on intranasal corticosteroids (ie flonase)
    - Recommended OTC 2nd generation anti-histamine (ie zytrec/claritin)
    - Started nasal saline irrigation
  - Cough completely gone after 3 months of therapy!

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Upper Airway Cough Syndrome (UACS)

- Likely *the* most common cause of chronic cough
- Mechanism of cough:
  - Nasal/sinus secretions flow into the nasopharynx (previously called post-nasal drip)
  - Secretions caused by:
    - Allergic rhinitis (important to obtain an allergy history)
    - Perennial non-allergic rhinitis
    - Vasomotor rhinitis
  - Secretions stimulate cough receptors within laryngeal mucosa
- Symptoms:
  - Frequent nose blowing
  - Frequent throat clearing
  - Sensation of 'fluid'/'liquid' in the back of the throat
- Physical exam:
  - Boggy nasal turbinates
  - 'cobblestoning' of the posterior pharynx
  - Presence of sections in the pharynx

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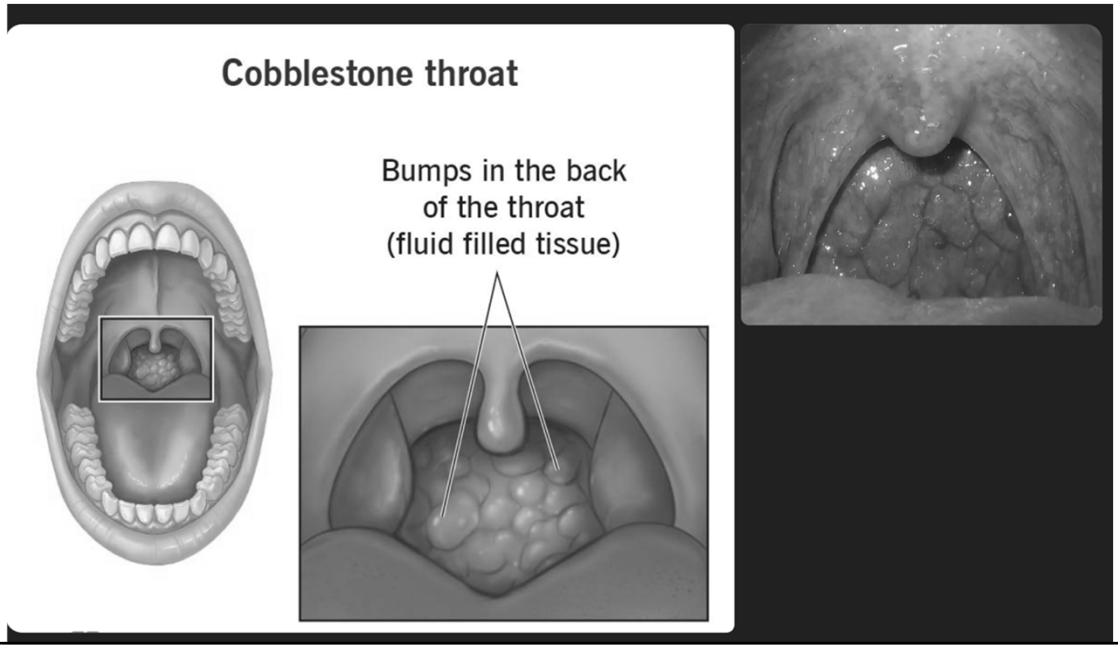
Upper Airway Cough Syndrome (UACS)



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Upper Airway Cough Syndrome (UACS)

- Diagnosis:
  - Clinical → based on history, physical, response to empiric treatment
  - Sinus CT scan → needed only if no improvement with treatment, persistent purulent nasal drainage, or suspicion for anatomic abnormality (ie deviated septum)
    - Obtain if → purulent drainage, facial pain/fullness, sensation of nasal blockage, impaired sense of smell
    - If significant sinus disease/abnormality → refer to ENT
- Treatment:
  - Allergen avoidance/mitigation
  - Intranasal steroids:
    - Most effective for *allergic* rhinitis
    - Can achieve effective within a few days to a few weeks
  - Intranasal azelastine
    - Histamine receptor blocker
    - Reduces hyperreactivity of the airways
    - Most effective for rhinorrhea caused by *non-allergic* rhinitis
  - Minimally sedating oral anti-histamines (2nd or 3rd generation)
    - More effective in *allergic* rhinitis
    - Still can be at least *somewhat* sedating, so use with caution in patients at risk for significant somnolence
  - Decongestants
    - Use with caution in patients with HTN, glaucoma, bladder outlet obstruction, concomitant MAO inhibitor therapy (contraindcated)

