Cough Assessement and Management in LTC

Alan Kaplan MD CCFP(EM) FCFP

Chair Family Physician Airways Group of Canada

Faculty/Presenter Disclosure

1. **Faculty:** Alan Kaplan MD CCFP(EM) FCFP

- **Relationships with financial sponsors:**
  - **Grants/Research Support:** BI, Novartis
  - **Speakers Bureau/Honoraria:** Ontario College of Family Physicians,
    - Astra Zeneca, Boehringer Ingelheim, Cipla, Covis, Griffols, Pfizer, Purdue, Merck Frosst, Novartis, Sanofi, Spectrum, Teva
  - **Consulting Fees:** Aerocrine, GSK, Merck, Mylan, Novo Nordisk, Novartis, Teva, Purdue, Pfizer
  - **Patents**: n/a

Other: Member of Health Canada Section on Allergy and Respiratory Therapeutics.

Member of Public Health Agency of Canada section on Respiratory Surveillance

Co chair Health Quality Ontario COPD community management

Editorial board of the Primary Care Respiratory Journal

Disclosure of Financial Support

- This program has received NO financial support in the form of an educational grant.
- This program has received NO in-kind support in the form of logistical support.

- **<u>Potential for conflict(s) of interest</u>:**
  - Alan Kaplan has received payment for speakers bureau or advisory boards for a number of companies, previously listed, which make medications for respiratory illnesses that will be discussed

Mitigating Potential Bias

- The FMF has reviewed and approved session learning objectives. The Planning Committee and Chairs have set guidelines for sessions to ensure the quality of content and presentations.
- The FMF have reviewed and approved speaker disclosures in the program to ensure mitigation of any biases.
- All the recommendations involving clinical medicine are based on evidence that is accepted within the profession; and all scientific research referred to, reported, or used in the CPD activity in support or justification of patient care recommendations conforms to the generally accepted standards.

Learning Objectives

- Upon completing this session, participants will be able to:

- 1. Define chronic cough;

- 2. Learn an algorithmic approach to diagnosing chronic cough; and

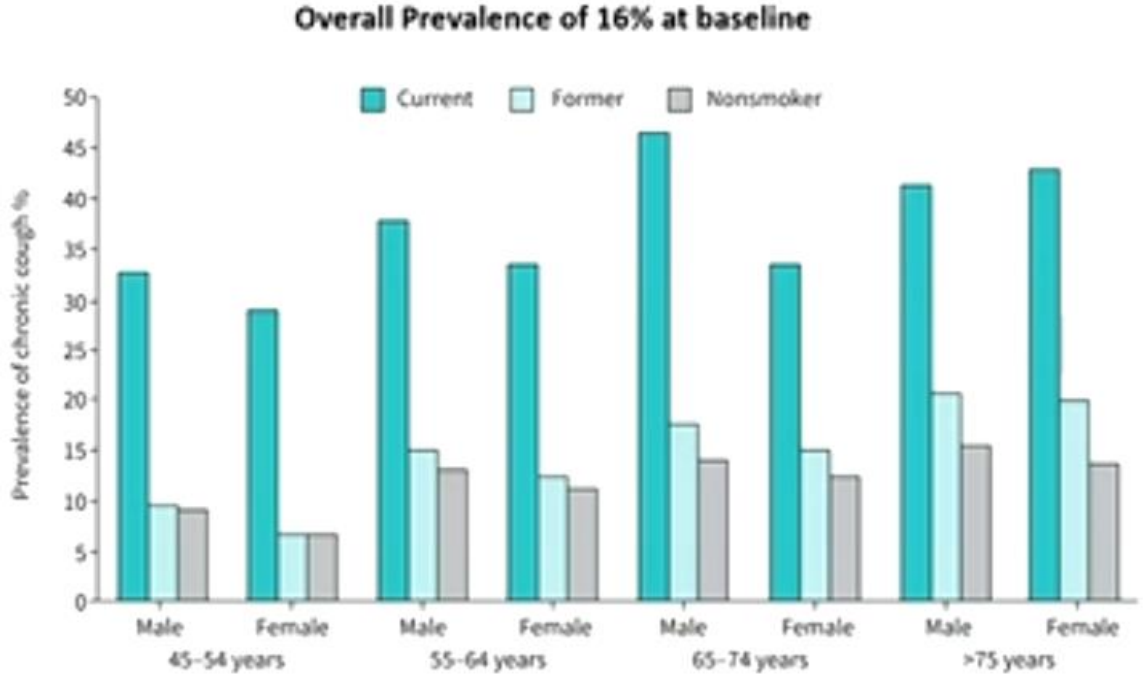
- 3. Review management strategies to some of the causes of chronic cough.

Cure for a Cough

- The owner of a drugstore walks in to find a guy leaning heavily against a wall with an odd look on his face.
- The owner asks the clerk, "What's with that guy over there by the wall?“
- The clerk says, "Well, he came in here at 7 A.M. to get something for his cough. I couldn't find the cough syrup, so I gave him an entire bottle of laxatives.“
- The owner says, "You idiot! You can't treat a cough with laxatives!“
- The clerk says, "Oh yeah? Look at him—he's afraid to cough!"

Canadian Data

High prevalence of chronic cough in the Canadian Longitudinal Study of Ageing (CLSA)

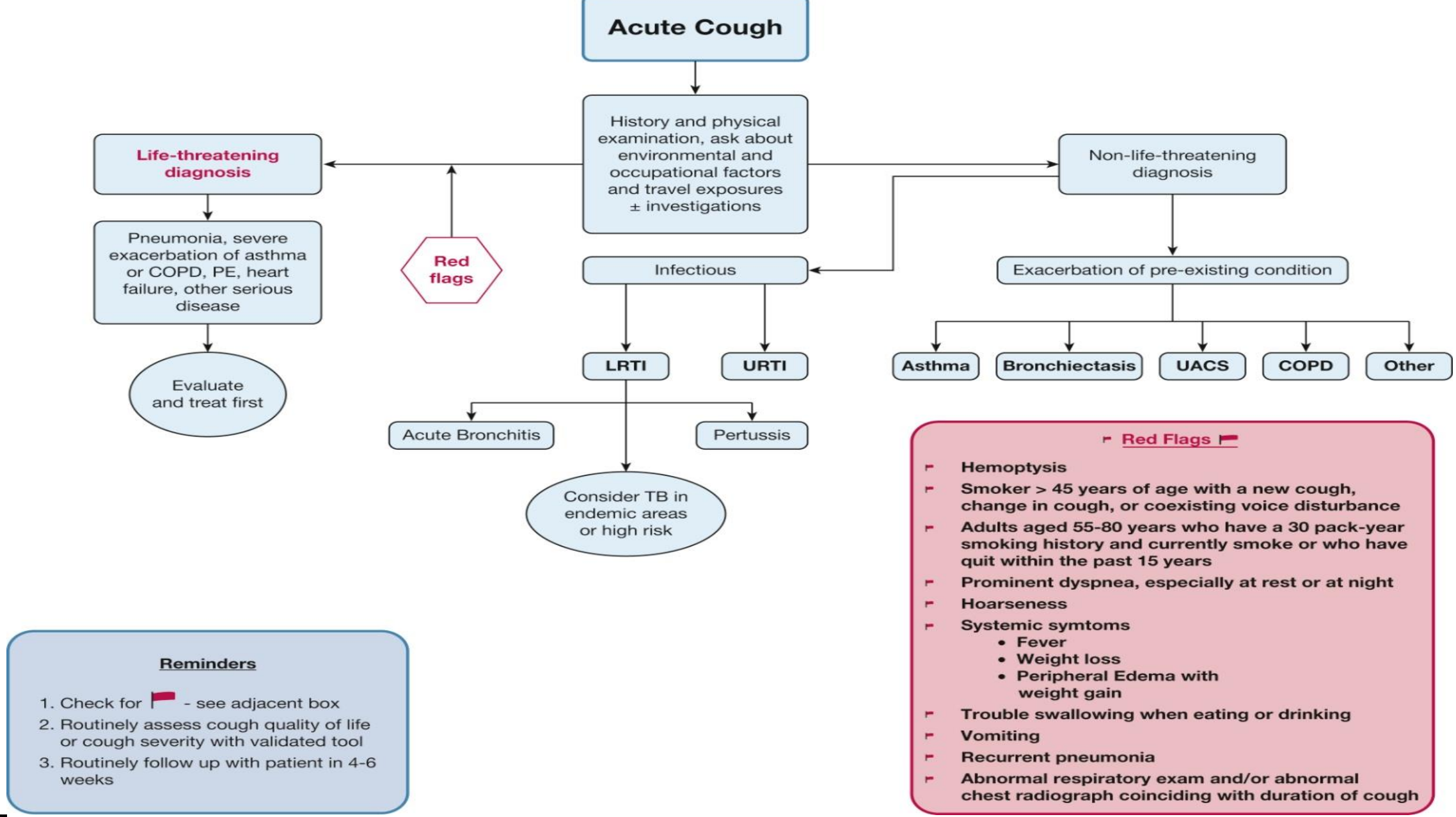


Satia et al. ERJ Open Res 2021

ACCP cough guidelines 2018

- *In an arbitrary fashion, cough is classified as:*
- • Acute (less than 3 weeks in duration)
- • Subacute (3 to 8 weeks)
- • Chronic or persistent (>8 weeks)

Irwin RS et al. Diagnosis and management of cough*Classification of Cough as a Symptom in Adults and Management Algorithms*
CHEST Volume 153, Issue 1, Pages 196-209 (January 2018)
DOI: 10.1016/j.chest.2017.10.016



