5 & a Half Cases of Chronic Cough

Augustine Lee, MD

Mayo Clinic Florida

Disclaimers

- No conflict of interest
- I am not crazy
- Will mention medications not FDA approved for chronic cough

Goals

- Some clinical pearls on chronic cough
- Updates on chronic cough mechanisms
- Convince you cough is sexy

A Case of the Tough Mucus

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

Prior Testing

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

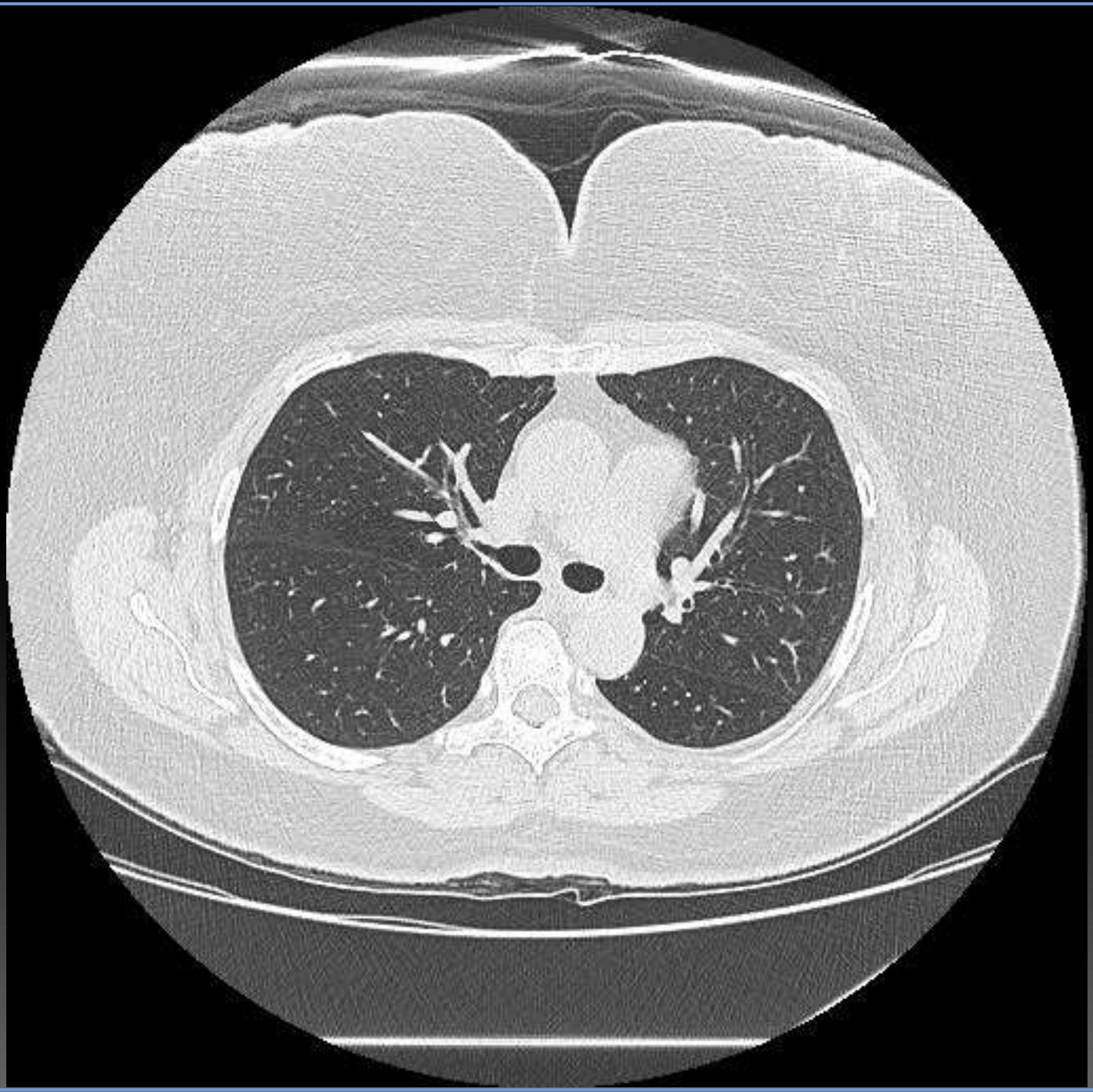

What am I supposed to do now?
STOP
WRONG WAY
DO NOT ENTER

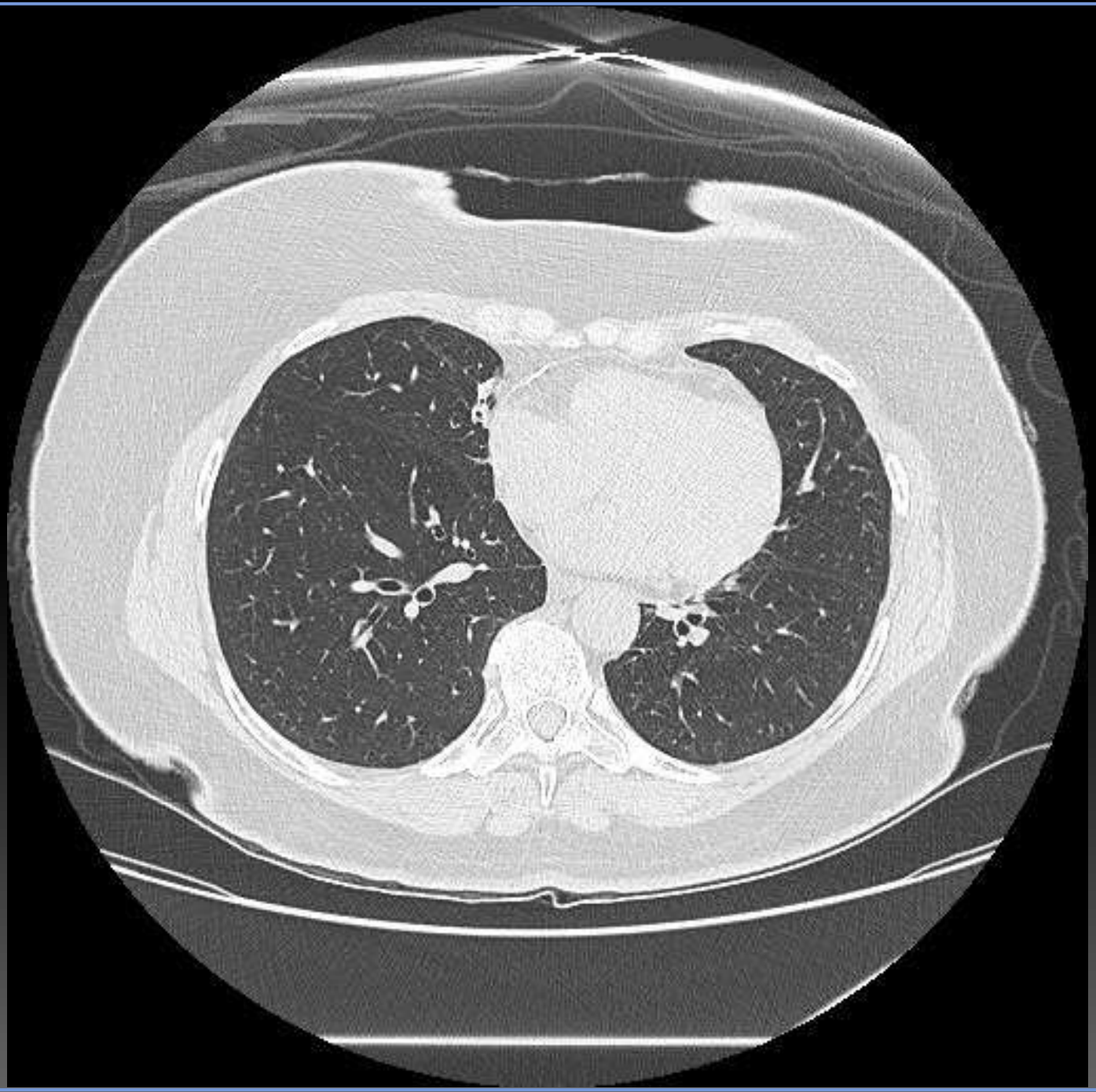
No diagnosis ?

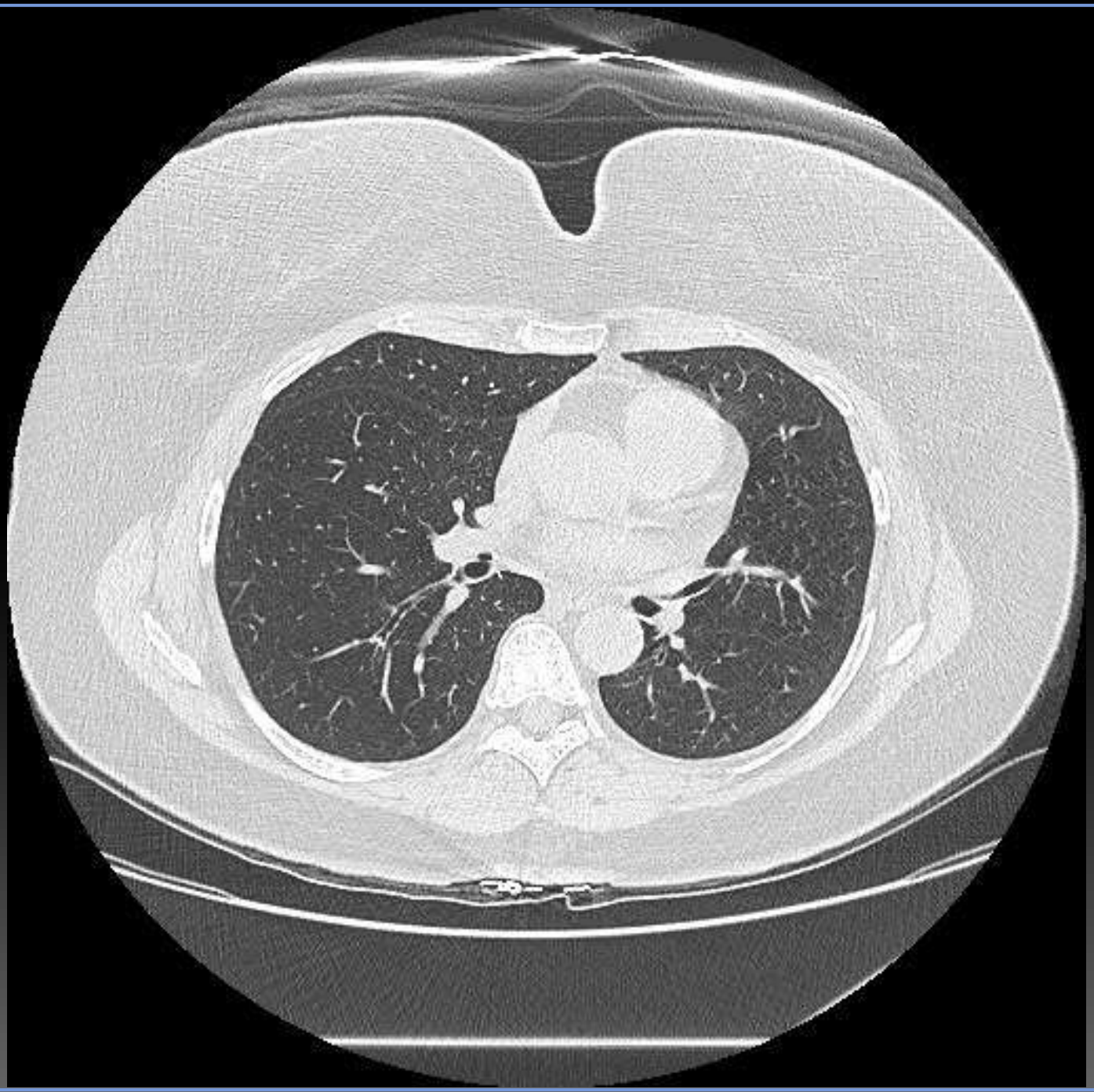
- Diagnosis: A cough that is trying to clear impacted mucus