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Prolonged Post-Infectious Cough

- Cough *can* persist for > 8 weeks after viral/bacterial URIs
  - Most common pathogens:
    - Bordatella pertussis (cough can persist for weeks to MONTHS)
    - Mycoplasma
    - COVID
    - Non-COVID viruses (RSV, rhinovirus)
  - Proposed mechanisms for cough:
    - Post-nasal drip
    - Enhanced sensitivity of airway nerves
    - Increased airway inflammation → increased airway hyperresponsiveness → cough, bronchial constriction
  - Diagnosis:
    - Clinical/history-based
    - Make sure an alternative diagnosis (ie asthma) isn't present
  - Treatment:
    - Nasal steroids
    - Anti-histamines
    - Albuterol
    - Inhaled anti-cholinergics (ipratroprium)

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Interstitial Lung Disease

- When to suspect?
  - Cough associated with dyspnea
  - Resting or exertional hypoxemia
  - Suspicious exposure/medication history
    - Factories, asbestos, farming, coal mining, sand blasting, molds, birds
    - Amiodarone, nitrofurantoin, daptomycin, methotrexate, sulfasalazine, bleomycin, immune checkpoint-inhibitors
  - History of autoimmune disease
    - Rheumatoid arthritis, SLE, dermatomyositis, scleroderma, Sjogren's syndrome, etc
  - Physical exam
    - Crackles
    - Digital clubbing
    - 'mechanic's hands'

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Interstitial Lung Disease

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Interstitial Lung Disease

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Interstitial Lung Disease

- Work-up:
  - CXR + PFTs
  - Chest CT (high resolution with inspiratory and expiratory images)
  - Pulmonary referral

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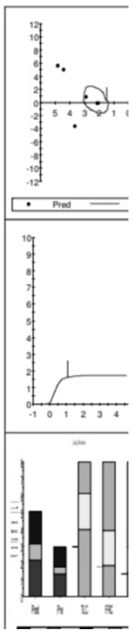
Interstitial Lung Disease

	Pre-Bronch					Post-Bronch		
	Pred	LLN	ULN	Actual	%Pred	Actual	%Pred	%Chng
---- SPIROMETRY ----								
FVC (L)	3.03	2.34	3.72	*1.74	*57			
FEV1 (L)	2.30	1.71	2.89	*1.62	*70			
FEV1/FVC (%)	76.15	66.32	85.97	*93.01	*122			
FEV1/SVC (%)	75.84	66.02	85.67	*100.62	*132			
FEF 25-75% (L/sec)	1.95	0.71	3.19	2.15	110			
FEF 25% (L/sec)	5.12			2.49	48			
FEF 50% (L/sec)				2.22				
FEF 75% (L/sec)	0.92	-0.17	2.01	1.62	176			
FEF Max (L/sec)	5.72	4.00	7.44	*3.53	*61			
FIF 50% (L/sec)	3.51	2.07	4.94	*1.58	*44			
FEF50%/FIF50% (%)	90-100			141				
FEV3 (L)				1.74				
FEV6 (L)	2.90	2.22	3.58	*1.74	*60			
---- LUNG VOLUMES								
TLC (Pleth) (L)	5.05	3.98	6.13	*2.96	*58			
SVC (L)	3.03	2.34	3.72	*1.61	*53			
IC (L)	1.91			1.19	62			
FRC (Pleth) (L)	2.88	1.84	3.93	*1.65	*57			
ERV (L)	0.96			0.30	31			
RV (Pleth) (L)	2.17	1.41	2.93	*1.35	*62			
RV/TLC (Pleth) (%)	43.05	32.13	53.97	45.58	105			
Vpant (L)				1.72				
---- DIFFUSION ----								
DLCOunc (ml/min/mm	20.63	13.13	28.13	*10.83	*52			
DLCOcor (ml/min/mm	20.63	13.13	28.13					
DL/VA (ml/min/mmHg/	4.30	2.70	5.90	4.13	96			
VA (L)	5.06	3.96	6.17	*2.62	*51			
IVC (L)				1.53				