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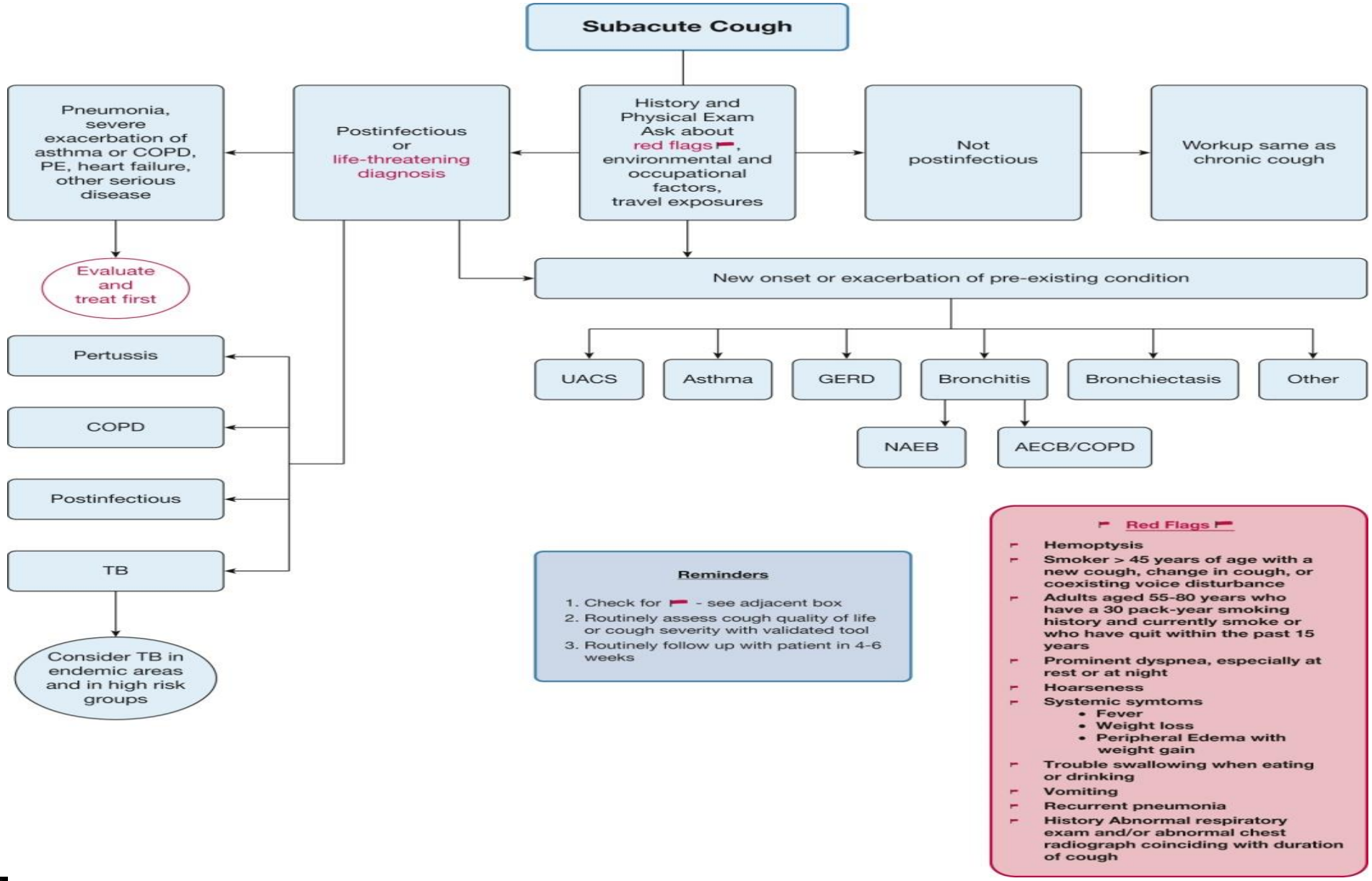

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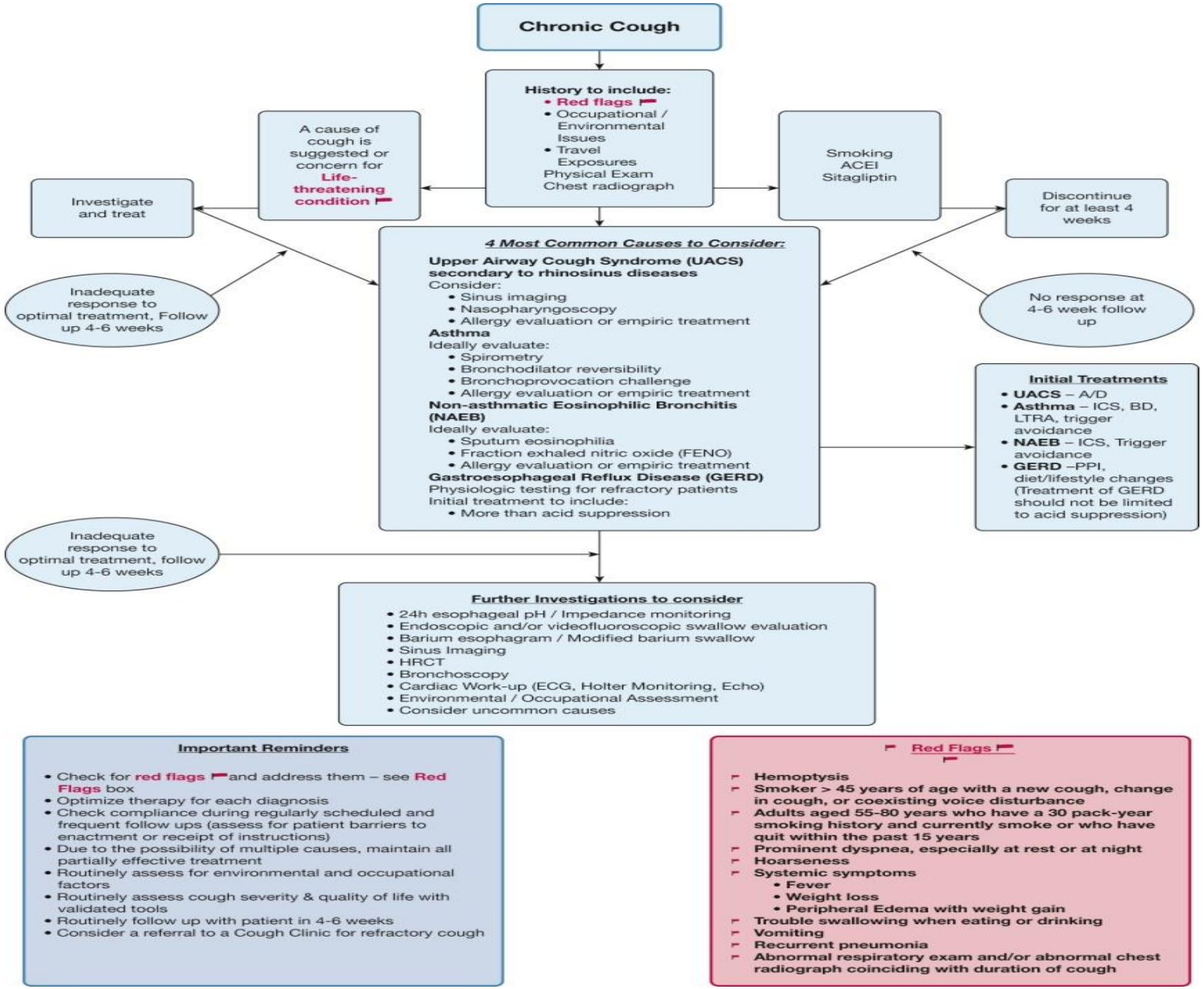


Irwin RS et al. *Classification of Cough as a Symptom in Adults and Management Algorithms*
CHEST Volume 153, Issue 1, Pages 196-209 (January 2018)

What happens in your setting?

- Does everyone you see with chronic cough come in with a failed trial of a puffer?

Cochrane Trusted evidence. Informed decisions. Better health.

Inhaled corticosteroids for subacute and chronic cough in adults (Review)

Johnstone KJ, Chang AB, Fong KM, Bowman RV, Yang IA

- In many cases people with cough lasting longer than three weeks are given inhaled corticosteroids (ICS), which are commonly used to treat asthma and other diseases involving airway inflammation.
- This review has shown that the effects of ICS for subacute and chronic cough are inconsistent!
- International cough guidelines recommend that a trial of ICS should only be considered in patients after thorough evaluation including **chest X-ray** and consideration of **spirometry** and other appropriate investigations.

Johnstone KJ, Chang AB, Fong KM, Bowman RV, Yang IA. Inhaled corticosteroids for subacute and chronic cough in adults. Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD009305.

Chronic Cough: message one

- Common things are common
- Patients who do not respond frequently have more than one cause
- GERD causes cough.
- Post-infectious cough is common
  - but what does this mean??

Chronic Cough: message two

- You can find almost every cause of cough with three steps
- History (including meds), Physical and CXR
- Diff dx with normal CXR (>95%): Asthma, UACS, GERD or infection
- Reasonable to give trials of therapy

Causes of Chronic Cough **after** big three: Asthma, GERD, UACS

- Non-asthmatic eosinophillic bronchitis
- Post infectious causes-- both bacterial and viral respiratory pathogens
- Complications of drug therapy
- Airway disorders– Chronic Bronchitis due to its various causes, Bronchiectasis, Neoplasms and foreign bodies
- Parenchymal lung disorders– Interstitial diseases, lung abscess, chronic infections, CHF
- Aspiration due to glottic insufficiency
- Zenkers diverticulum
- Neurogenic cough (post viral vagal neuropathy)

Kaplan A. A 54 year-old man with a chronic cough – A primary care perspective from Canada. *Prim Care Respir J* 2012;**21**(3):342-343.