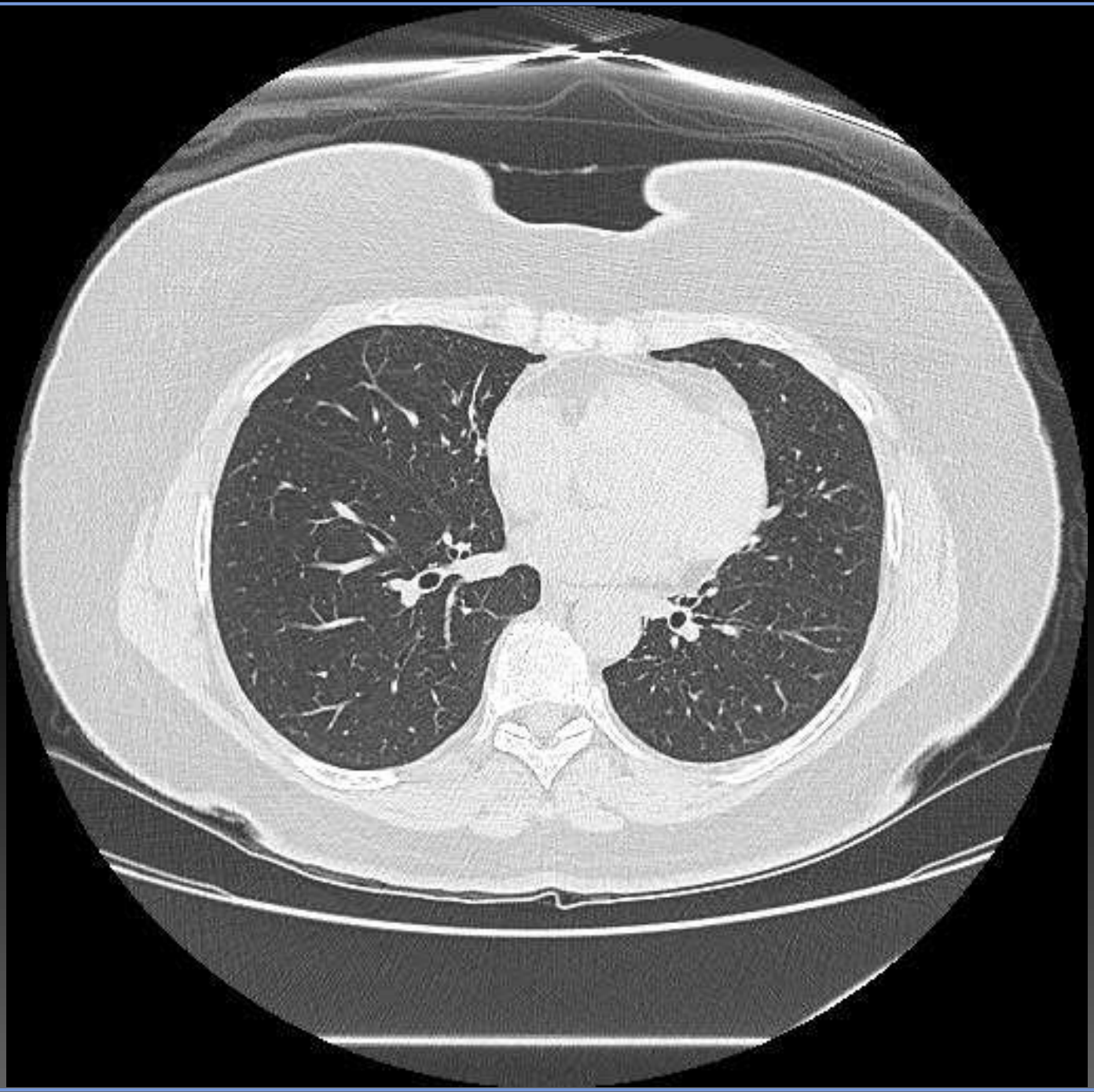
- Treatment:
  - Counseling (lots…)
  - Secretion mobilization
    - Airway hydration: 7% hypertonic saline
    - Oscillatory PEP
    - +/- VEST
    - Future? : macrolides

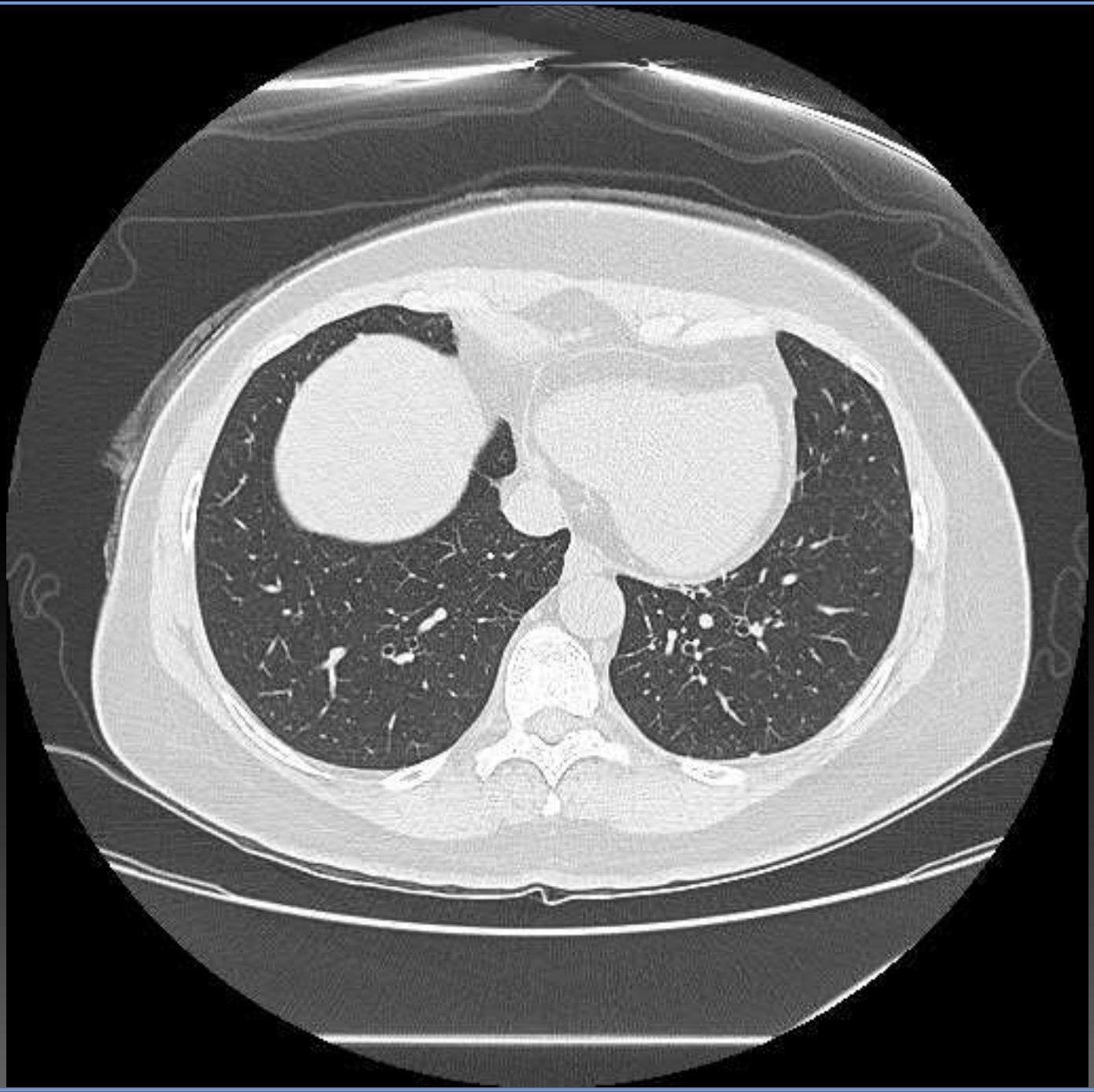
- 3 months follow-up
  - 90% better.
  - CSQL 42











Non-CF Bronchiectasis

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

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

Non-CF Bronchiectasis

- Treat underlying condition?
  - ?MAC
  - ?Obstructive lung disease
  - ?Aspiration
- Bronchial hygiene
  - Airway hydration: Saline nebs
  - Secretion mobilization: Oscillatory PEP, VEST/CPT, etc.
  - +/- Reduce inflammation & mucus generation: mucolytics, inhalers, antibiotics

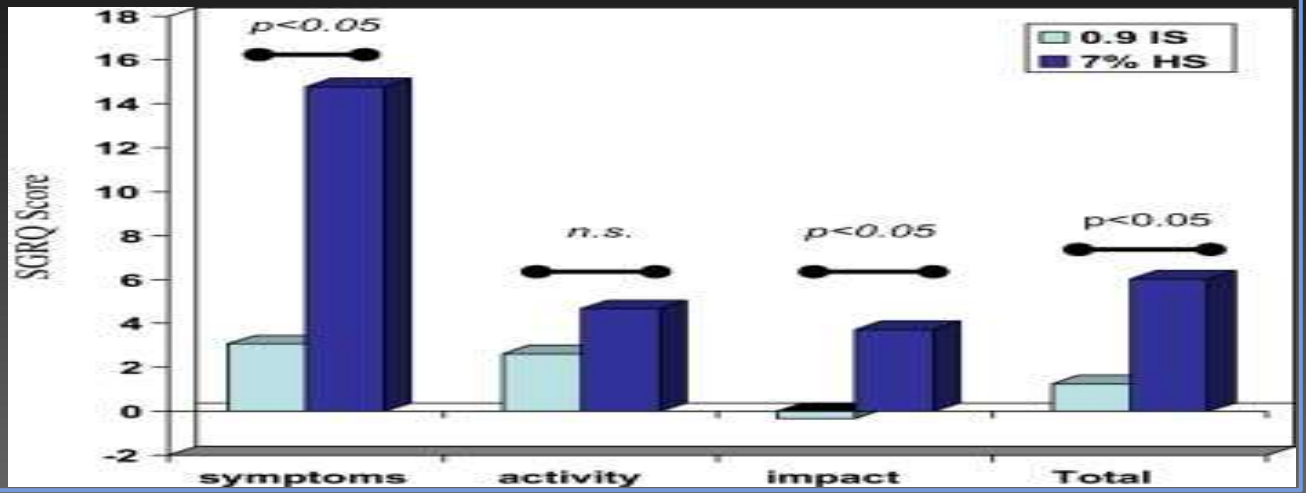
Sjogrens

- Chronic cough is leading symptom
  - ~41-50%
- Airway
  - Bronchiectasis, bronchiolitis
- Interstitial
  - NSIP, UIP, LIP
- Lymphoproliferative, +/- amyloid
  - LIP ~ Cystic lung disease with Nodules
- Xerotrachea
  - Dry cough, dry respiratory mucosa, no other physiologic or radiographic abnormality
  - ?Cevimeline/pilocarpine, airway hydration, biotene products…

- *Respiratory Medicine 2011 Dec; 105(12):1831–1835*

"Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis"

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



Lesson's (for me)

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

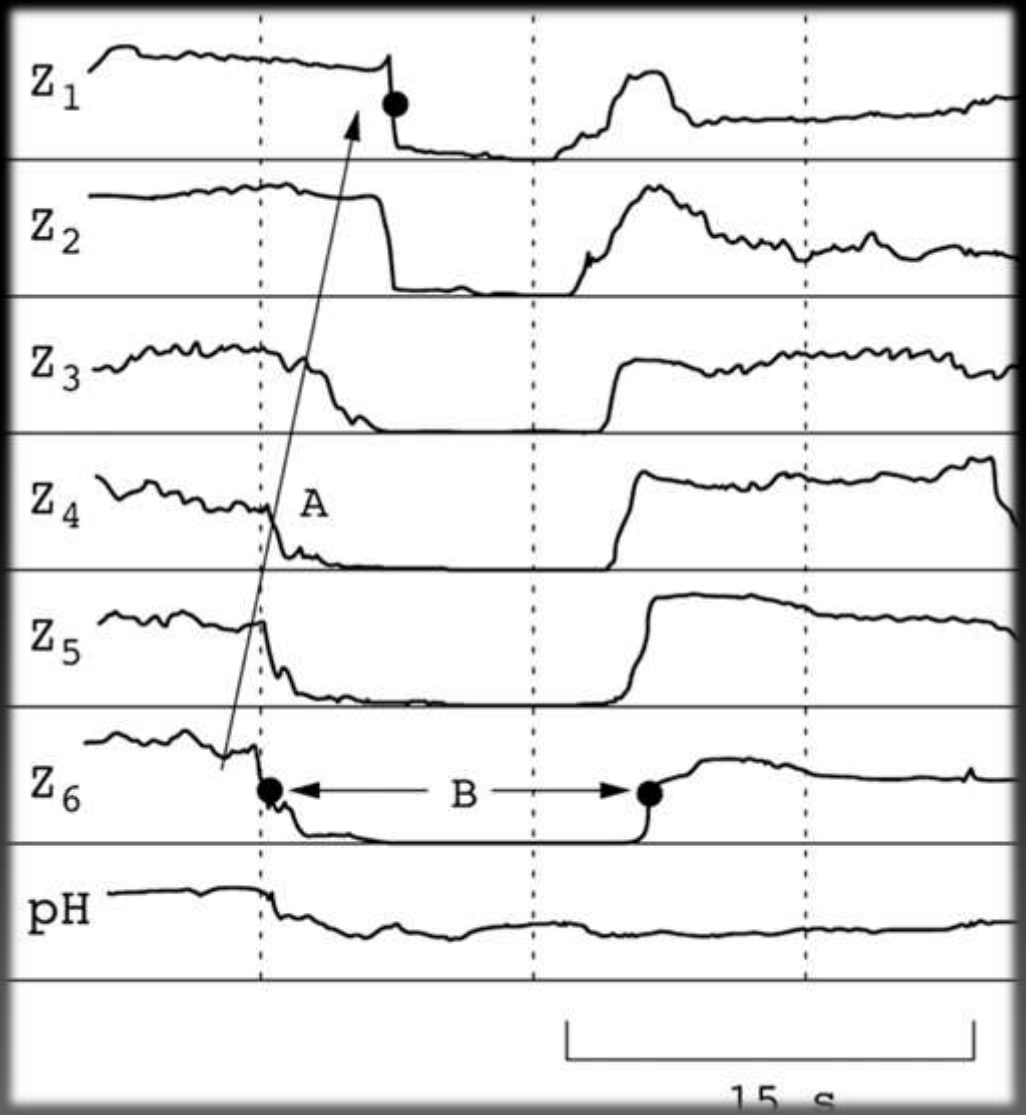
Proton pump inhibitors galore

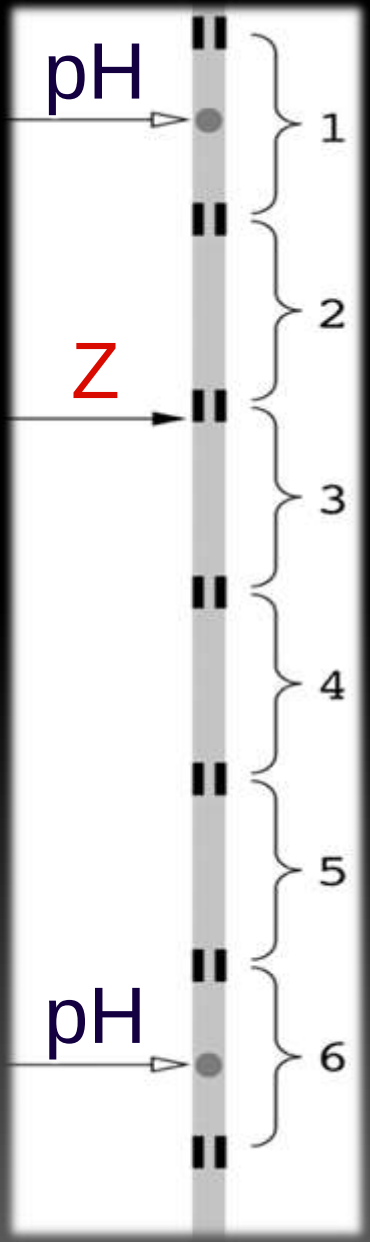
- 69 yo F (DM), Cough for 15 years
  - Minimal occasional white mucus
  - Severe and disruptive with CSQL 80/112
  - No reflux symptoms: i.e. heartburn, regurgitation
- Prior Testing
  - CXR, allergy test (cats), EGD (gastritis), ENT, sinus CT
- Treatments
  - High dose BID PPI's +H2, systemic steroids, inhalers, allergy shots, nasal sprays & rinses
- Testing
  - HRCT chest (h/o melanoma) → Incidental micronodules, proving stable
  - Normal PFT (negative methacholine at 25mg/mL)
  - Impedance-pH study