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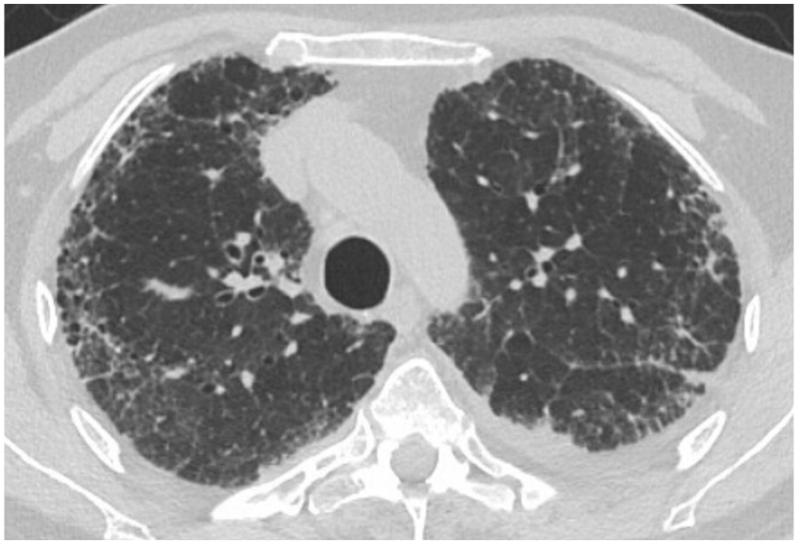
Interstitial Lung Disease



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Chronic Cough - Interstitial Lung Disease

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Lung Cancer

- Cough is present in 50-75% of lung cancer patients at the time of diagnosis
- BUT…..
  - Lung cancer is the etiology of chronic cough in less than 2% of cases
- Suspect if/when:
  - Cough is associated with hemoptysis
  - Cough persists despite smoking cessation
  - Focal/unilateral wheezing (could be a sign of bronchial obstruction)
    - Especially important to think about in persistent cough/wheezing in younger/non-smoking patients
- Don’t forget about lung cancer screening (if the patient meets criteria)

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Lung Cancer - Case

- 35 year old healthy female presents with dry cough for 6 months
- Non-smoker
- Can 'hear herself wheeze'
- Unilateral wheezing on exam
- Chest X-ray normal
- Chest CT…..

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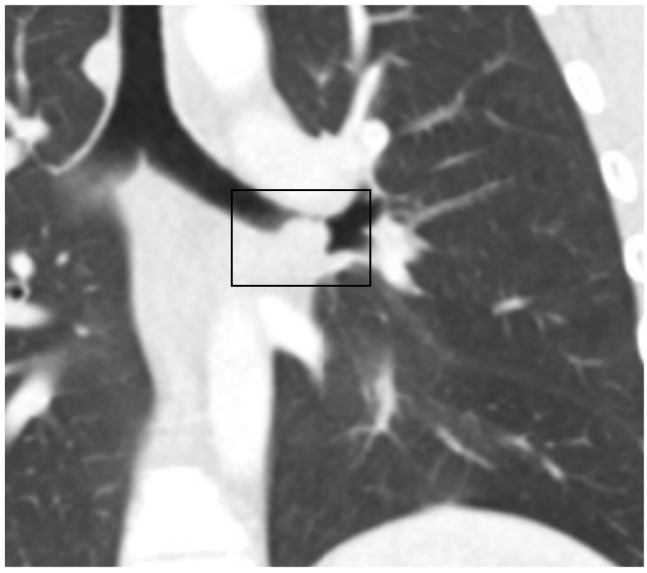
Lung Cancer



Endobronchial carcinoid tumor

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Bronchiectasis

- Accounts for less than 2% of patients with chronic cough
- When to suspect?
  - Mucopurulent cough
  - Frequent pneumonias
  - Abnormal lung exam
    - Wheezes, rhonchi, inspiratory squeaks, crackles
- Work-up:
  - CXR, PFTs → non-specific
  - Chest CT
  - Pulmonary referral