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 symtoms
  - 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

Upper Airway Cough Syndrome (UACS)

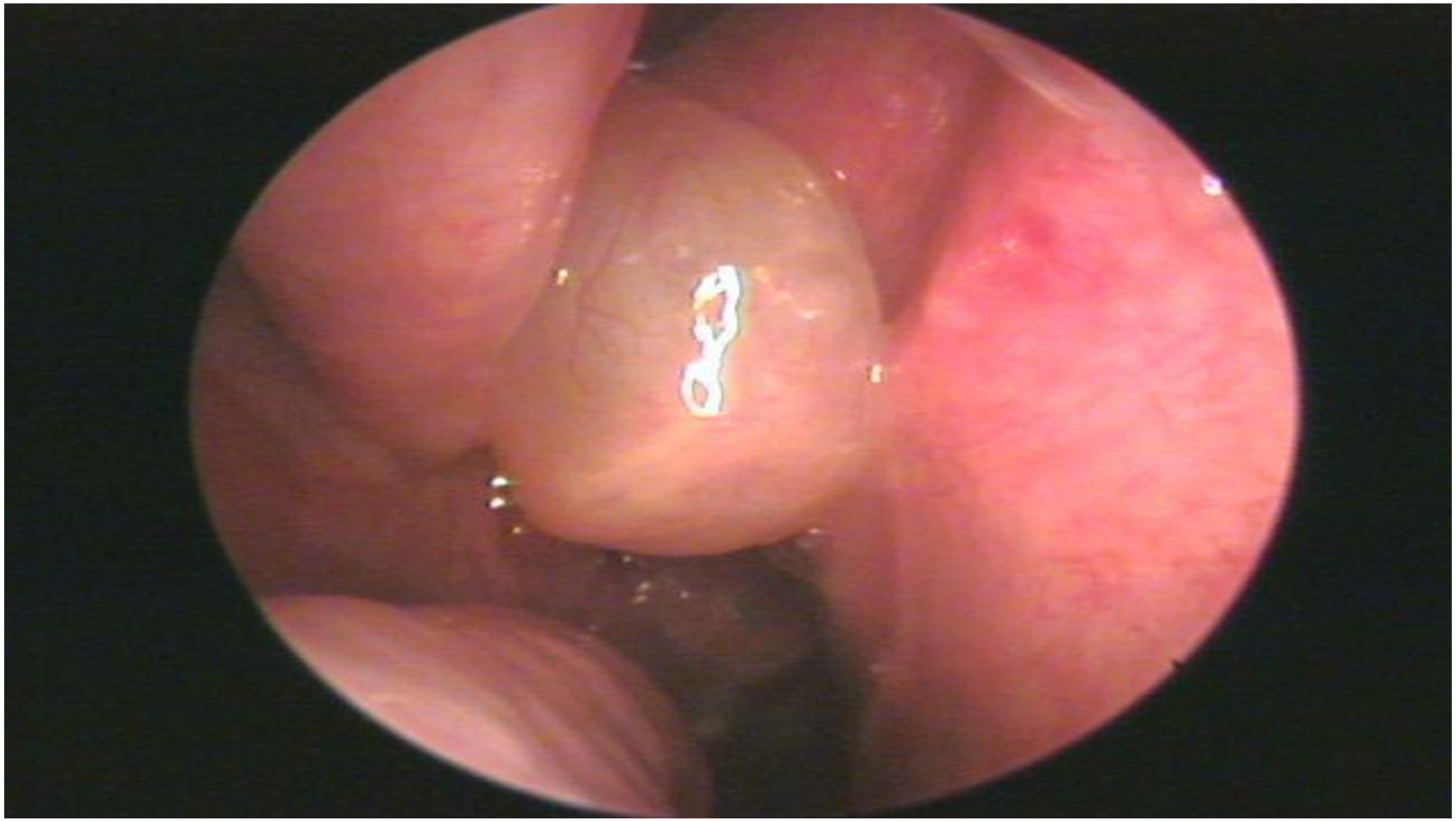
- Signs (may be absent): inflamed nasal mucosa, secretions in posterior oropharynx, ‘cobblestone’ of nasopharynx
- Consider underlying causes: allergies, chronic sinusitis, overuse of alpha-agonist nasal sprays
- Diagnostic/Therapeutic trial: 1st generation oral anti-histamine/decongestant combination/nasal ICS for 1-2 weeks (NOT nasal decongestants > 3 days!)

What if there is a stuffy nose?