Impedance-pH (off meds)

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

MII-pH (multichannel intraluminal impedance-pH)

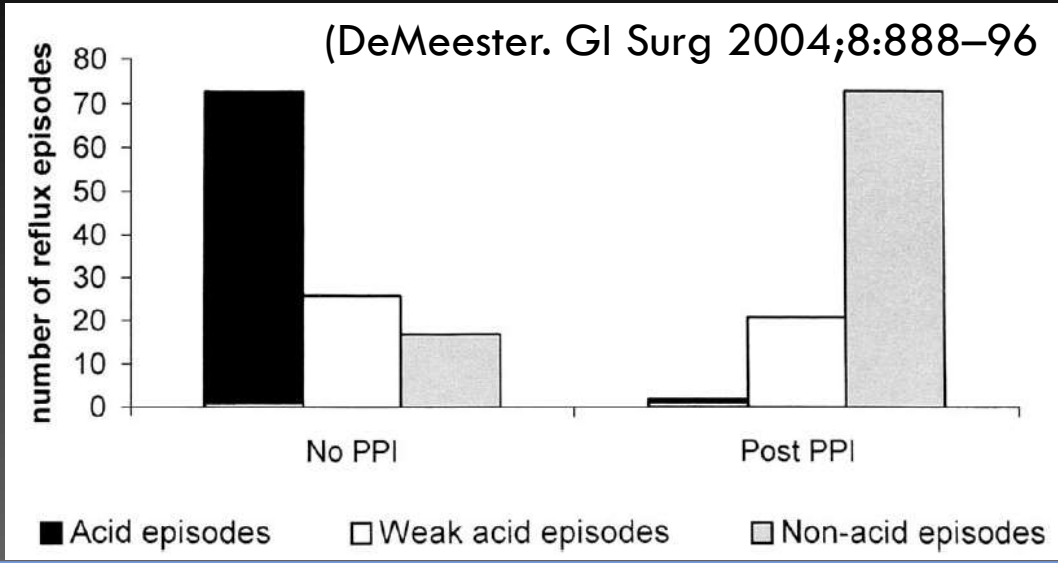




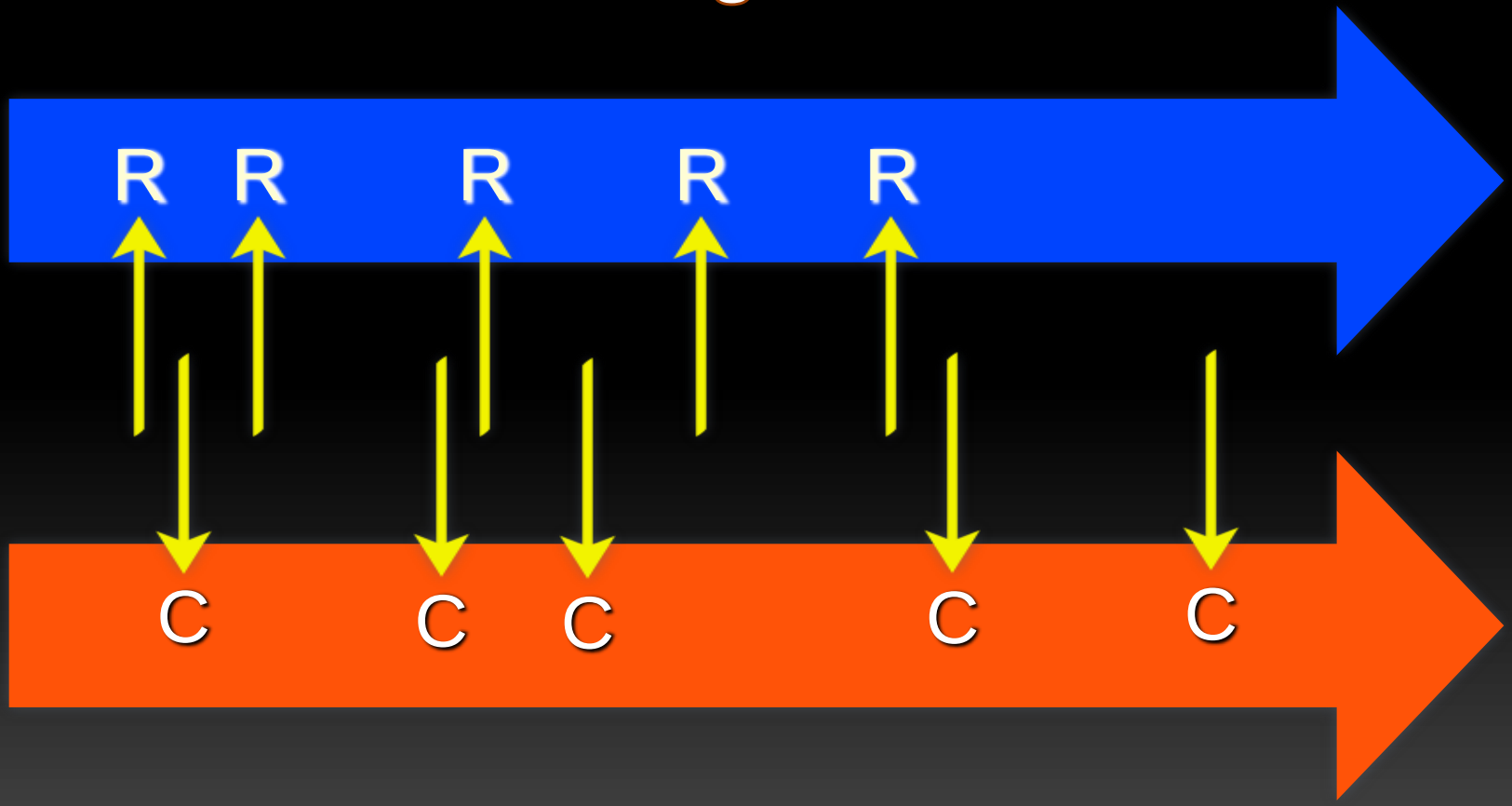
DelBuono ArchDisChild 2005

GERD pathophysiology

- Gastric juices reflux into the esophagus
  - Transient lower esophageal sphincter relaxations (TLESR)
  - Increased gastric-esophageal pressure gradient
  - EGJ: LES/Crural diaphragm
- Diagnosis?
  - Questionnaire? EGD? Esophageal x-ray? BRAVO? MII-pH?
- Treating with PPI's…
  - Non-acid reflux matters…



SAP: Reflux → Cough ?



Is the apparent relationship between reflux and cough occurring more than just by chance alone?

SAP: symptom association probability

- 2x2 contingency table of reflux to cough relationships
  - Fisher's exact test on the contingency (i.e. p value)
  - SAP is the 1-p value x100.
- SAP >95% is considered temporally associated more than by chance alone

- Fallacies
  - The "window"
  - The patient underestimates cough episodes
  - Impedance-pH catheter can suppress cough
  - The mathematics & the algorithmic calculation of the SAP is actually not quite as mathematical as sold

So what to do after high dose PPI/H2?

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

Lessons (for me)

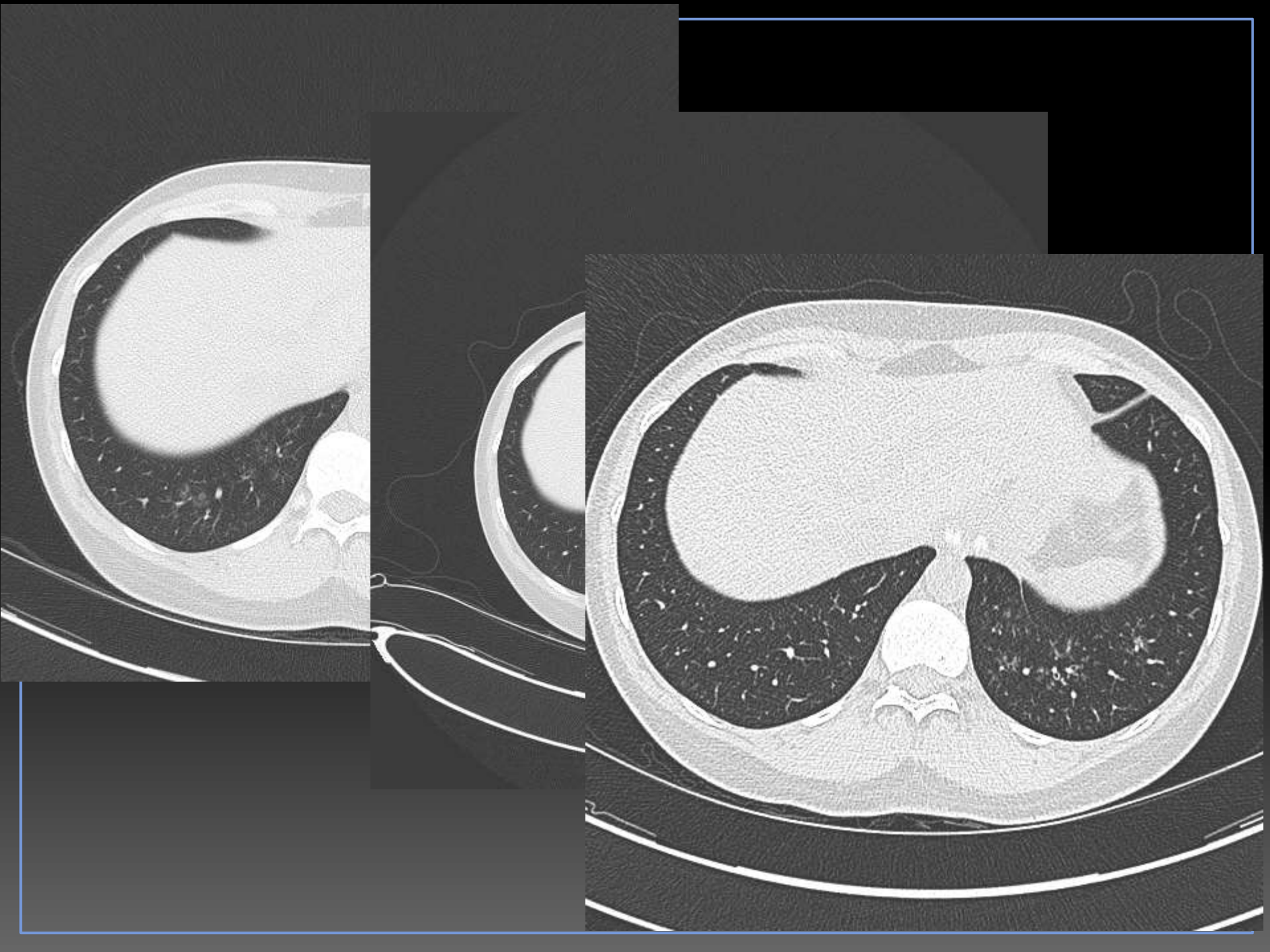
- Reflux can truly be asymptomatic
- Reflux is not a problem of excess acid
- PPI's are not the end-all of reflux
- Impedance based testing with temporal association studies may give you better logic or the value of interventions or not

Out there treatment for cough

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

Failed and Tried

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



Reflux surgery?

