Chronic Cough

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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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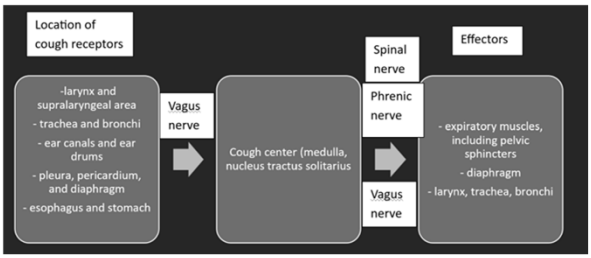
Why Do We Cough?



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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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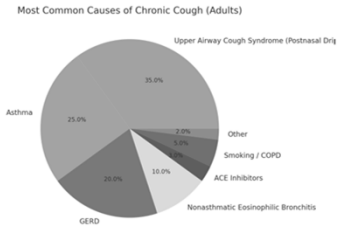
Chronic Cough



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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

- Pulmonary function testing:

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

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		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 propionate DPI) 55, 113, 232 mg Dosed twice daily	N/A	N/A	113mcg	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® (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 360mcg*	N/A	720mcg*	720mcg*	N/A	N/A	1440mcg*
Pulmicort Respules® (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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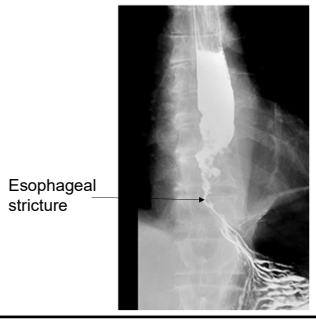
GERD



- GI referral for EGD…

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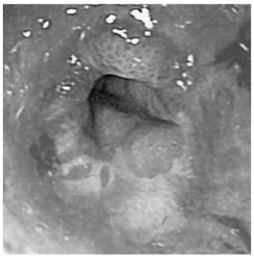
GERD



- 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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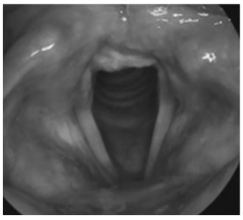
Chronic Cough - LPR

- 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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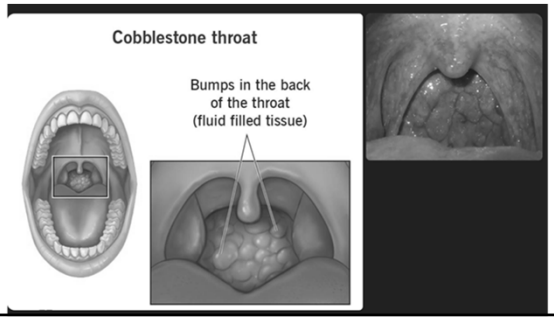
Upper Airway Cough Syndrome (UACS)



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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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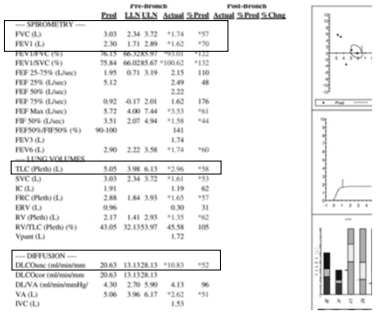
Interstitial Lung Disease



	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		
Vpast (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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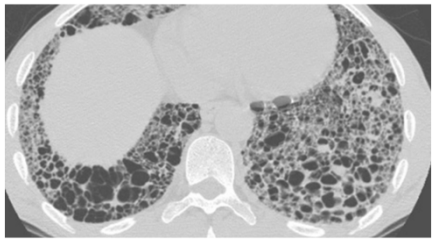
Chronic Cough - Interstitial Lung Disease



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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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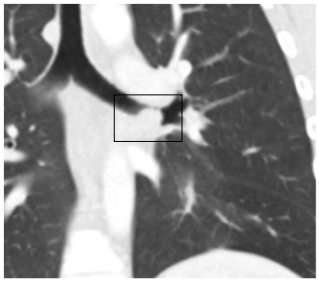
Lung Cancer



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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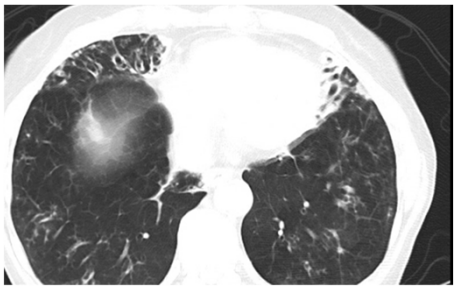
Bronchiectasis



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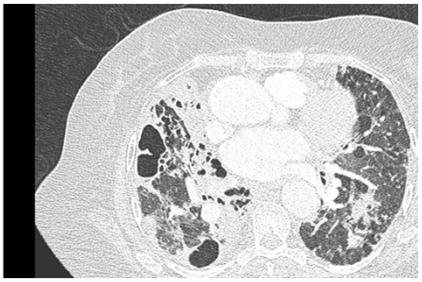
Bronchiectasis



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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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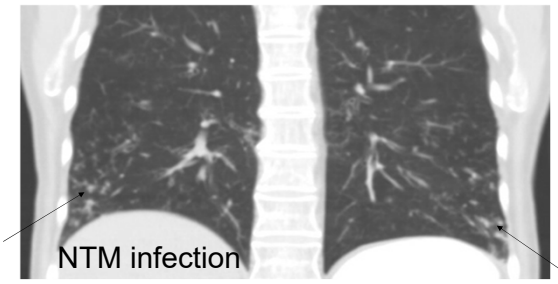
Indolent Infection



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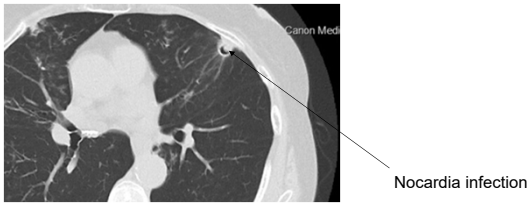
Indolent Infection



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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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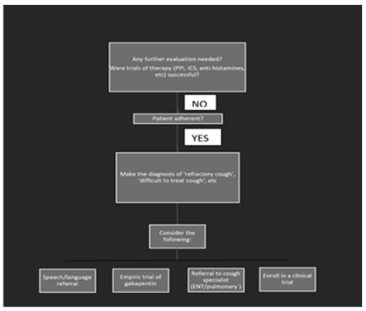
Refractory Chronic Cough - Management



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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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