Diagnosis

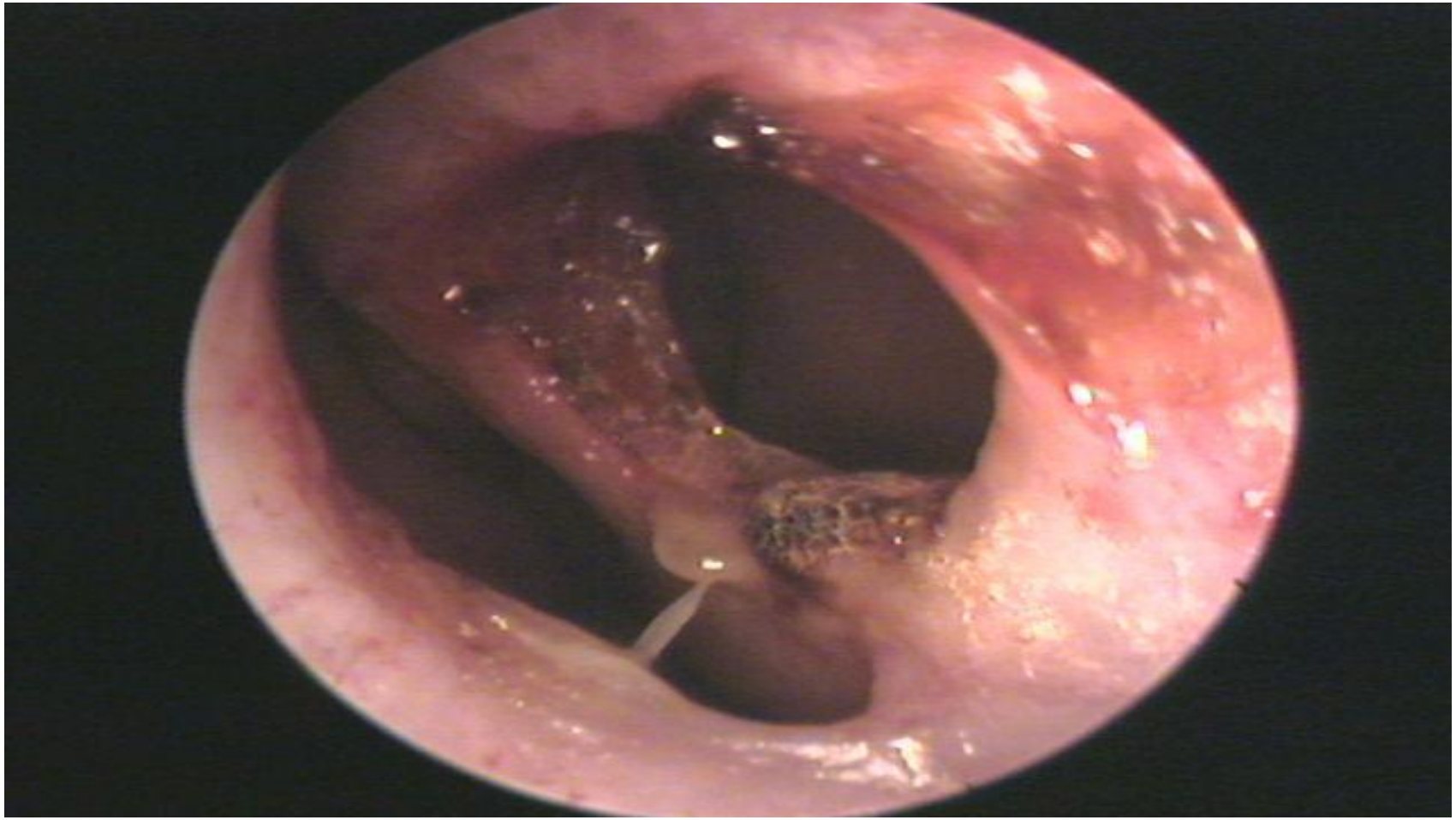
- Anterior rhinoscopy
- Nasal endoscopy

Nasal Polyp

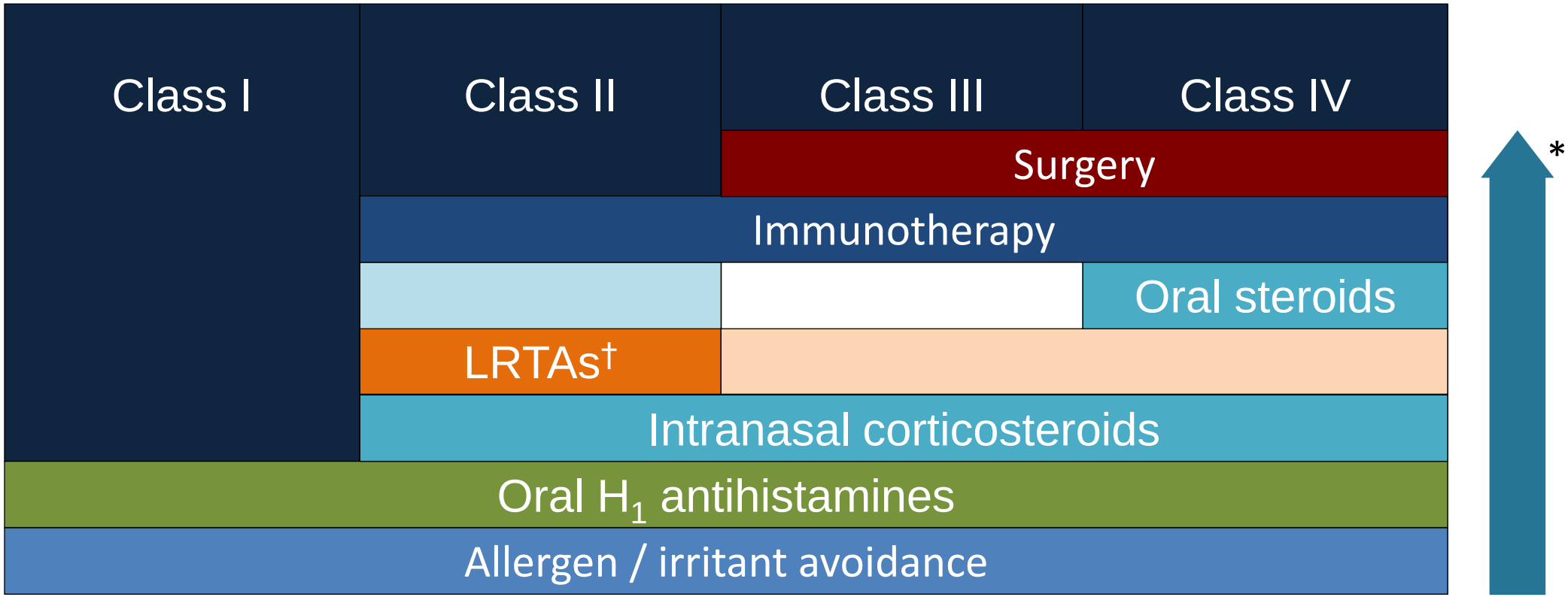


What is this?

How about this?



AR Treatment Guidelines



LTRAs: leukotriene receptor antagonsists

*Step up if there is no response or incomplete response to treatment, regardless of class

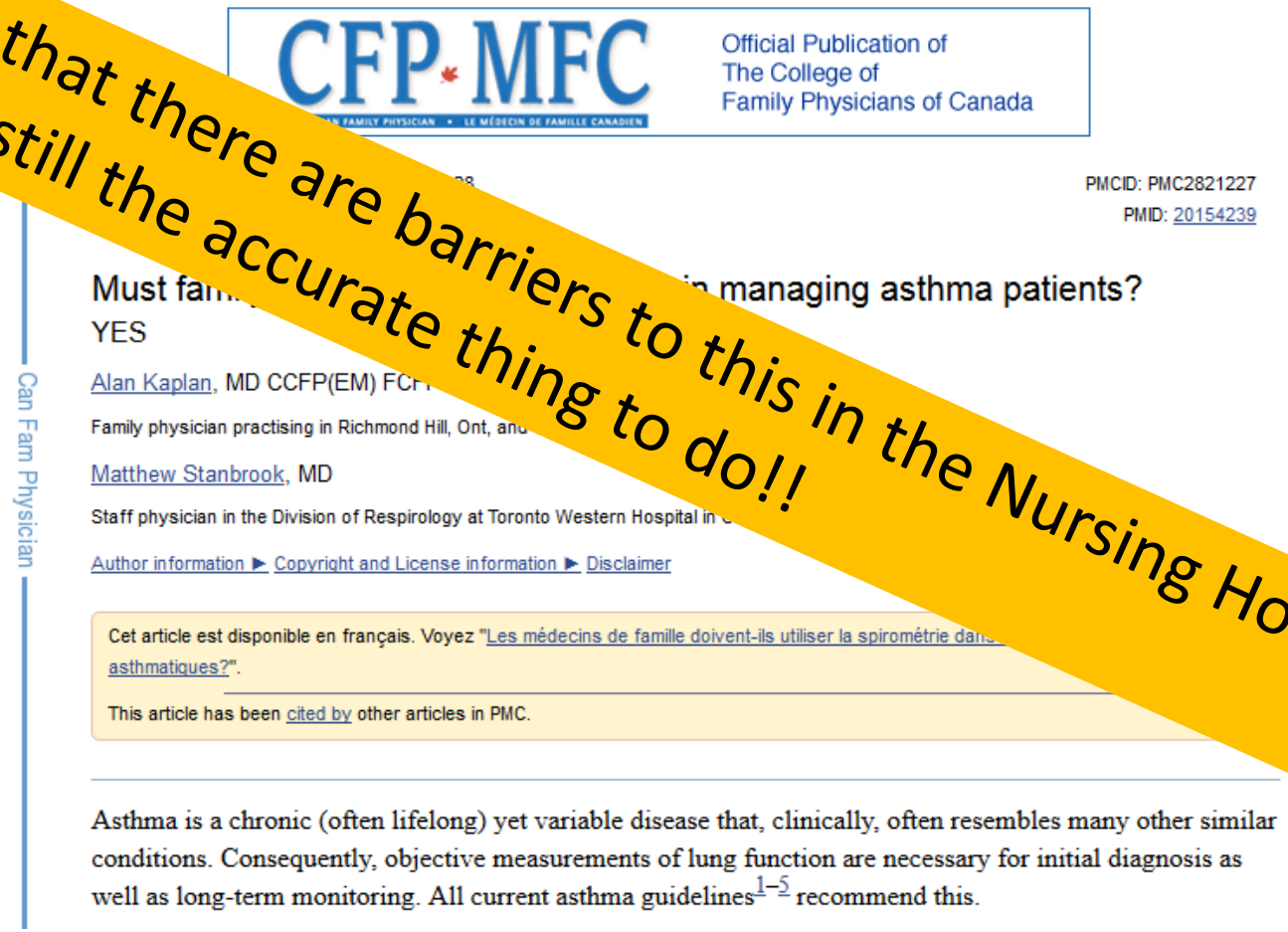
†LTRAs may be used in class III and IV, but there is less supporting evidence

**Oral steroids may be considered for class II (severe intermittent), but there is little supporting evidence

Adapted from: Small P, et al. J Otolaryngol 2007; 36 (Suppl 1):S5-S27.

Use Spirometry!

I know that there are barriers to this in the Nursing Home!!
But it is still the accurate thing to do!!



CFP·MFC
Official Publication of
The College of
Family Physicians of Canada

PMCID: PMC2821227
PMID: 20154239

Must fa… …n managing asthma patients?

YES

Alan Kaplan, MD CCFP(EM) FC…

Family physician practising in Richmond Hill, Ont, and…

Matthew Stanbrook, MD

Staff physician in the Division of Respirology at Toronto Western Hospital in …

Asthma is a chronic (often lifelong) yet variable disease that, clinically, often resembles many other similar conditions. Consequently, objective measurements of lung function are necessary for initial diagnosis as well as long-term monitoring. All current asthma guidelines[1–5] recommend this.

Can Fam Physician

Gastroesophageal Reflux Disease (GERD)

- Reflux can be the cause of the cough or its consequence.
- It may or may not cause typical symptoms such as heartburn, sour taste in mouth or regurgitation.
- Cough may be the ONLY symptom (in as many as 40%!)
- Responsible for approximately 25% of cases.

Chronic Bronchitis

- Chronic bronchitis is defined as a cough with sputum expectoration for at least 3 consecutive months for at least 2 consecutive years.
- Can exist in absence of COPD
- New term: PRISM: Preserved Respiratory Function in Symptomatic Smokers (topic for another day!)

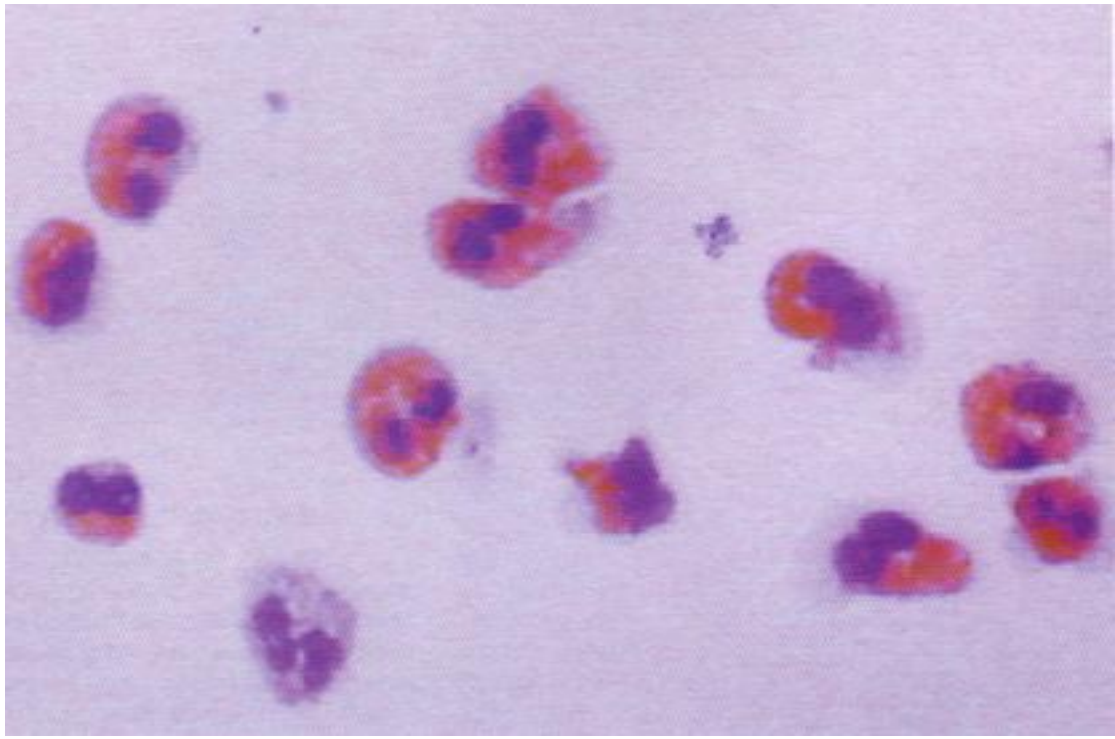
Non-asthmatic eosinophilic bronchitis (NAEB)

- Difficult diagnosis for the primary care physician to make. Patients present with bronchial eosiniophilia on sputum analysis, without bronchial hyperresponsiveness.
- The cough may respond to inhaled corticosteroids, like in asthma, but sometimes however requiring oral steroids.