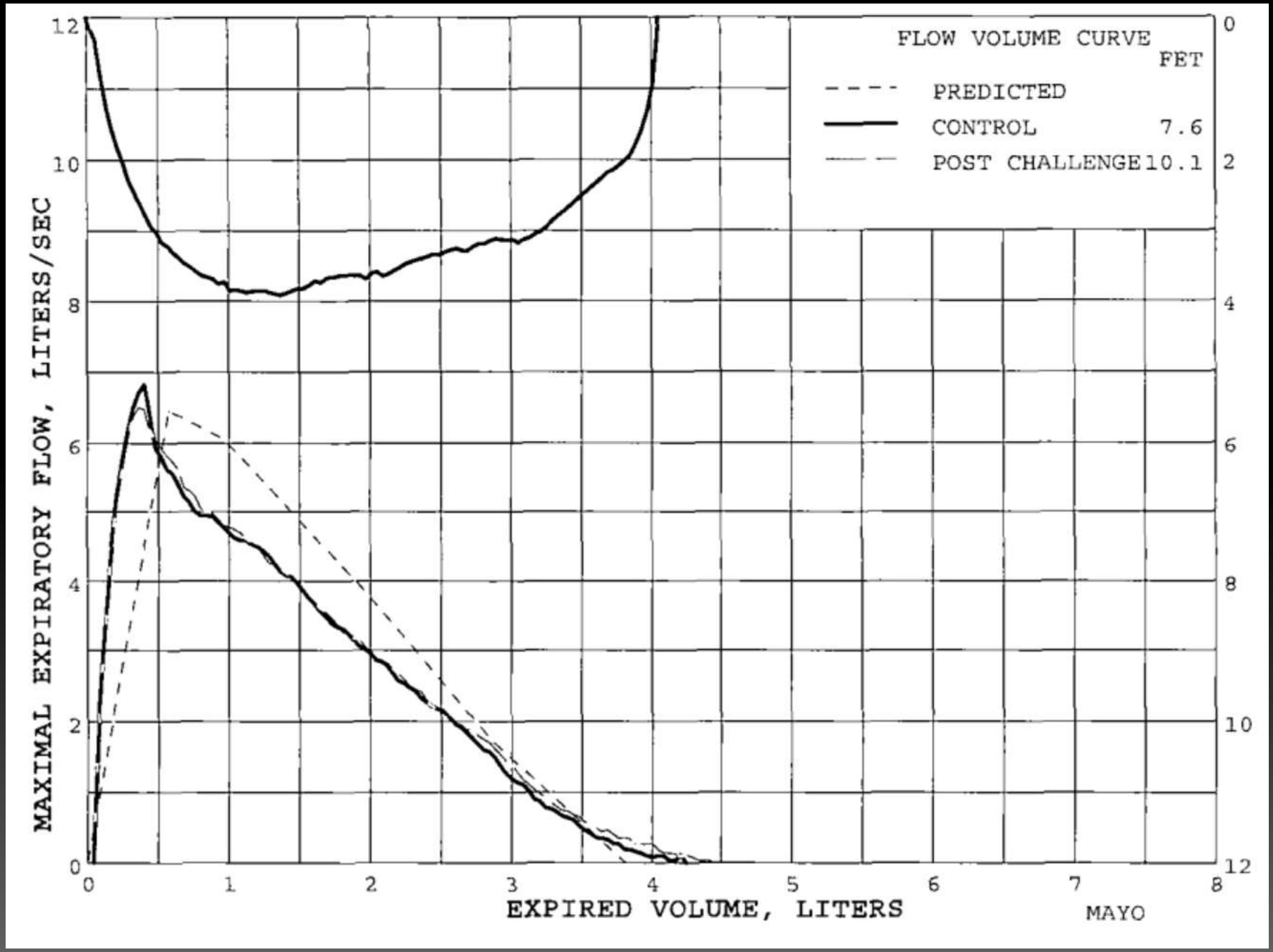
- Reflux? Yes!
  - EGD, BRAVO DeMeester 40
- GI Symptomatic Reflux? Yes!
  - Heartburn, regurgitation
- Resp. Reflux related? Maybe…
  - 5 episode of cough… (SAP neg.)
  - But the CT's c/w aspiration?

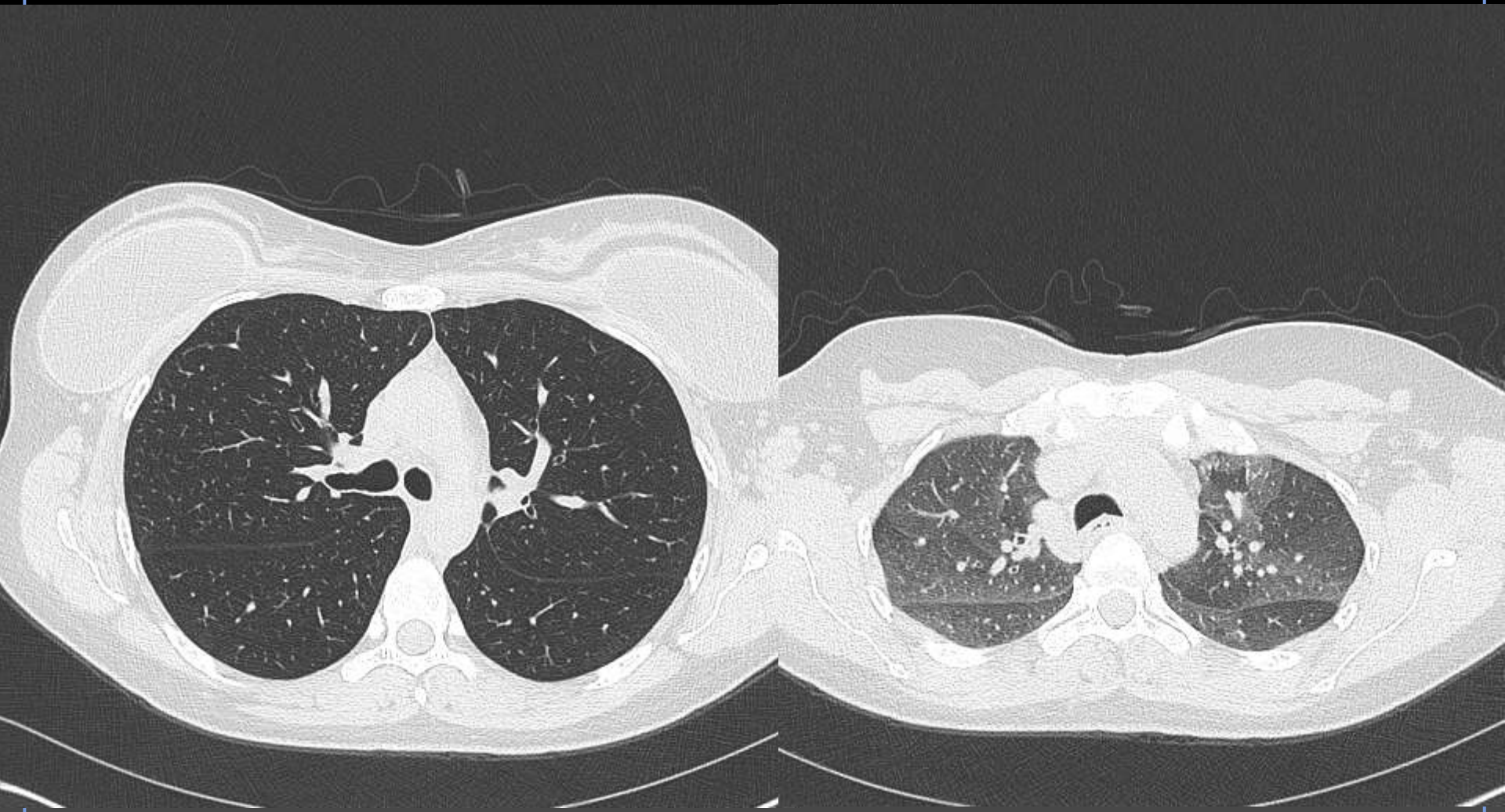
Nissen fundoplication

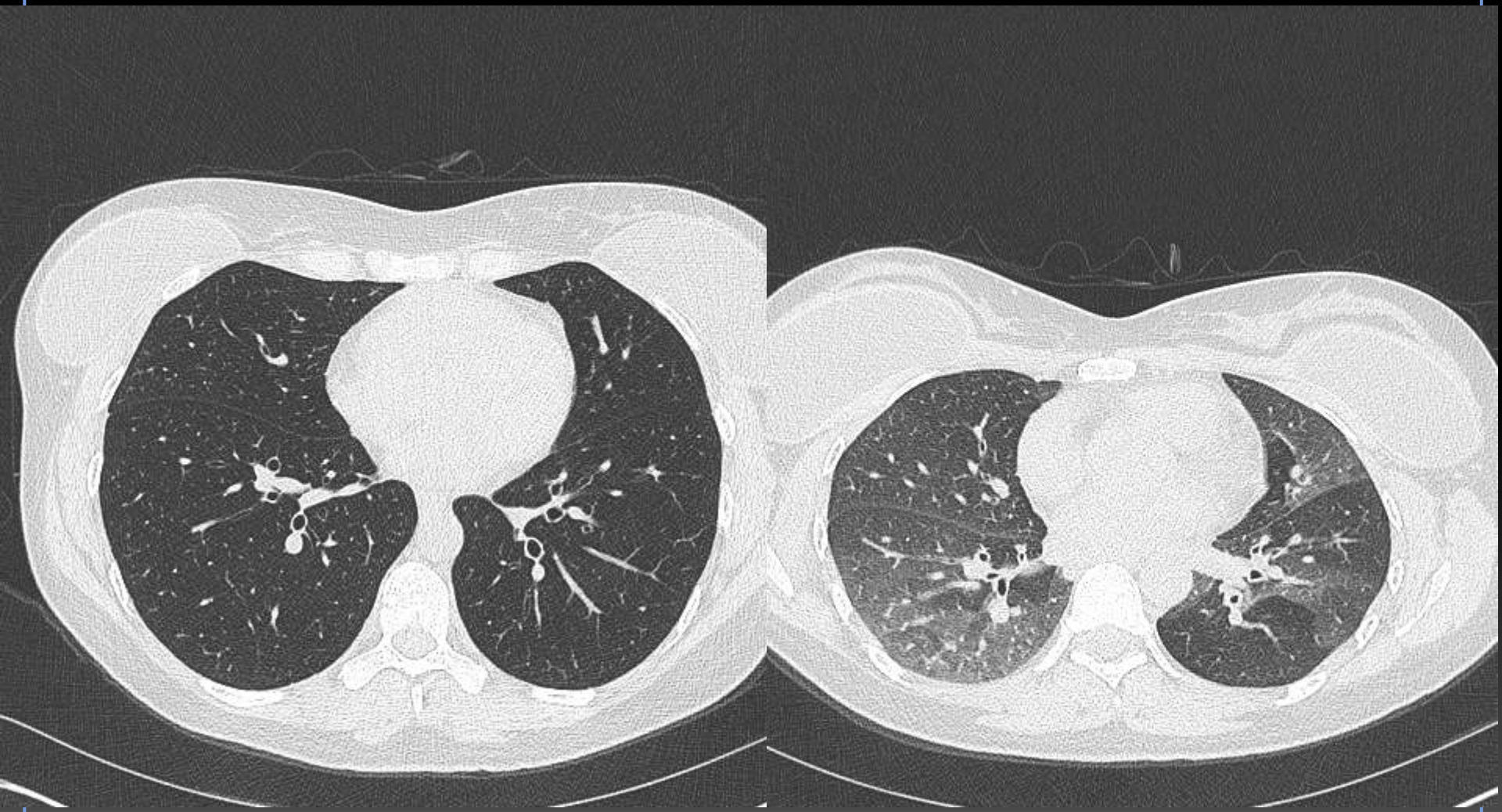
- Complete resolution of heartburn, regurgitation, nocturnal aspirations
- Complete resolution of cough….
  - For a couple weeks
  - Then returned…
- Now what?

Post-fundoplication

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


FLOW VOLUME CURVE
FET
PREDICTED
CONTROL 7.6
POST CHALLENGE 10.1
MAXIMAL EXPIRATORY FLOW, LITERS/SEC
EXPIRED VOLUME, LITERS
MAYO
0
1
2
3
4
5
6
7
8
12
10
8
6
4
2
0
0
2
4
6
8
10
12





Inflammatory Airway Disease ?

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

Patterns of airway involvement in IBD. Papanikolaou. 2014 Nov; 5(4) 560

IBD & the Lungs

- Airway disease
  - Most prevalent manifestation
    - HRCT series 22-89%: Airway thickening/dilation, TIB, Mosaicism, centrilobular (Independent of symptoms, PFT)
  - Accounts for 40-63% of clinically significant pulmonary complaints
  - Can follow IBD by many years or decades
  - Usually IBD inactive when respiratory symptoms active/activate
  - Can lead to irreversible stenoses if untreated
- Airway Manifestations
  - Chronic suppurative & nonsuppurative bronchitis, Bronchiectasis, Bronchiolitis (granulomatous, diffuse panbronchiolitis, bronchiolitis obliterans), Stenoses, Asthma

Treatment ?

- Treat associated disorder (e.g. asthma, IBD)
- Avoid steroids per the reviewer
- Maybe she had a mild flare of IBD?
- Infliximab (IBD dosing)
  - Induction: 5 mg/kg at weeks 2 & 6
  - Maintenance: 5 (or 10) mg/kg every 8 weeks
- Cough nearly resolved after first infusions, running backup to 2 miles/day, but the cough partially rebounding at 4 weeks before getting knocked down at the 8 week infusion

Lessons learned

- Even when it is clear reflux is occurring pathologically, be skeptical as to whether reflux surgery will help
- Purulence ≠ Infection
- "Airway disease" is the most common manifestation of IBD, with HRCT being the most sensitive, independent of symptoms/PFT, and can occur decades after active IBD.