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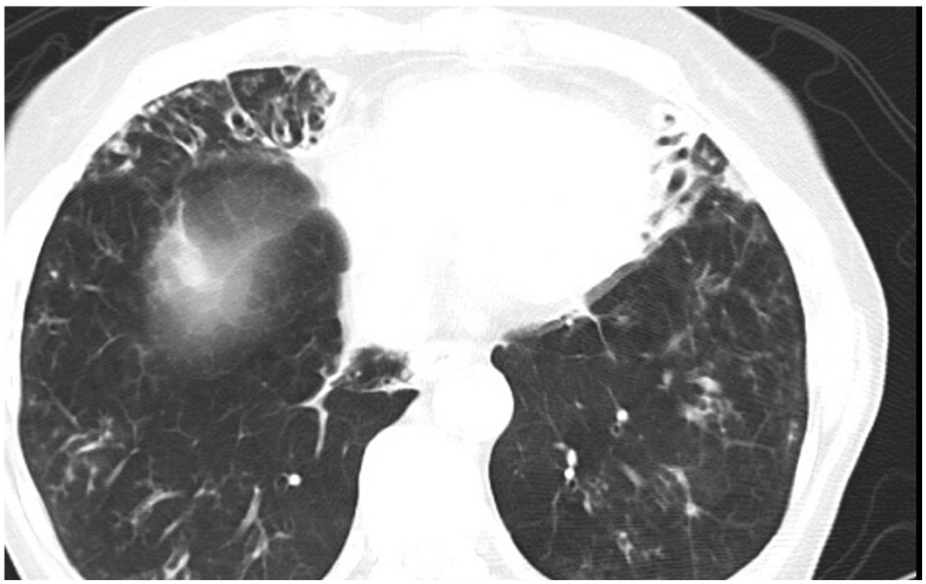
Bronchiectasis



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Bronchiectasis

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Indolent Infection

- When to suspect:
  - Cough +
    - Fever
    - Fatigue
    - Weight loss
    - Hemoptysis
    - Immunocompromised state
    - Abnormal lung sounds (squeaks, rhonchi)
  - No improvement with 'conventional' therapies (ie inhalers, GERD treatment, etc)

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Indolent Infection

- Most common pathogens:
  - Non-tuberculous mycobacterial (NTM) infections
  - Fungi (histoplasmosis, coccidiomycosis, blastomycosis)
  - Nocardia
  - Lung abscess
- Work-up:
  - CXR, bacterial AND AFB sputum cultures (if suspicion for NTM infection)
  - Chest CT
  - Pulmonary referral

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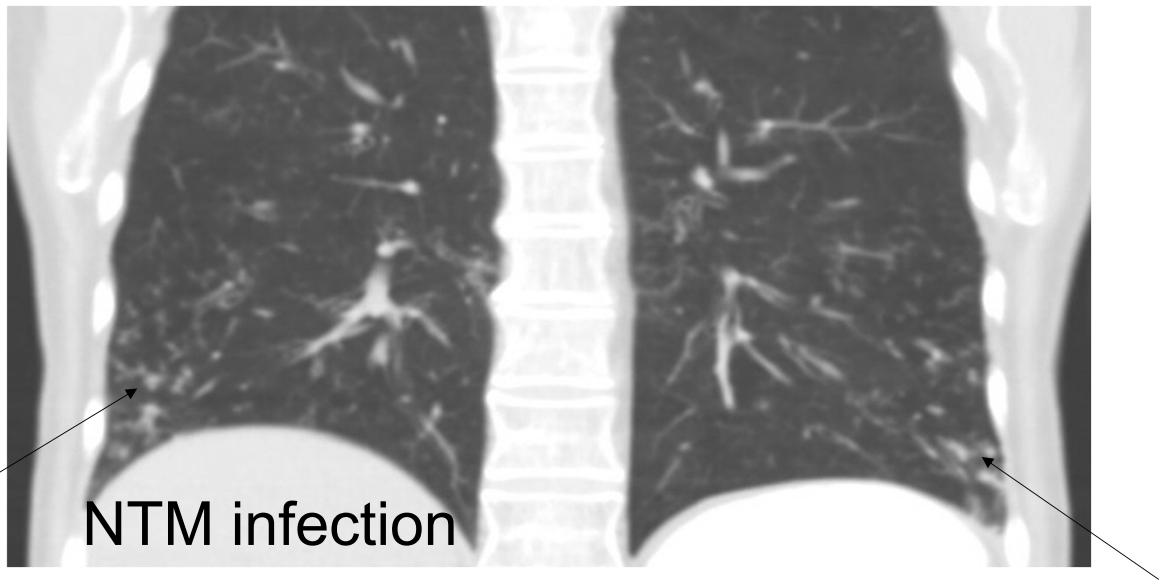
Indolent Infection