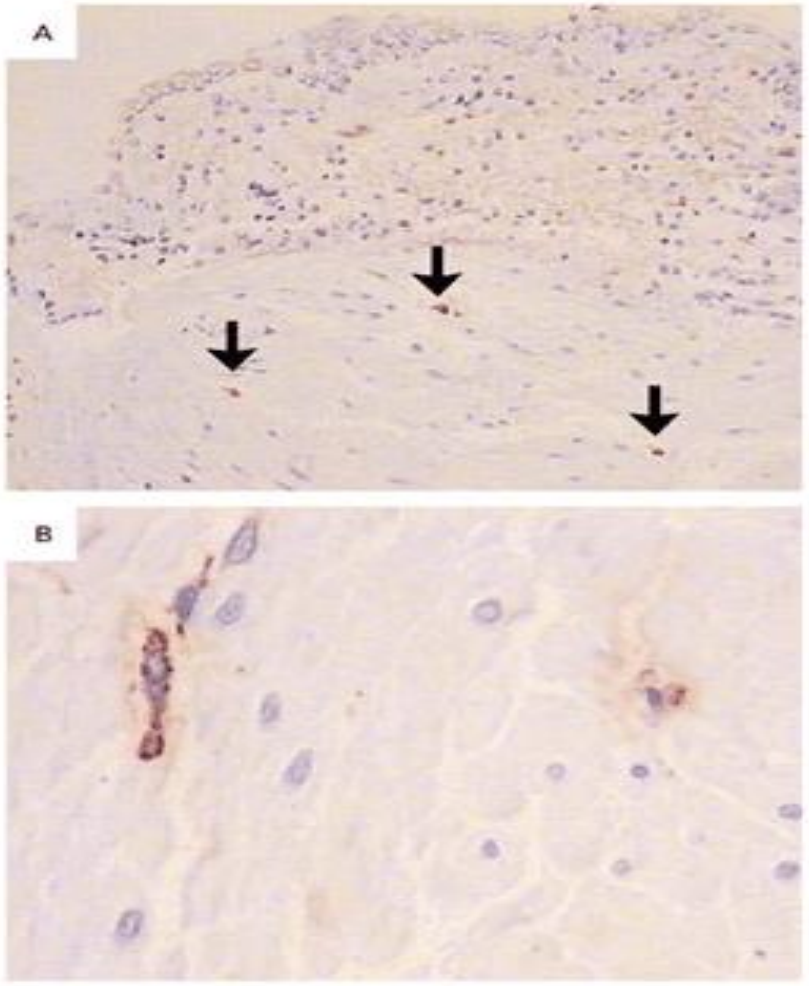
Non-Asthmatic Eosinophilic Bronchitis (NAEB)

- Eosinophilic airway inflammation WITHOUT variable airflow obstruction or airway hyperresponsiveness

- Diagnostic tests:
  - Spirometry: normal
  - Methacholine challenge:
  - normal
  - Induced sputum: >3% eosinophils



Diagnostic: bronchial biopsy



Brightling et. Al. NEJM 2002;346:1699

Asthma vs. NAEB:
Different localization
Mast cells in smooth muscle of asthma only on bronchial biopsy

Sputum eosinophils another potential diagnostic option
Not very available, though

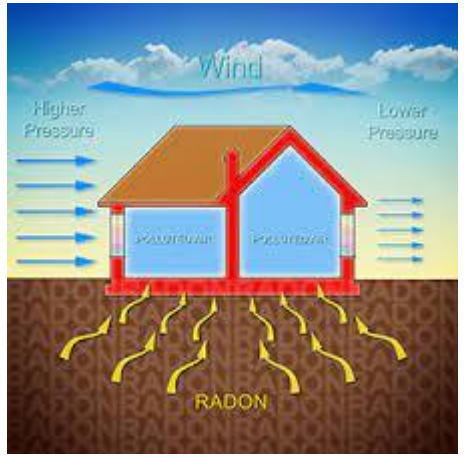
NAEB: tough problem!

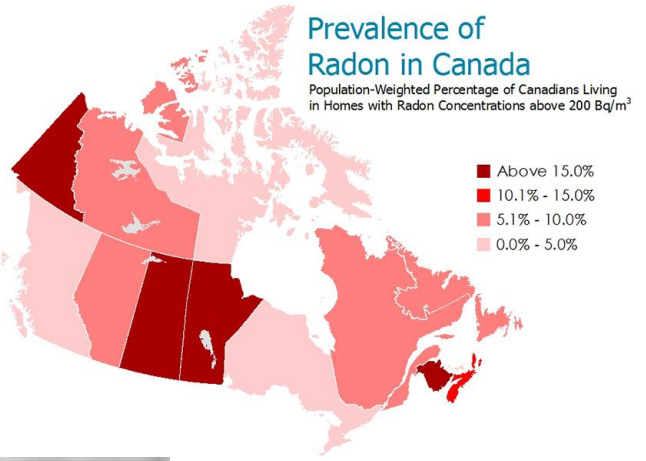
- One year follow-up of 367 patients with normal lung function and eosinophilic inflammation noted that:
  - **55 percent remained symptomatic with normal lung function,**
  - **32 percent were free of symptoms**
  - **13 percent developed asthma**

Case ONE

67 y/o man, life-long non-smoker, complains of 12 weeks of non-productive cough. He's had a couple of "colds" this winter, but this cough is 'different'. He has no current nasal or sinus symptoms, rarely has heartburn, and never wheezes. He's on no meds. Vitals and physical exam are normal. Your next step would be:

A) Prescribe a 1st generation antihistamine/decongestant
B) Prescribe an inhaled corticosteroid for asthma
C) Order an induced sputum to look for eosinophils
D) Order a chest x-ray
E) All of the above





10-20% of lung cancer occurs in never smokers!
Also: A new cough or a recent change in chronic "smoker's cough"
A cough that persists more than one month following smoking cessation
Hemoptysis that does not occur in the setting of an airway infection

CHRONIC COUGH
(>8 WEEKS)

History, physical exam and chest X-ray

Possible cause of cough identified → Investigate and treat → Inadequate response to optimal treatment

Smoking, use of ACEIs → Discontinue → No response

- **Upper airway cough syndrome (UACS)**: empiric treatment
- **Asthma**: evaluate if possible (spirometry, bronchodilator reversibility test, bronchial provocation test) or treat empirically
- **Non-asthmatic eosinophilic bronchitis (NAEB)**: look for esinophils in sputum; if not present, treat empirically
- **Gastroesophageal reflux disease (GERD)**: empiric treatment

Inadequate response to optimal treatment

COMPLEMENTARY INVESTIGATION OR REFERRAL TO SPECIALIST

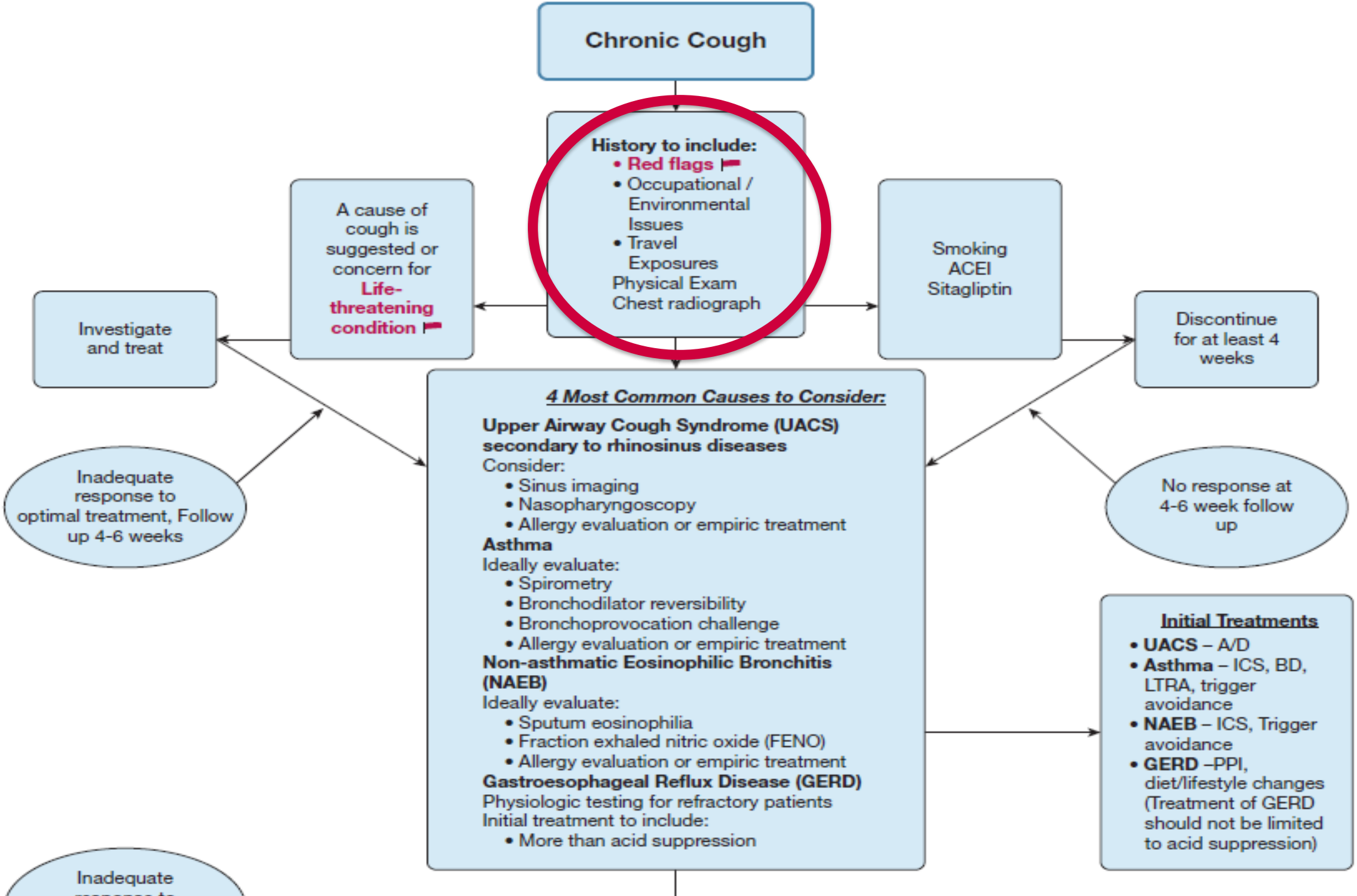
OTHER EXAMINATIONS TO CONSIDER:

- 24-hour esophageal pH monitoring
- Endoscopic or videofluoroscopic evaluation of swallowing
- Esophageal transit study
- Sinus imaging
- High-resolution chest CT scan
- Bronchoscopy
- Echocardiogram
- Environmental evaluation
- Consider the possibility of other rare causes

Consider the possibility of several concomitant causes

Important general considerations:

- **Optimize the treatment for each diagnosis**
- **Verify compliance with therapy**
- **Because of the possibility of more than 1 cause, continue all partially effective treatments**

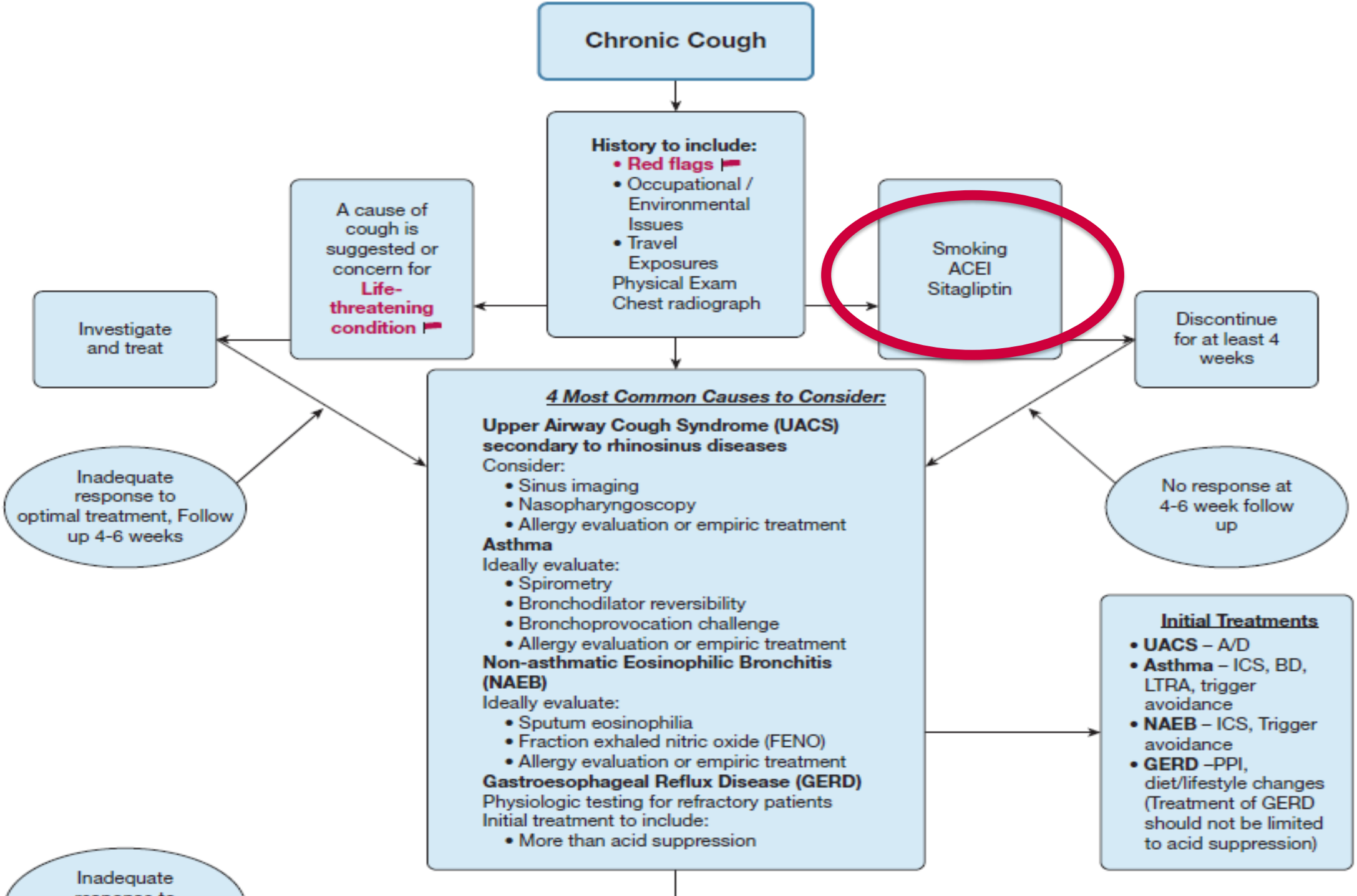

Chronic Cough
History to include:
• Red flags
• Occupational / Environmental Issues
• Travel Exposures
Physical Exam
Chest radiograph
A cause of cough is suggested or concern for Life-threatening condition
Investigate and treat
Smoking
ACEI
Sitagliptin
Discontinue for at least 4 weeks
4 Most Common Causes to Consider:
Upper Airway Cough Syndrome (UACS) secondary to rhinosinus diseases
Consider:
• Sinus imaging
• Nasopharyngoscopy
• Allergy evaluation or empiric treatment
Asthma
Ideally evaluate:
• Spirometry
• Bronchodilator reversibility
• Bronchoprovocation challenge
• Allergy evaluation or empiric treatment
Non-asthmatic Eosinophilic Bronchitis (NAEB)
Ideally evaluate:
• Sputum eosinophilia
• Fraction exhaled nitric oxide (FENO)
• Allergy evaluation or empiric treatment
Gastroesophageal Reflux Disease (GERD)
Physiologic testing for refractory patients
Initial treatment to include:
• More than acid suppression
Inadequate response to optimal treatment, Follow up 4-6 weeks
No response at 4-6 week follow up
Initial Treatments
• UACS – A/D
• Asthma – ICS, BD, LTRA, trigger avoidance
• NAEB – ICS, Trigger avoidance
• GERD –PPI, diet/lifestyle changes (Treatment of GERD should not be limited to acid suppression)
Inadequate

All that coughs is not UACS, Asthma, GERD, or NAEB!

Case Two: L. Tase

67 y/o man, life-long non-smoker, complains of 12 weeks of non-productive cough. He has no current nasal or sinus symptoms, rarely has heartburn, and never wheezes. He has no fever or chills or night sweats. He has a history of treated hypertension. Vitals and physical exam are normal. CXR is normal. Your next step would be:

A) Prescribe an inhaled corticosteroid for asthma
B) Order an induced sputum to look for eosinophils
C) Give nasal ICS for possible post nasal drip
D) All of the above
E) None of the above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Inadequate

ACE-inhibitor therapy

- Angiotensin converting enzyme (ACE) inhibitors (enalapril, captopril, lisinopril, ramipril, etc.)
- Dry cough in 3-30% patients
- Spirometry Normal
- NOT more common in asthmatics
- Begins 1 week to 6 months after drug started
- Usually resolves 1-7 days after stopping therapy, but can take 4 weeks

Sometimes it can even be an ARB!

American Journal of Health-System Pharmacy

Volume 57(10) 15 May 2000 pp 996-997

Losartan-induced cough after lisinopril therapy

[Letters]

Conigliaro, Rosemarie L. M.D.; Gleason, Patrick P. Pharm.D.