Reflux related cough that is not due to reflux

- 40 yo, never smoker, h/o asthma

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

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

Asthma

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

Reflux testing (Impedance-pH)

- Off medications

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

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

Thus, no pathologic reflux, yet there is a temporal association between reflux and cough. Is this reflux-cough?

Reflux-Cough Temporal Association

Smith, Houghton. Gasto 2010, 139:754

- 78 chronic coughers
  - Impedance/pH
  - Acoustic ambulatory cough monitor
- Symptom associated probability (SAP)
- Cough reflex sensitivity
  - Citric acid inhalational challenge

Reflux mediated Cough
(>95% SAP)

	SAP+ (R→C) N=34 (48%)	SAP- (R→C) N=37	P-value
All Reflux events	62	69.5	0.16
Acid Reflux events	39	36	0.31
% time pH<4	3.6%	2.9%	0.59
Non-acid Reflux events	23	20.5	0.97
Citric acid cough sensitivity (Log C5)	-0.9M	-0.6M	**0.03**

Implications

- Both acid and non-acid reflux can be associated with reflux mediated cough !
  - Acid suppression is not the panacea for reflux mediated cough.
- Reflux (total, acid, non-acid) was no more common in those with reflux mediated cough !
  - Pathological levels of reflux is not necessary for reflux to mediate cough. Or, the absence of pathological reflux does not exclude reflux mediated cough.
- However, the cough sensitivity was increased in those with reflux mediated cough !
  - So, supports that reflux isn't necessarily the fundamental problem in reflux mediated cough, but more that reflux is triggering a heightened cough reflex sensitivity.

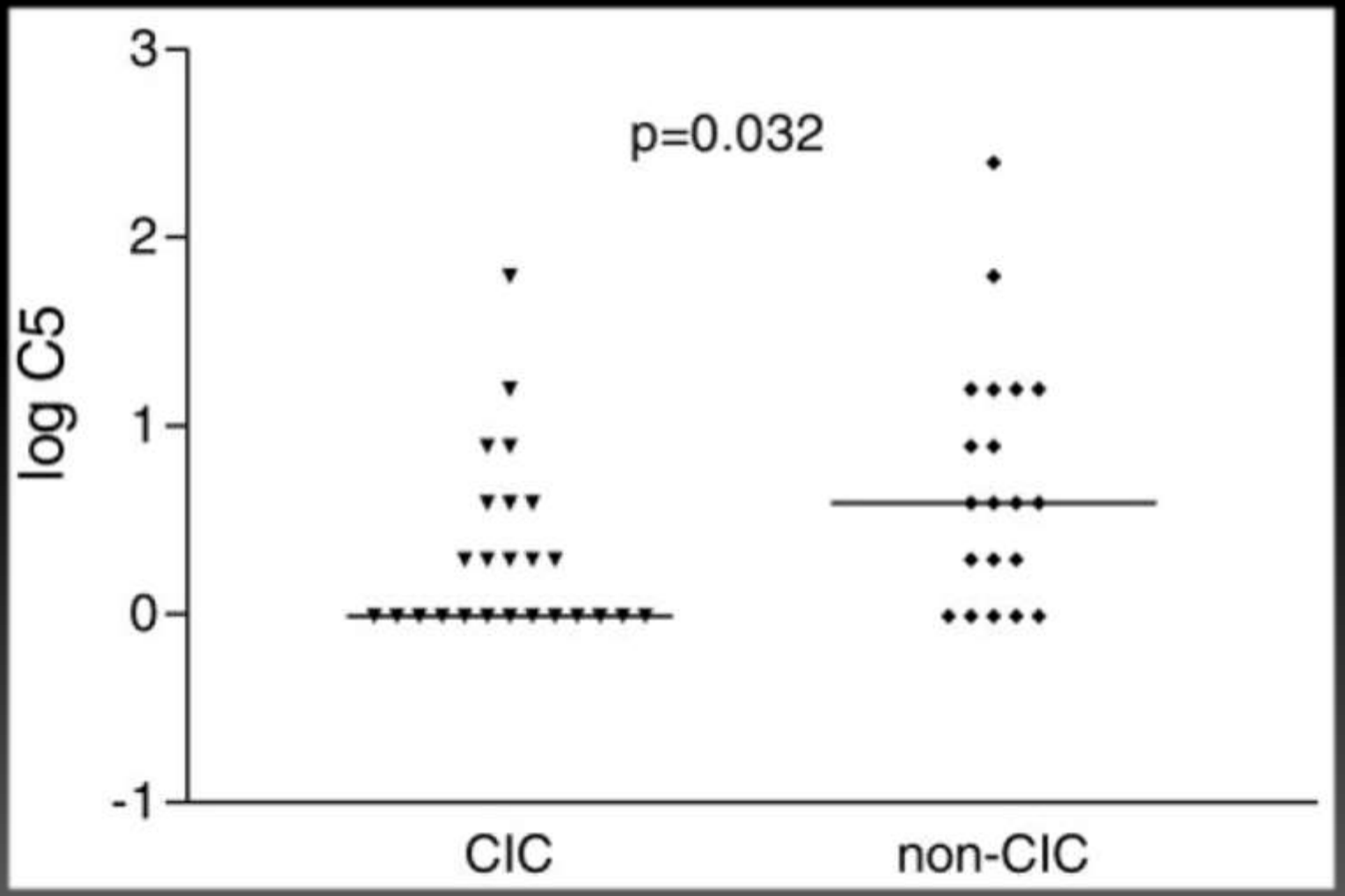
Cough hypersensitivity syndrome

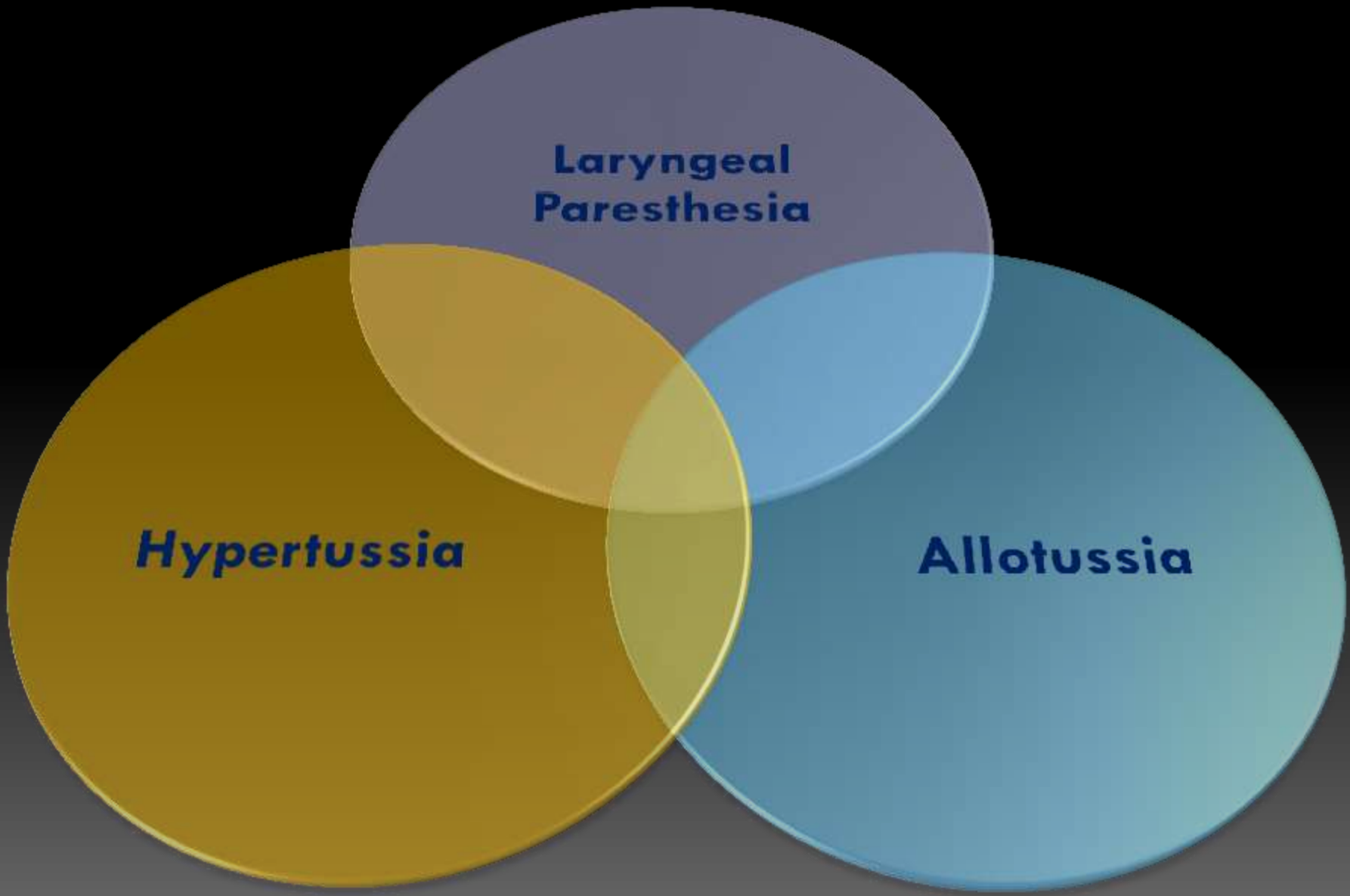
- Women
- Peri-menopausal
- Autoimmune associations (hypothyroidism)
- Airway inflammation (lymphocytes, mast cells)
- Multiple non-allergic sensitivities
  - Odors, perfumes, cleansing agents, dusts, talking, speech, laughing, dry air, deep breath, etc.

Cough Challenge Tests

Chronic idiopathic cough, 42%

Haque, Chest 2005; 127:1710.