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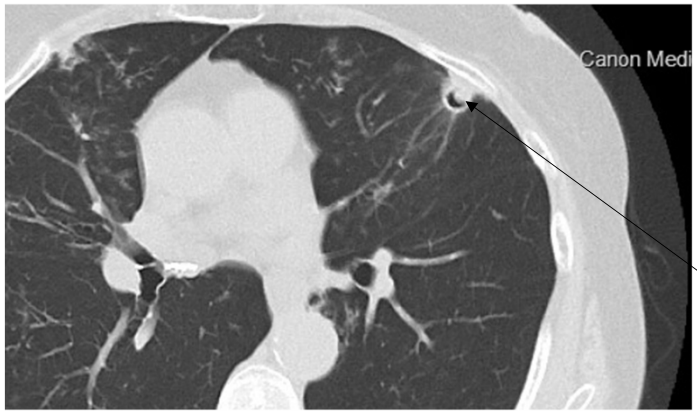
Indolent Infection



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Medication-induced Chronic Cough

- Angiotensin-converting enzyme (ACE) inhibitors
  - Females > males
  - More common in Chinese patients
  - Pathogenesis
    - ???
    - Increases sensitivity of the cough reflex due to accumulation of bradykinin?
  - *Usually* begins within one week of initiating ACE inhibitor therapy but can be delayed up to *six months*
  - Dry cough, itchy throat
  - Normal pulmonary function tests
  - Typically resolves within one to four days of discontinuing therapy but can take up to four weeks to three months
  - Generally *recurs* with re-challenge, even if using a different ACE inhibitor
  - Angiotensin II receptor blockers (ARBs) do NOT appear to be a cause of chronic cough
    - ARBs do not increase kinin levels

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Medication-induced Chronic Cough

- Other culprit medications:
  - Calcium channel blockers
  - Bisphosphonates
    - Both can worsen pre-existing reflux
  - Very rare:
    - Glaucoma medications
      - Timolol
      - Latanoprost
    - Anti-epileptics
      - Topiramate
      - Phenytoin
    - Immunosuppressants
      - Methotrexate
      - Mycophenolate mofetil
- Sitagliptin appears to *not* be a common culprit (though this is debatable)
- This is probably a diagnosis of *exclusion*

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Chronic Cough – Other Etiologies

- Chronic bronchitis
  - Cough + sputum production over at least a 3 month period for more than 2 consecutive years
  - Exclusively in smokers/former smokers
  - Chronic cough in a smoker is *not* enough to diagnose COPD
    - Need PFTs!
- Chronic/recurrent aspiration
  - Suspect when coughing after eating/drinking
  - Higher risk patients:
    - Elderly, poor dentition, neuromuscular condition, head/neck cancer patients

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Chronic Cough – Other Etiologies

- Foreign body aspiration
  - Most times will have an acute presentation after known event
  - However, aspiration of smaller, non-dissolvable objects can occlude smaller/distal airways
    - Suspect if:
      - Focal wheezing
      - Foul-smelling sputum
      - Isolated lobar atelectasis on chest imaging
      - Persistent consolidation on chest imaging
- Somatic cough disorder
  - Often referred to as 'psychogenic cough' or 'habit cough'
  - Diagnosis of exclusion
  - Cough often absent when distracted/when sleeping
  - Consider evaluation for depression, anxiety, domestic violence, etc.

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Case

- 45 year old female presents with dry cough that started 2 years ago
  - Greatly interferes with her life
  - Normal PFTs, chest X-ray, chest CT, swallow evaluation, esophageal pH monitoring, bronchoscopy, ENT evaluation
  - Cough has persisted despite:
    - Inhalers
    - GERD therapy
    - Anti-histamines
    - Nasal steroids
    - OTC cough suppressants
  - Physical exam completely normal with no wheezing, post-nasal drainage, etc
  - Otherwise healthy and takes no medications
  - Diagnosis?