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Baraniuk and Jamieson *Allergy, Asthma & Clinical Immunology* 2010, **6**:8
http://www.aacijournal.com/content/6/1/8

ALLERGY, ASTHMA & CLINICAL IMMUNOLOGY

RESEARC Open Access

Rhino h and fatigue in patients taking sitagliptin

Sitagliptin has been reported to have a syndrome including cough, dyspnea, fatigue and rhinorrhea, interestingly more often in patients with ACE induced cough and/or a history of allergic rhinitis. Rhinorrhea, cough and fatigue generally improved in the first week off sitagliptin, while PEFR took 1 to 3 weeks to improve

James N Baraniuk[1] and Mary J Jamie

Abstract

Sitagliptin is a dipeptidyl peptidase-4 (DPP IV, CD26) inhibitor indicated for t l line therapy after metformin. We report fifteen sitagliptin intolerant patients who de rhinorrhea, cough, dyspnea, and fatigue. Symptoms typically developed within 1 to 8 wee ed within 1 week of stopping the drug. Peak expiratory flow rates increased 34% in 8 patients who ste n. Similar changes were found in 4 out of 5 persons who had confirmatory readministration. Chart review id 17 patients who tolerated sitagliptin and had no symptomatic changes. The sitagliptin intolerant group had higher rates of clinically diagnosed allergic rhinitis (15/15 vs. 6/18; p = 0.00005), Fisher's Exact test) and angiotensin converting enzyme inhibitor - induced cough (6/13 vs. 1/18; p = 0.012). Nasal and inhaled glucocorticoids may control the underlying allergic inflammation and abrogate this new sitagliptin - induced pharmacological syndrome. Potential mucosal and central nervous system mechanisms include disruption of neuropeptides and/or cytokines that rely on DPP IV for activation or inactivation, and T cell dysfunction

Chronic Cough, continued:

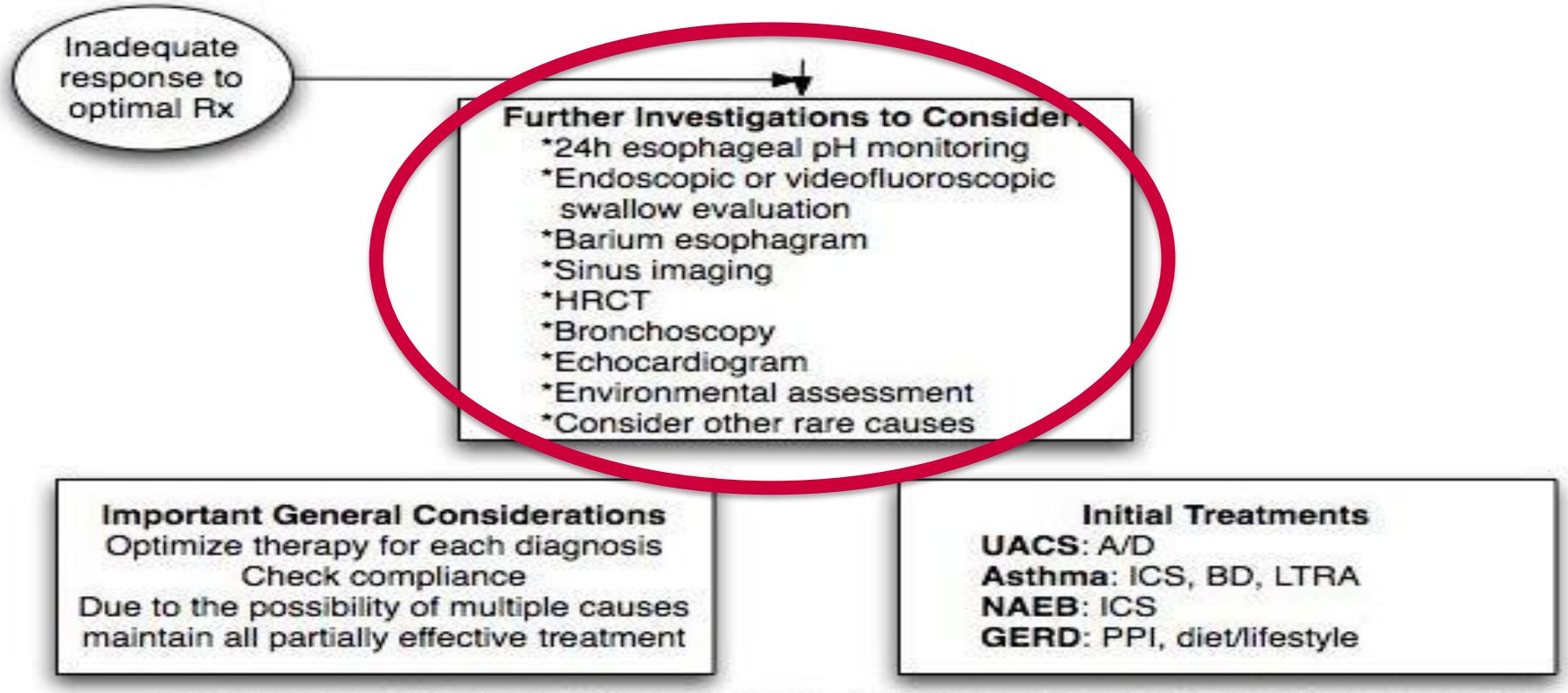
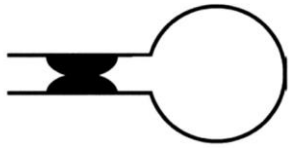


Figure 3. Chronic cough algorithm for the management of patients aged ≥ 15 years with cough lasting > 8 weeks. ACE-I = ACE inhibitor; BD = bronchodilator; LTRA = leukotriene receptor antagonist; ICS = inhaled corticosteroid.

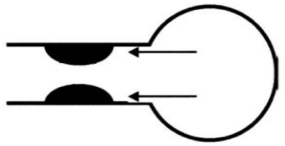
Bronchiectasis

Airway Clearance devices

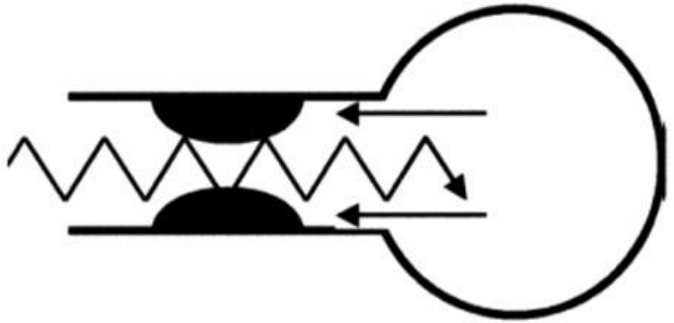
- Eg Aerobika, Flutter, Acapella
- Helps relieve mucus



Airway with a mucus plug, normal exhalation with no positive expiratory pressure applied. Airway stays closed.



Airway with positive expiratory pressure applied. Airway is opened allowing pressure to build behind the mucus plug.

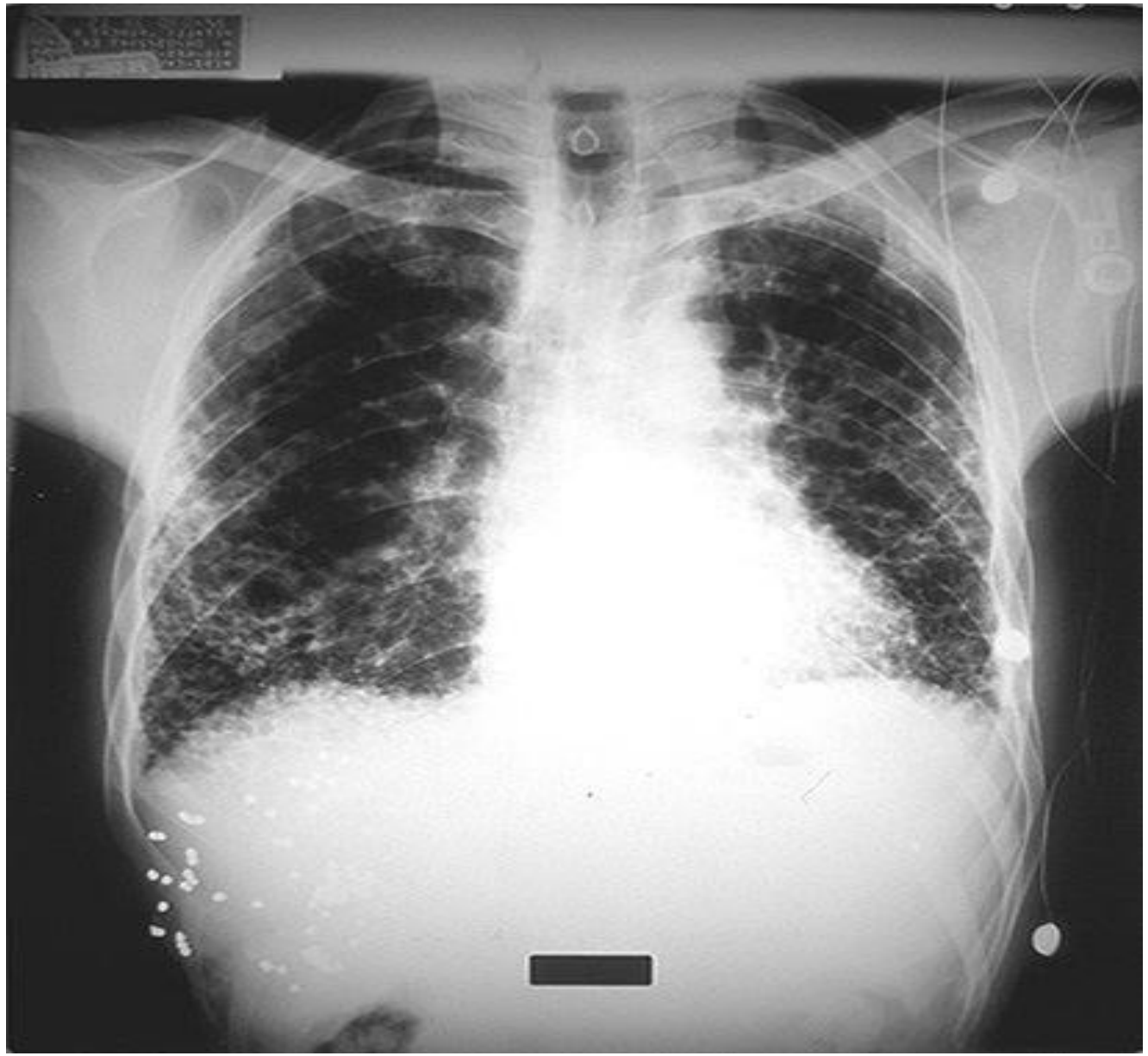


Airway with oscillating positive expiratory pressure applied. Airways stay open allowing pressure to build behind the mucus plug while vibrations help thin, shear and mobilize mucus.