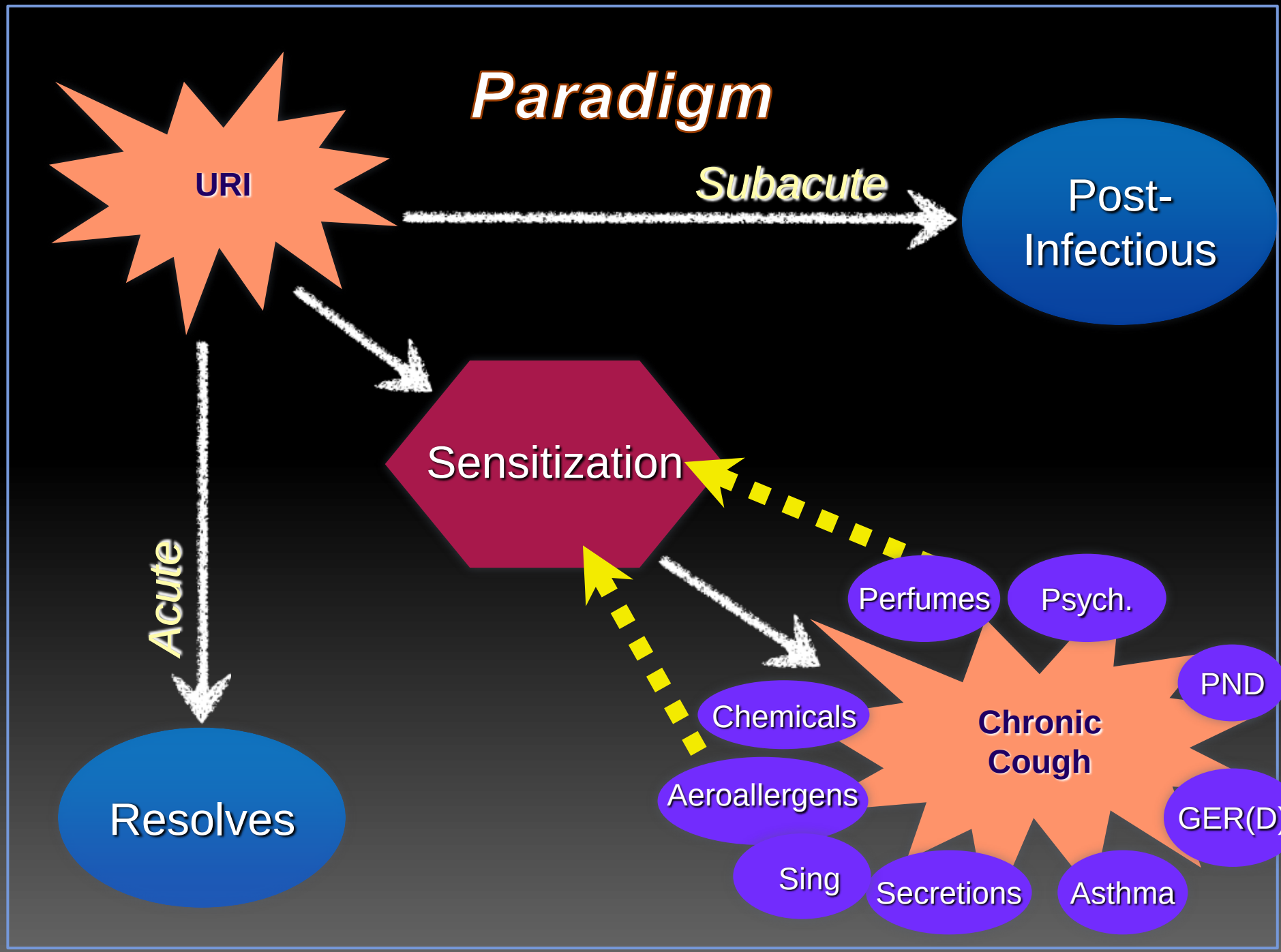


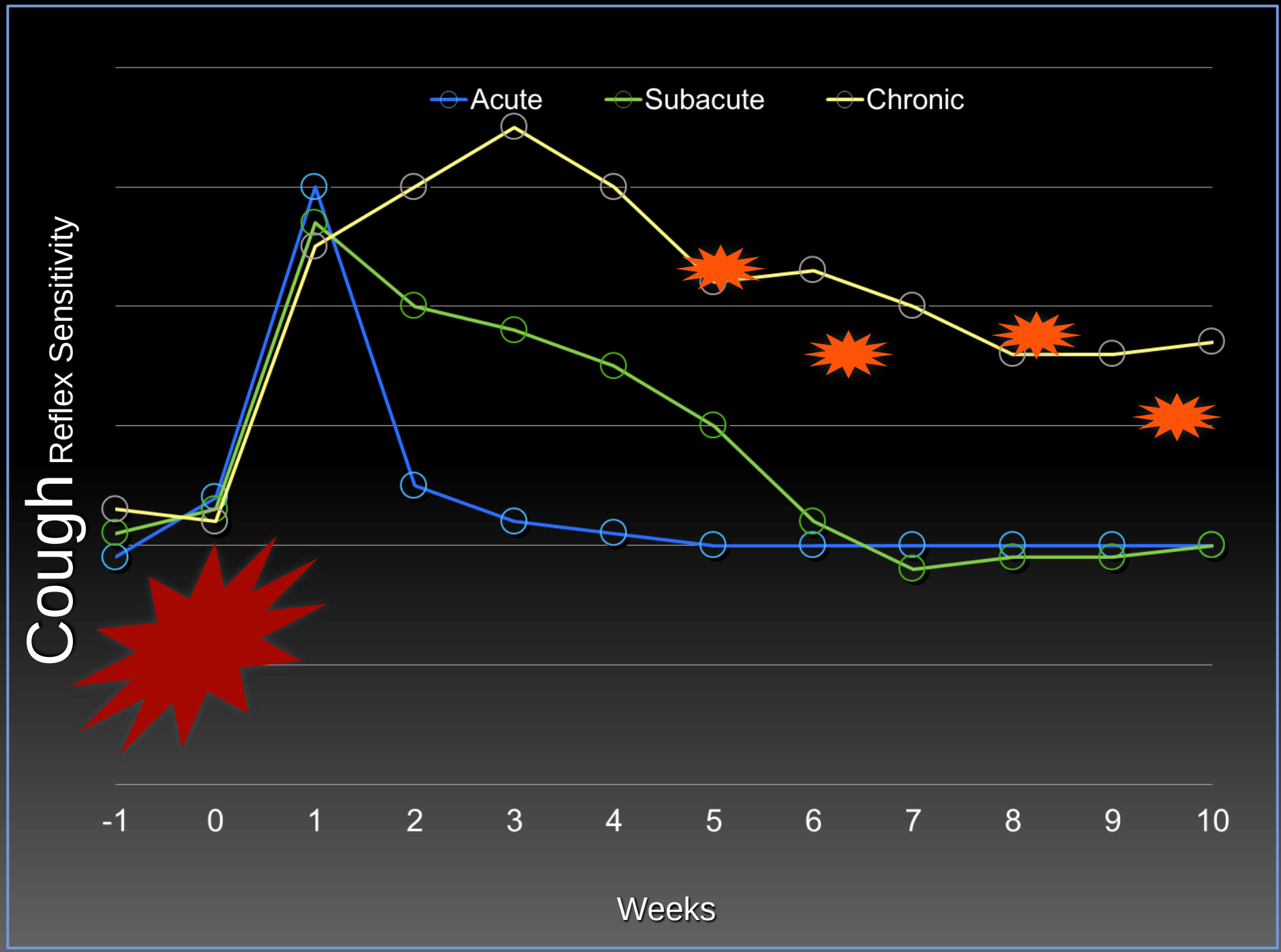

Laryngeal
Paresthesia
Hypertussia
Allotussia

Neuropathy Analogy

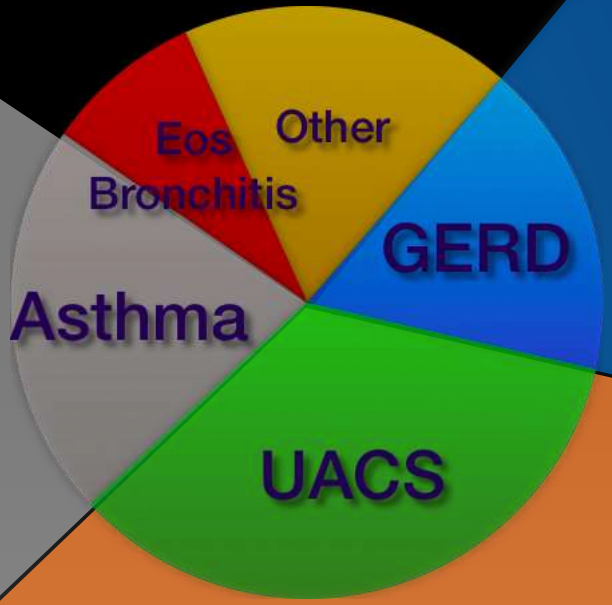
Neuropathy	Cough hypersensitivity
Hyperalgesia	Hypertussia
Allodynia	Allotussia
Paresthesia	Laryngeal paresthesia
Central sensitization	Central / Peripheral sensitization

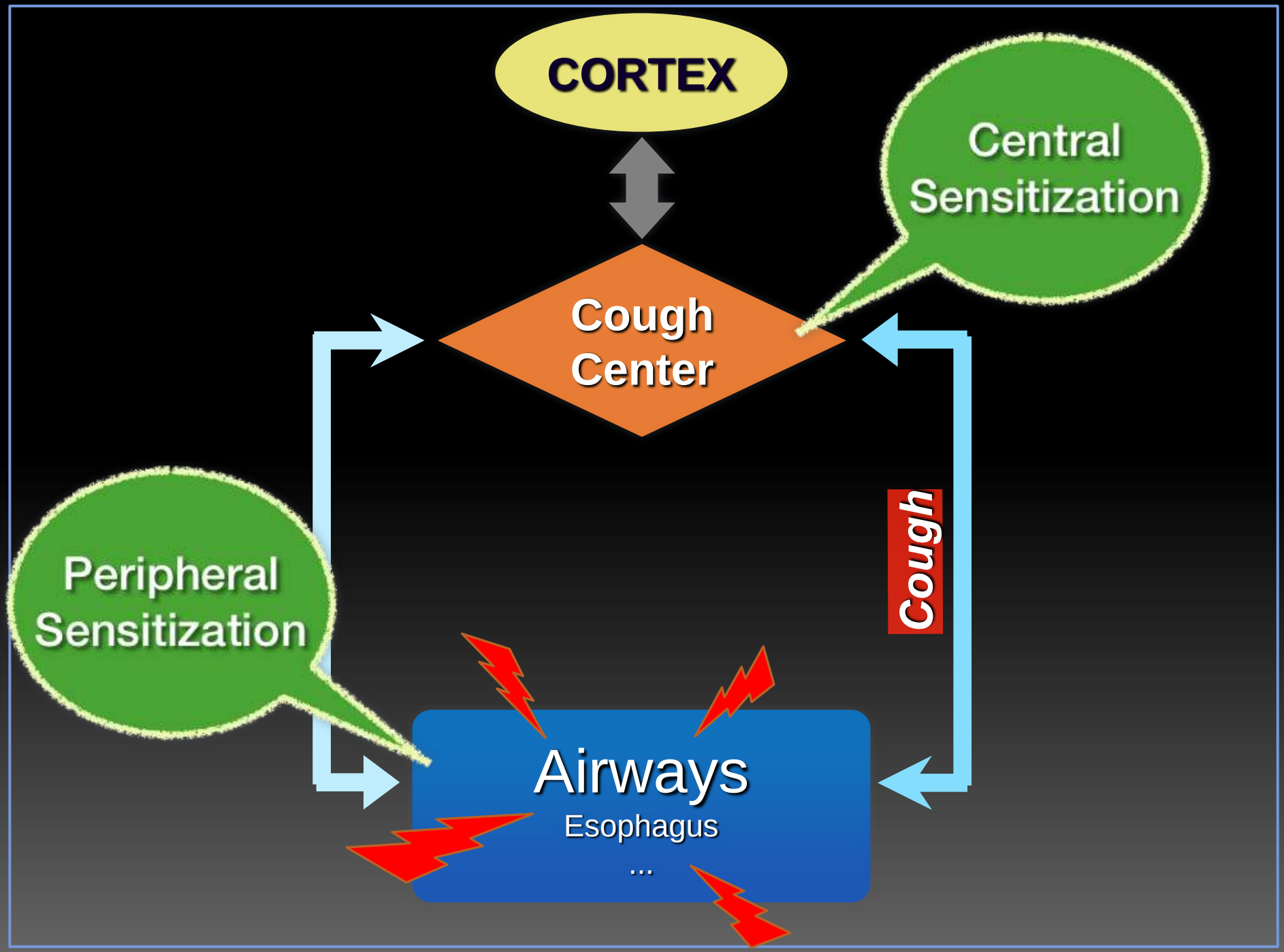
Ryan, Lancet 2012 Nov.


Paradigm
URI
Subacute
Post-Infectious
Sensitization
Acute
Resolves
Perfumes
Psych.
PND
Chemicals
Chronic Cough
Aeroallergens
GER(D)
Sing
Secretions
Asthma


Acute
Subacute
Chronic
Cough Reflex Sensitivity
-1
0
1
2
3
4
5
6
7
8
9
10
Weeks

Paradox ?

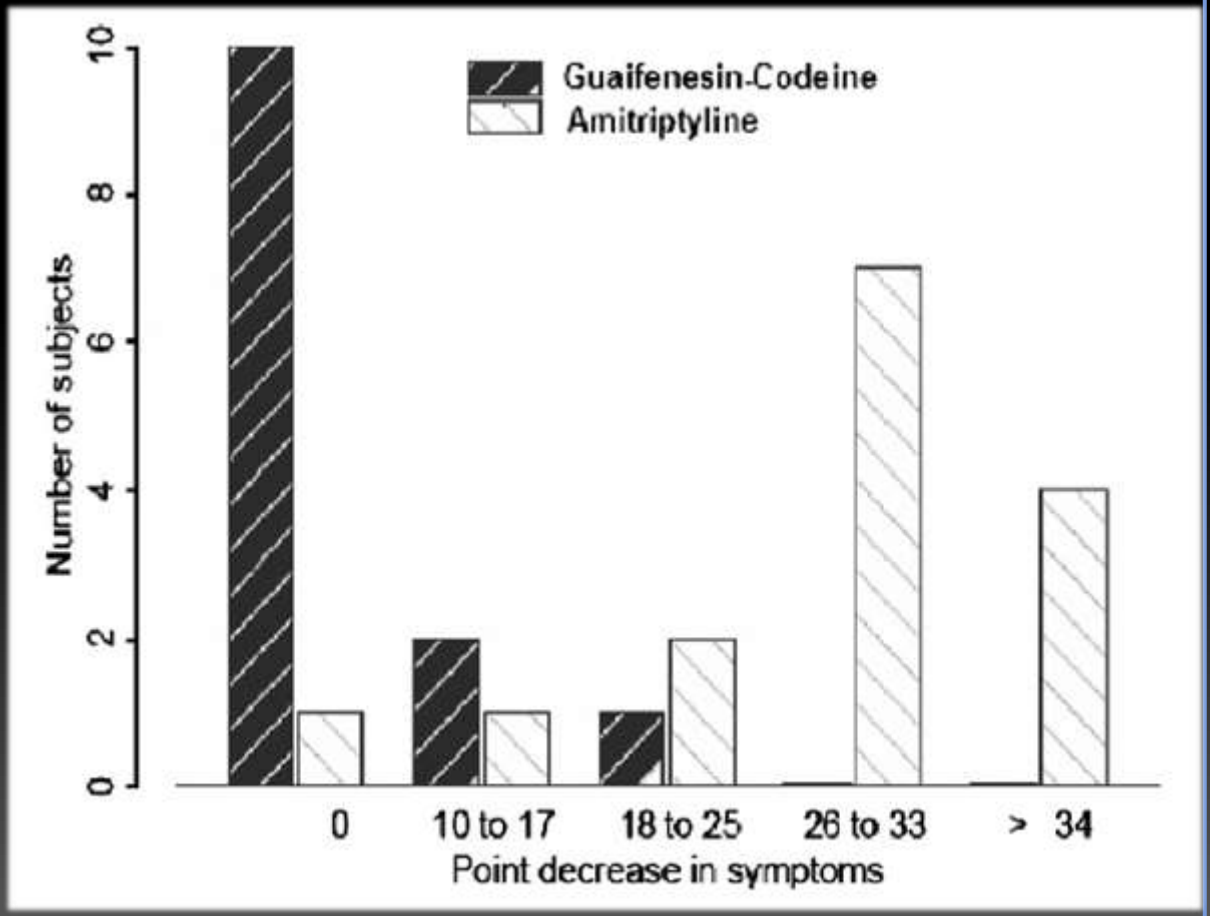



CORTEX
Central Sensitization
Cough Center
Peripheral Sensitization
Cough
Airways
Esophagus
...