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Unexplained Chronic Cough

- Also known as:
  - Chronic idiopathic cough
  - Refractory chronic cough
  - Neurogenic cough
  - Cough hypersensitivity syndrome
- Cough persists despite:
  - thorough evaluation into the cause of cough (PFTs, chest imaging, reflux work-up, pulmonary/ENT evaluation)

    AND
  - empiric treatments (inhalers, GERD treatment, treatment of rhinosinusitis, etc)

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Refractory Chronic Cough - Management

- Non-pharmacologic interventions:
  - Multimodality speech therapy
- Pharmacologic interventions:
  - Antitussive agents
    - Dextromethorphan → decreases sensitivity of cough receptors
    - Benzonatate (Tessalon perles) → anesthetizes the 'stretch' receptors in the lungs/pleura
    - Guaifenesin → reduces airway viscosity; inhibits cough reflex sensitivity
    - Nebulized lidocaine → not recommended long-term (increases choking/aspiration risk as it numbs up oropharynx)

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Refractory Chronic Cough - Management

- Pharmacologic interventions (cont.)
  - Gabapentin and pregabalin
    - Gamma aminobutyric acid analogs → inhibit neurotransmitter release
    - Initiate gabapentin at a low dose (ie 300 mg at night) with gradual increases until cough relief
      - Somnolence is major side effect
      - Use very cautiously in patients with significant kidney disease (ie gabapentin toxicity)
  - Opiates
    - Morphine and codeine
    - Major side effects include respiratory depression, somnolence, constipation
    - Would use only in *extreme* circumstances (pneumothorax from coughing, palliation in metastatic cancer patients)

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Refractory Chronic Cough - Management

- Pharmacologic interventions (cont.)
  - Investigational approaches:
    - P2X3 antagonists → blunt sensitivity of airway sensory nerve fibers
      - Gefapixant
        - Significant risk of serious taste disturbance (benefit may not outweigh risk?)
        - Not FDA-approved
    - Superior laryngeal nerve block
      - Questionable benefit

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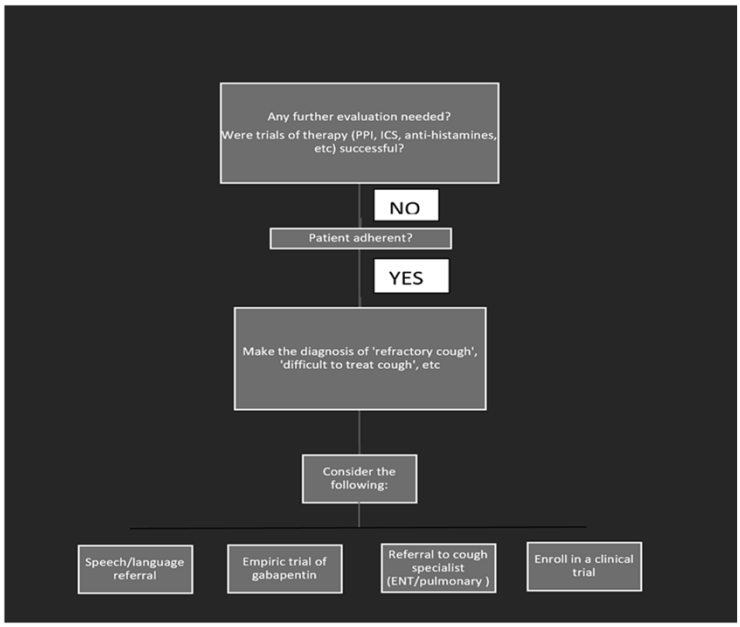
Refractory Chronic Cough - Management



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Chronic Cough – Summary/Basic Approach

- Initiate a history/physical-guided investigation
  - Smoker with 12 months of a purulent cough does not need a GERD work-up
  - Non-smoker with cough + heartburn + throat clearing does not need pulmonary function testing/chest CT
- Expedited work-up for ‘red flag’ signs/symptoms
  - Cough +
    - Hemoptysis, weight loss → chest imaging, pulmonary referral
    - Dysphagia, weight loss → barium swallow, gastroenterology referral
    - Voice hoarseness, tobacco abuse → ENT referral

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Chronic Cough – Summary/Basic Approach

- If no red flags present:
  - Can treat most common causes of chronic cough empirically
    - GERD (lifestyle modifications, time-limited trial of PPI)
    - Asthma (short/long-acting bronchodilators, inhaled steroids)
    - Upper airway cough syndrome (nasal steroids, decongestants, anti-histamines)
- If cough persists after 1-3 months of therapy, consider referral to:
  - Gastroenterology
  - Pulmonology
  - ENT

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Chronic Cough – Guidelines

- American College of Chest Physicians guidelines:

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Chronic Cough – CHEST Guidelines

4 Most Common Causes to Consider:
1. Upper Airway Cough Syndrome (UACS) secondary to rhinosinus diseases Consider: • Sinus imaging • Nasopharyngoscopy • Allergy evaluation or empiric treatment
2. Asthma Ideally evaluate: • Spirometry • Bronchodilator reversibility • Bronchoprovocation challenge • Allergy evaluation or empiric treatment

source: https://doi.org/10.1016/j.chest.2017.10.016

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Chronic Cough – CHEST Guidelines

4 Most Common Causes to Consider:
3. Non-asthmatic Eosinophilic Bronchitis (NAEB) Ideally evaluate: • Sputum eosinophilia • Fraction exhaled nitric oxide (FENO) • Allergy evaluation or empiric treatment
4. Gastroesophageal Reflux Disease (GERD) Physiologic testing for refractory patients Initial treatment to include: • More than acid suppression

source: https://doi.org/10.1016/j.chest.2017.10.016

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Chronic Cough – CHEST Guidelines

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 enactment 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 a referral to a Cough Clinic for refractory cough

Red Flags

- **Hemoptysis**
- **Smoker > 45 years of age with a new cough, change in cough, or coexisting voice disturbance**
- **Adults aged 55-80 years who have a 30 pack-year smoking history and currently smoke or who have quit within the past 15 years**
- **Prominent dyspnea, especially at rest or 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**

source: https://doi.org/10.1016/j.chest.2017.10.016

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Chronic Cough – Imaging

- American College of Radiology recommendations:

Variant 1. Chronic cough lasting more than 8 weeks. No known risk factors for lung cancer. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	☢
CT chest with IV contrast	May Be Appropriate	☢☢☢
CT chest without IV contrast	May Be Appropriate	☢☢☢
MRI chest without and with IV contrast	Usually Not Appropriate	O
MRI chest without IV contrast	Usually Not Appropriate	O
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

https://doi.org/10.1016/j.chest.2017.10.016

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Chronic Cough – Imaging

- American College of Radiology recommendations:

Variant 2. Chronic cough lasting more than 8 weeks. Increased risk for lung cancer. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	
CT chest with IV contrast	May Be Appropriate	
CT chest without IV contrast	May Be Appropriate	
MRI chest without and with IV contrast	Usually Not Appropriate	O
MRI chest without IV contrast	Usually Not Appropriate	O
CT chest without and with IV contrast	Usually Not Appropriate	
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	

https://doi.org/10.1016/j.chest.2017.10.016

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Variant 3. Chronic cough lasting more than 8 weeks. Persistent symptoms despite initial clinical evaluation and empiric treatment. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Radiography chest	Usually Appropriate	
CT chest with IV contrast	Usually Appropriate	
CT chest without IV contrast	Usually Appropriate	
CT maxillofacial without IV contrast	May Be Appropriate	
Fluoroscopy biphasic esophagram	Usually Not Appropriate	
MRI heart function and morphology without and with IV contrast	Usually Not Appropriate	O
CT maxillofacial with IV contrast	Usually Not Appropriate	
CT chest without and with IV contrast	Usually Not Appropriate	
CT maxillofacial without and with IV contrast	Usually Not Appropriate	
V/Q scan lung	Usually Not Appropriate	
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	
SPECT or SPECT/CT MPI rest and stress	Usually Not Appropriate	

https://doi.org/10.1016/j.chest.2017.10.016

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Chronic Cough – Key Points/Pearls

- Use a stepwise approach
  - Try to avoid the kitchen sink approach
- Watch out for 'red flag' signs/symptoms
  - Weight loss, hemoptysis, hypoxia
- Evaluate for/treat the most common causes first (ie asthma, GERD, chronic rhinosinusitis)
- Persistent/refractory cough can be very distressing to both patients *and* providers
  - Keep a relatively low threshold to refer to pulmonary, ENT, GI, etc
- Expectation management may be necessary/key
  - The longer something is going on, the less likely it is to formally diagnosed/treated

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