Amitriptyline in Post-Viral Chronic Cough

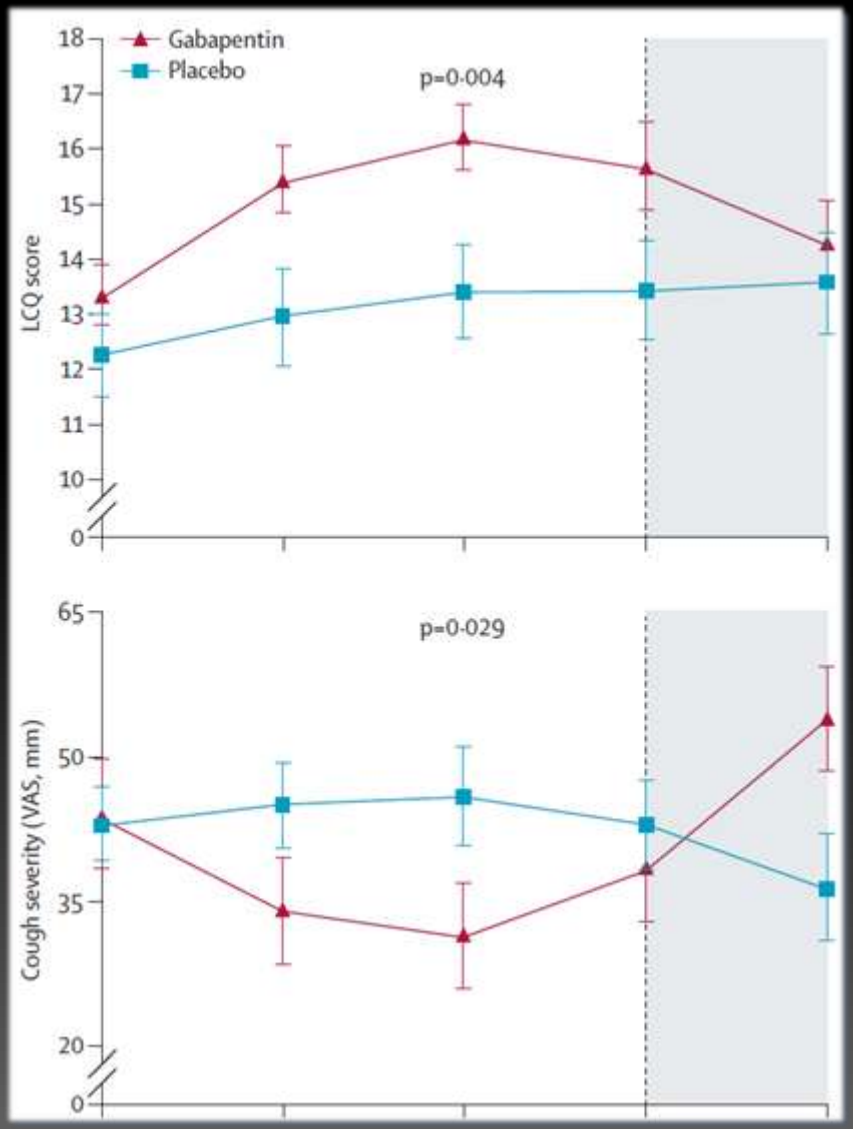
Jeyakumar, Laryngoscope 2006; 116:2108

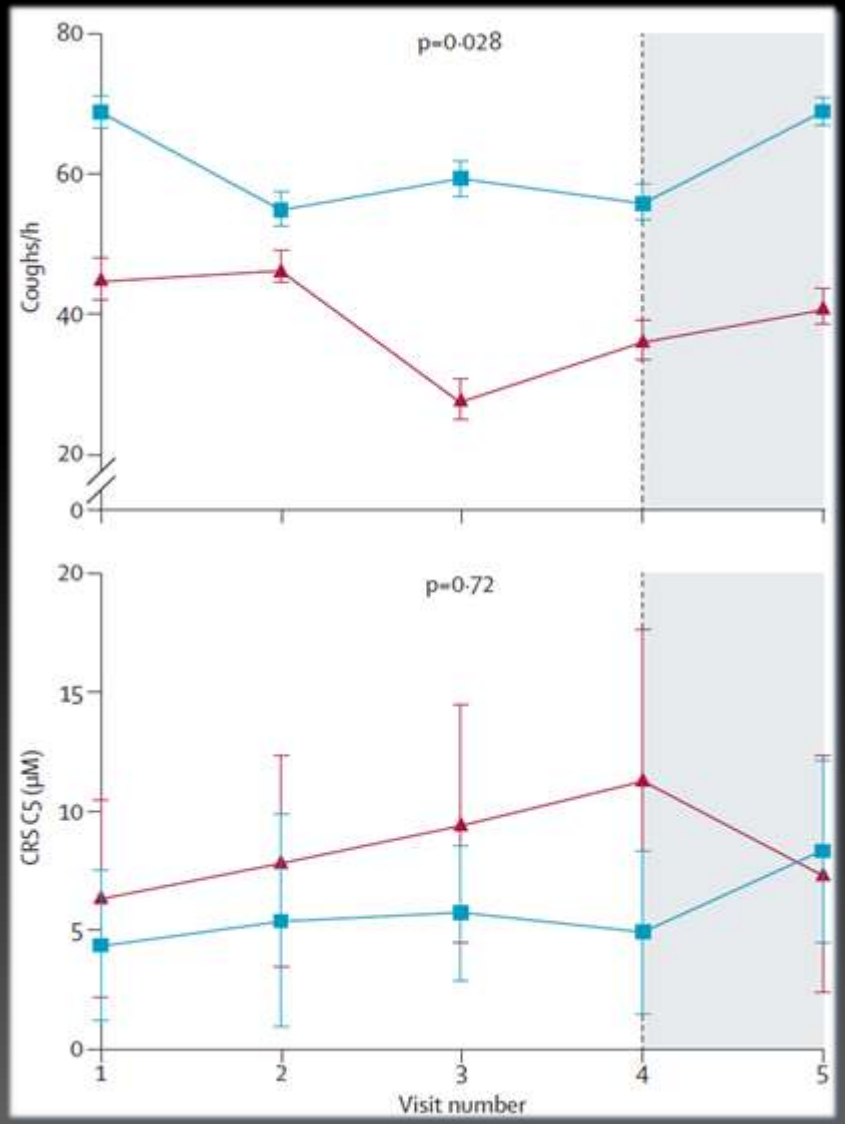
- 28 patients
  - 10 days
- RCT, non-blinded
  - Amitriptyline 10mg
  - Codeine, Guaifenesin



Cough QOL

Gabapentin for refractory chronic cough: a RDBPCT.





Ryan, Lancet 2012 Nov.

Response according to Capsaicin Cough Reflex Hypersensitivity

	Gabapentin (n=32)		Placebo (n=30)		p value
	No CS (n=13)	CS (n=19)	No CS (n=10)	CS (n=20)	
Baseline	13·9 (9·5)	13·5 (8·6)	12·2 (9·9)	12·9 (9·5)	..
Week 4	15·0 (9·5)	16·2 (10·1)	14·1 (11·5)	13·6 (10·7)	0·240
Week 8	15·3 (8·7)	17·1 (10·6)*	13·7 (12·2)	14·2 (10·4)	0·001

Data are mean score (SD). Adjusted p value for significance=0·0042.
LCQ= Leicester cough questionnaire. *Gabapentin without CS *vs* placebo without CS, p=0·0006. Gabapentin without CS *vs* placebo with CS, p=0·0003. Gabapentin without CS *vs* gabapentin with CS, p=0·021. CS=central sensitisation.

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

Therapeutic plan

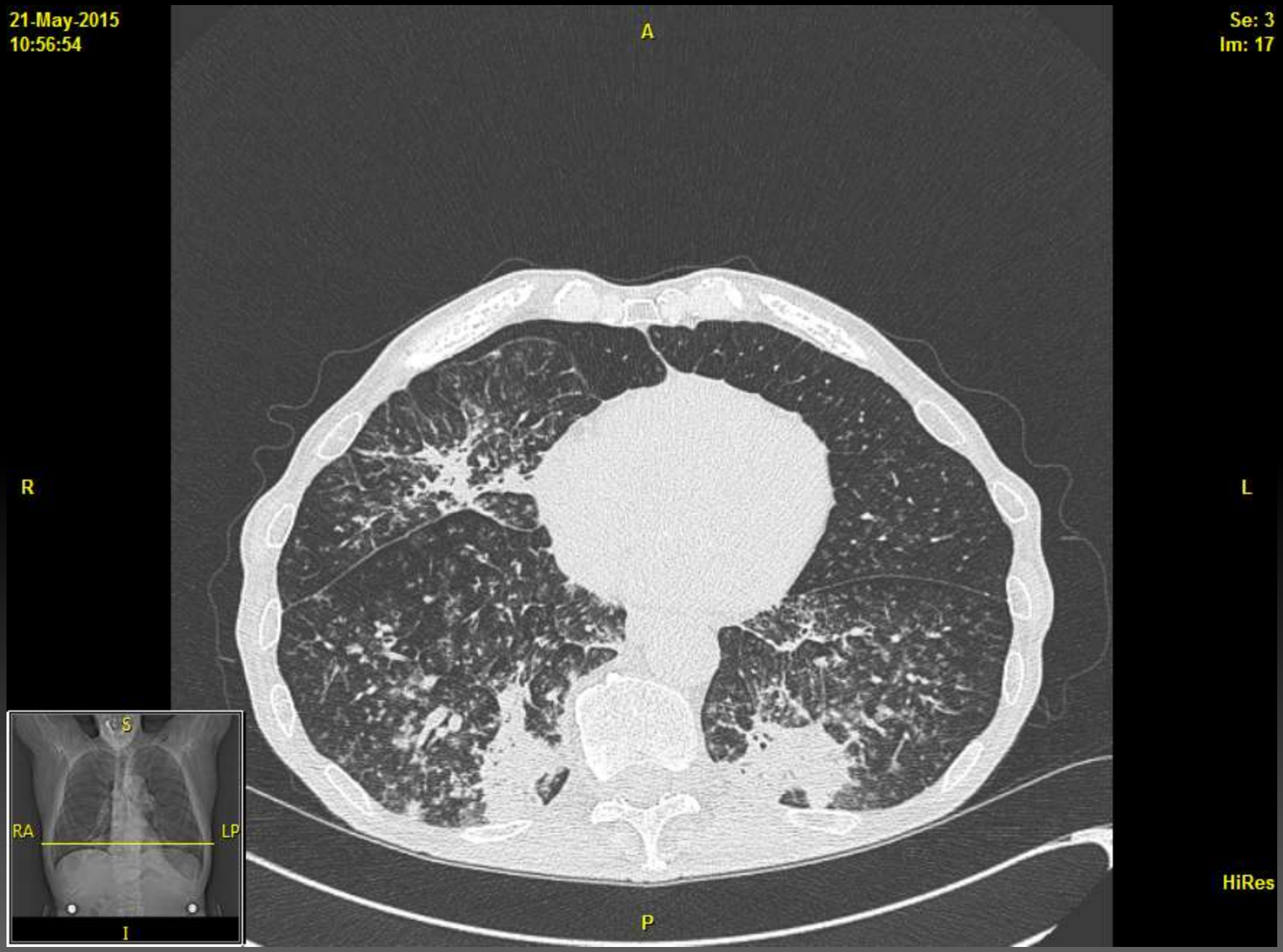
- Maximized asthma therapy, weaning steroids
- Treat reflux, behavioral as well as trial of PPI
- Started gabapentin, PRN lidocaine nebulizer
- Suppressive behavioral techniques, lozenges, sips
- Outcome @ 4months: Down to 2 mg methylprednisolone so far, weaning slowly…

Lessons learned

- Reflux can cause cough even when there is no reflux. I.e. Cough hypersensitivity syndrome
- Some data exists showing that treating it as a “neuropathy” may have meaningful clinical benefit
- Hypertussia, allotussia, and laryngeal paresthesia might be new lingo to add to our characterization of chronic coughers
- Can co-exist with other diseases: e.g. reflux, asthma, etc.

A case of the too little cough

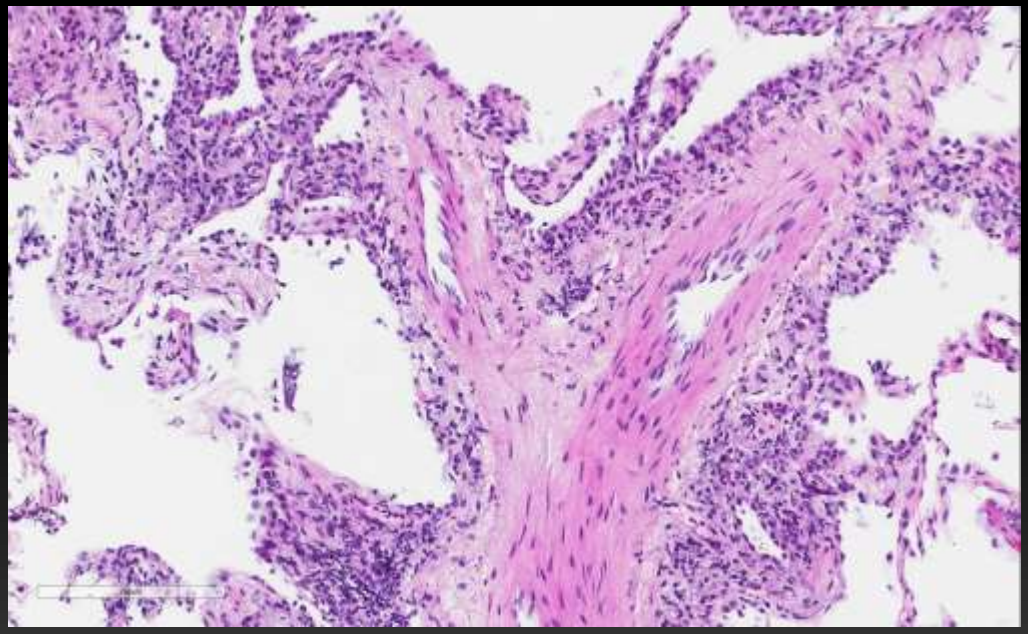
- 76 yo, former smoker, moderate COPD
- Main complaint of 30# weight loss over 2.5 years
- Tonsillar cancer in 2002, irradiated, very severe mucositis, required PEG for nutrition
- Diagnoses of pneumonia multiple times though didn't think he had much fevers or sputum at those times
- Severe dryness of mouth, no apparent dysphagia, no cough, but some dyspnea


21-May-2015
10:56:54
A
Se: 3
Im: 17
R
L
S
RA
LP
I
P
HiRes

Swallow video

Bronchoscopy with biopsies

- Organizing pneumonia
- Bronchiolitis

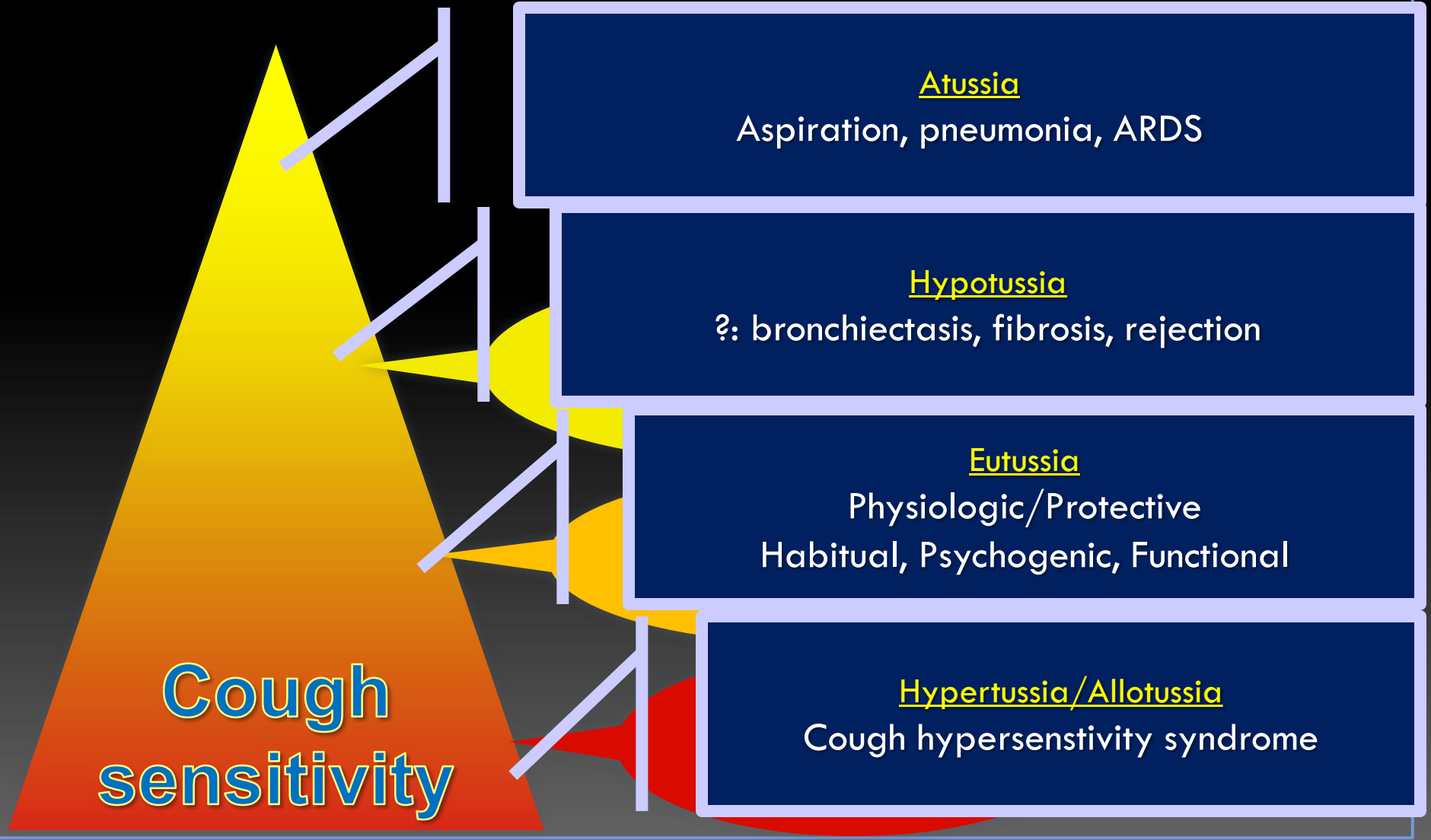


- Review of outside specimens: Foreign body granulomas, apparent vegetable matter

Treatments

- PEG/J
- NPO
- Treat COPD
- Voodoo:
  - ACE-inhibitor
  - Secretion mobilization, airway hydration

Lessons learned

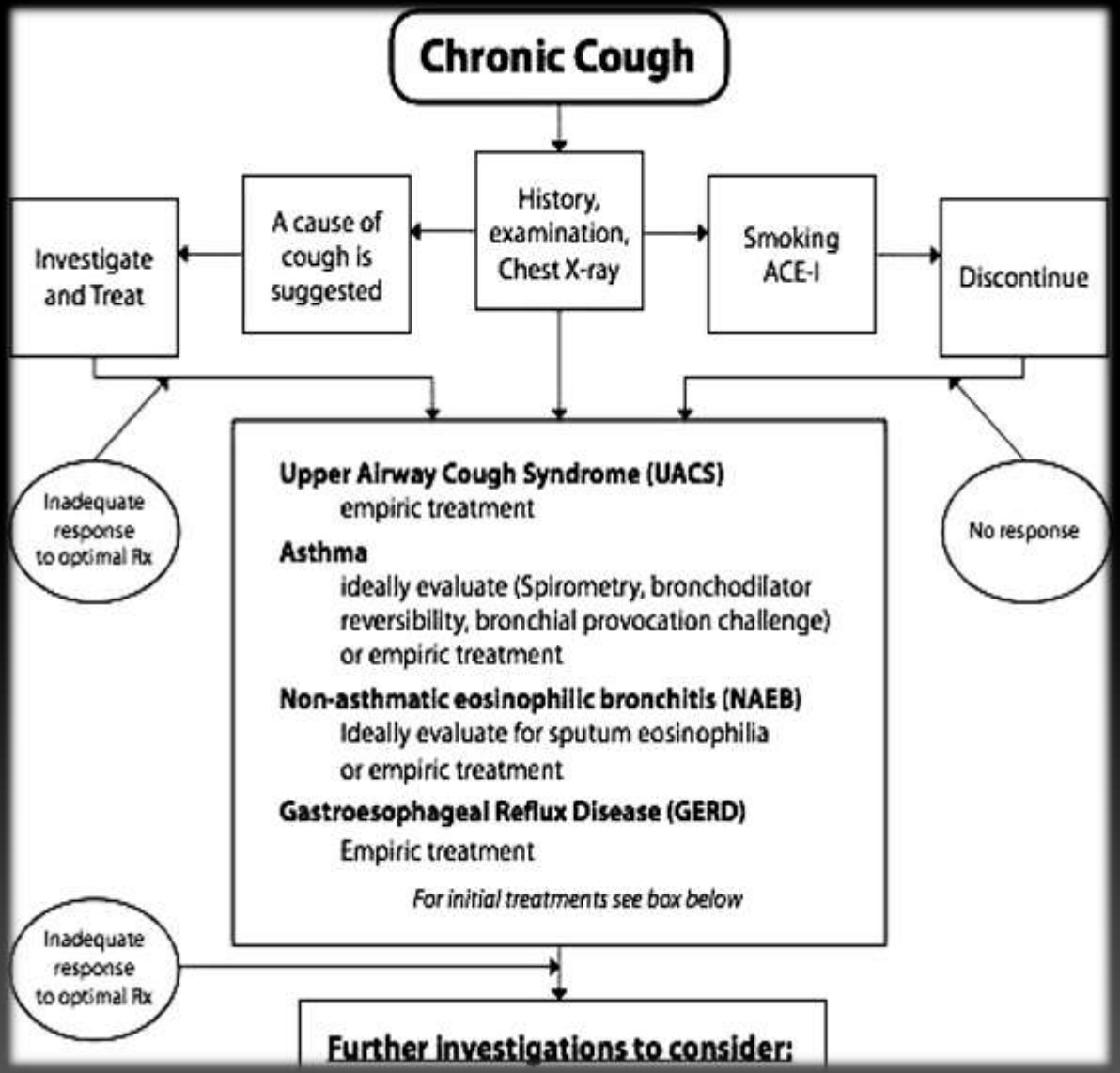


I Surrender

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

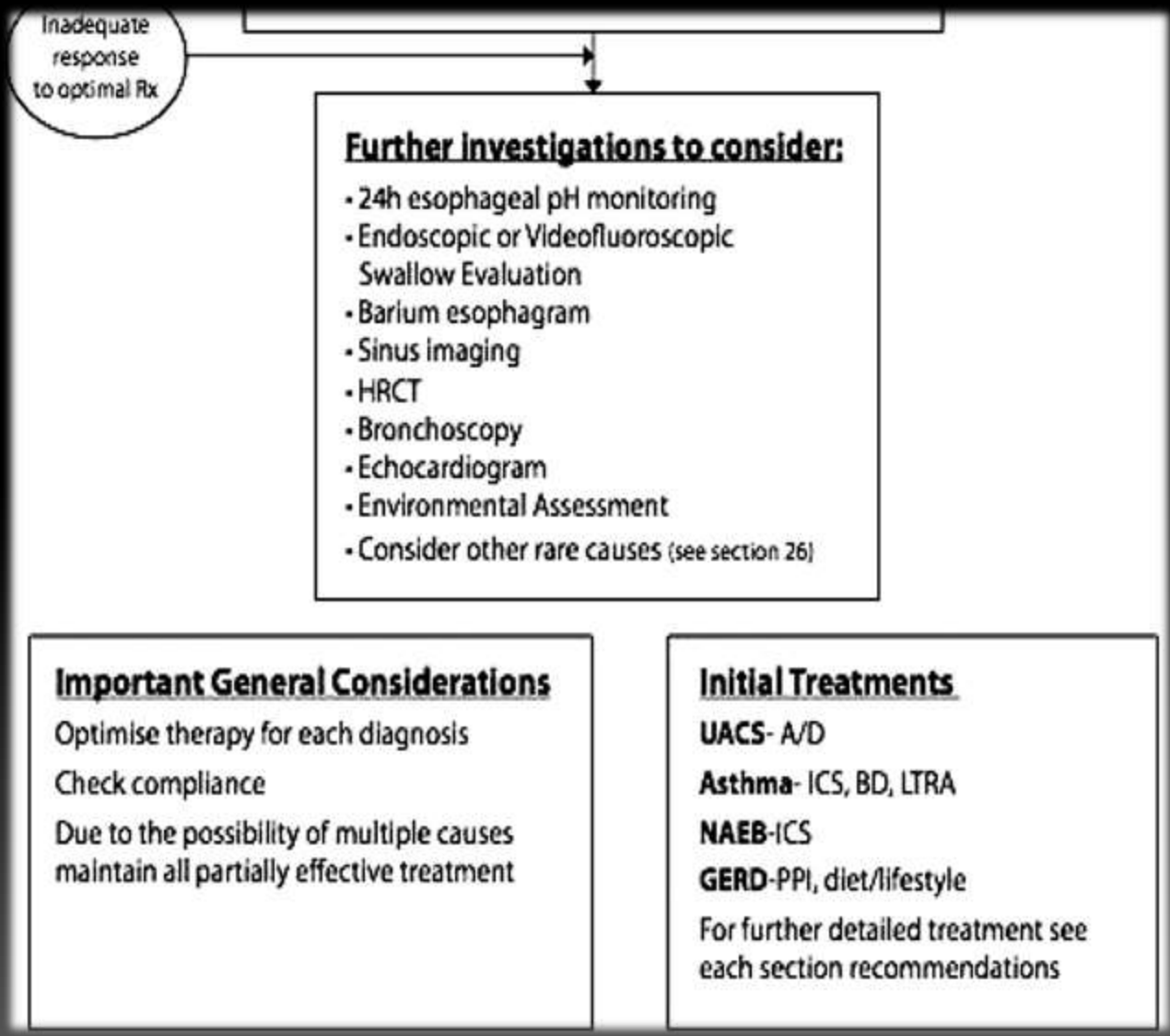
- Work-up
  - PFT with methacholine normal.
  - HRCT normal
  - Negative sputum eosinophils (& outside bronchoscopy)
  - CT sinus & nasal endoscopy normal
  - Impedance-pH normal

Chronic cough algorithm (ACCP 2006)



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

Chronic cough algorithm (ACCP 2006)



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

"Diagnoses"

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

Therapeutic challenges

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

- Now what…

Treatment

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

Lessons learned

- Tailor expectations
- Huge placebo effect, take advantage of it
  - Some patients just want reassurance that there is no cancer
- Cough without a disease is still a problem for your patient…
  - Cough is no longer a symptom, but the disease itself
- Quality of life matters
  - Treat it symptomatically, balancing risks/benefits, with an informed discussion

Thanks!