Interstitial lung disease

- Consider other conditions like Rheumatoid Arthritis and Systemic Sclerosis
- Consider meds: Amiodarone, Methtrexate and Macrobid
- If all negative may be idiopathic, called IPF or Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis



- Velcro like crackles
- Important to consider this diagnosis in chronic coughers,

- Do not just treat with puffers, Do spirometry!!

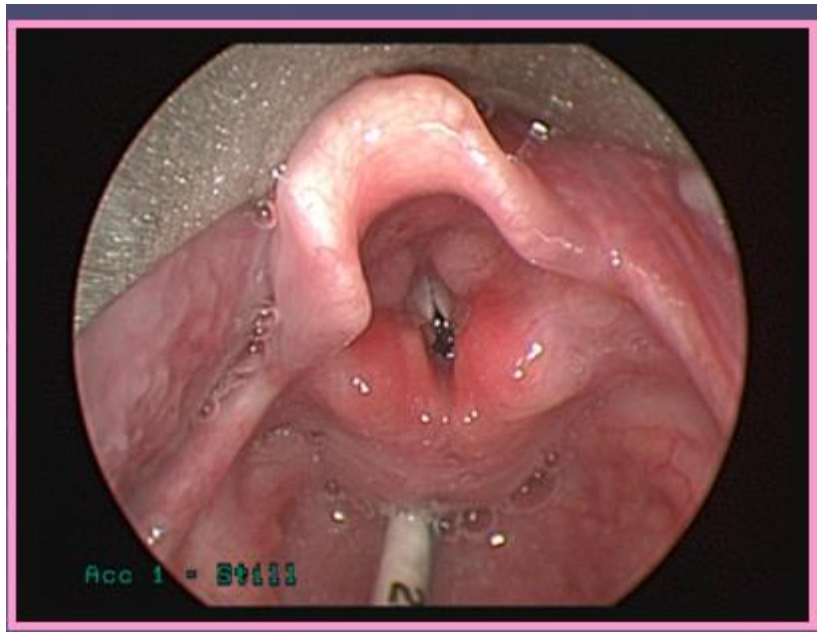
Laryngotracheal Aspiration
A common problem in LTC!!

- A good history essential
- Observe drinking 3 to 6 oz of water
- Chest X-ray usually makes the diagnosis
- Those with oral-pharyngeal dysphagia, an evaluation is indicated by a speech-language pathologist is best
- Patients with dysphagia may need videofluoroscopic swallow evaluation
- Nutritional advice and exercises help some

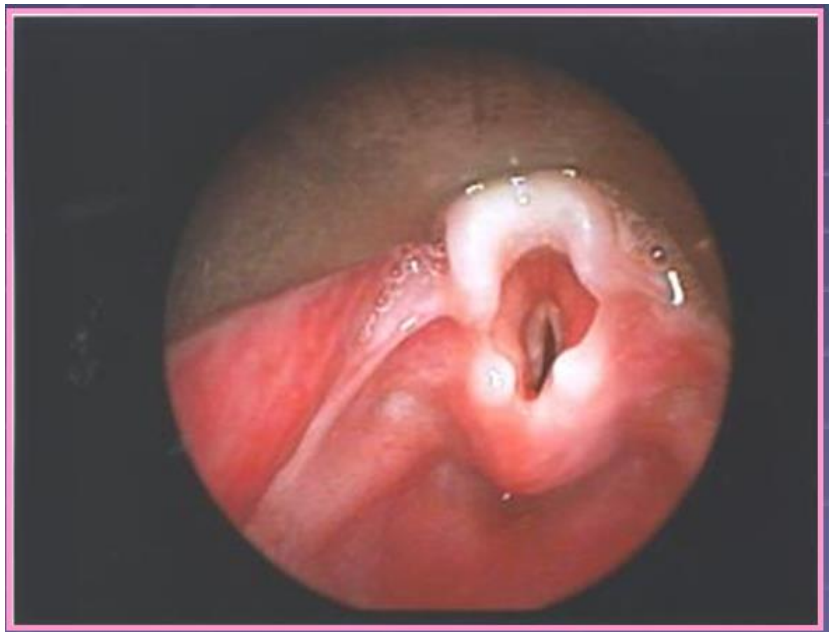
Could be brachiomalacia?

- Abnormally soft or pliable tracheal cartilages.
- Excessive narrowing may occur during exhalation,
- Classification of the condition is based on the anatomic area that is involved (eg, tracheomalacia, tracheobronchomalacia, bronchomalacia).
- Clinical signs: stridor, wheezing, respiratory distress, and hyperinflation, either diffuse or localized.
- Cough usually disappears during sleep, and growth is not impaired but become evident during agitation or respiratory infections.
- Diagnosis is established by airway fluoroscopy or flexible fiberoptic bronchoscopy.

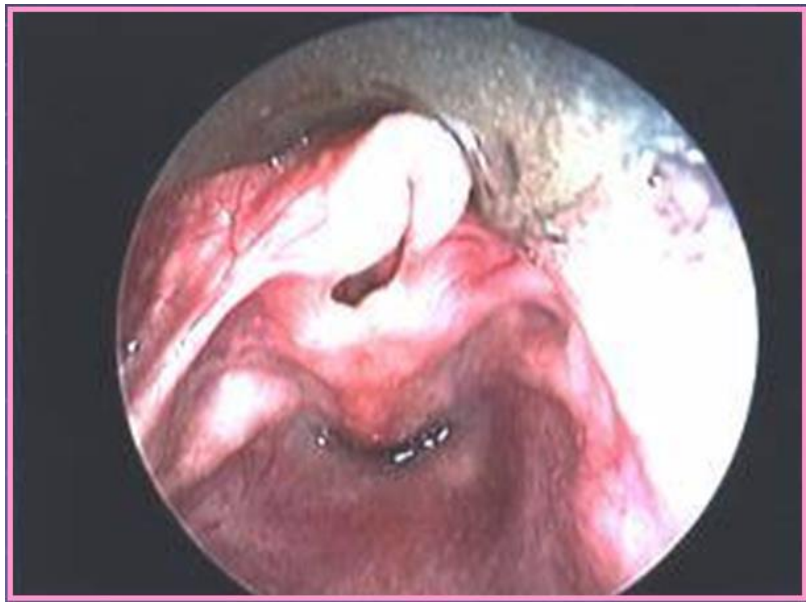
Normal Laryngoscopy



Mild



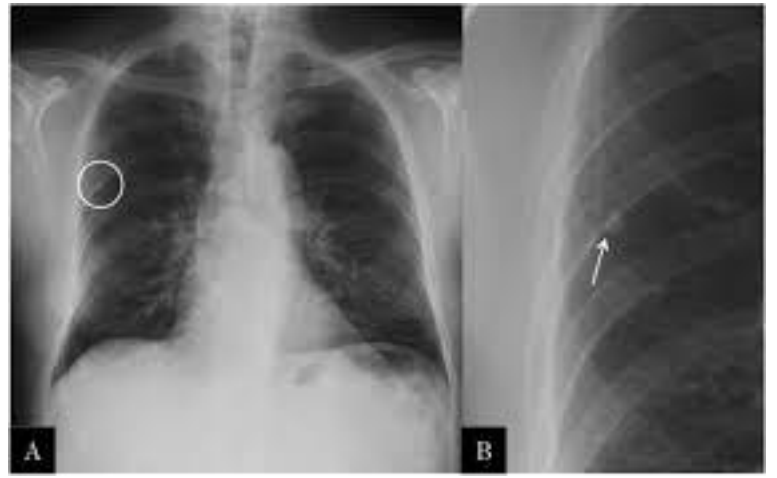
Severe



What if your patient

- also had night sweats, weight loss and hemoptysis?

Did you know?



- There is an increased risk of TB in those on long term ICS?
- If radiologic evidence of past TB (granuloma, scars etc) the hazard ratio is 27X![1]
- Normal CXR, the hazard ratio is still 10X[1]
- In Canadian database study: the risk was doubled in those on ICS>1,000 ug/day[2]
- Remember Nontuberculous mycobacteria (NTM)

1. Kim et al. ICS is associated with increased TB risk. CHEST 2013; 143(4): 1018-1024 (**FROM KOREA!)**
2. Brassard et al. ICS and Risk of TB in Patients with Respiratory Diseases. American Journal of Respiratory and Critical Care Medicine, Vol. 183, No. 5 (2011), pp. 675-678. (**from CANADA!)**

Consider also

- Aspiration of foreign body
- Pertussis, caught from grandchild
- Other infections caught from staff or family..

Pertussis: Clinical Phases
Typical Course of Pertussis

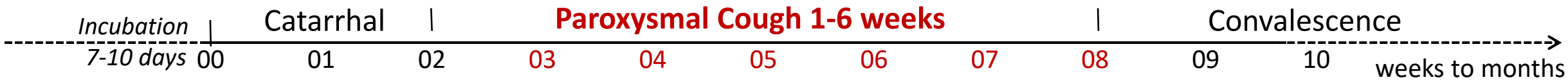
Catarrhal:
Mild cough
Runny nose
Mild fever
Apnea in infants

Paroxysmal

Cough
Cough Paroxysmal
Cough Whooping
Vomiting
Cyanosis
Apnea

Convalescent:
Cough
less paroxysmal
disappears
in weeks to months

*The illness can be milder and the typical "whoop" absent in children, teens, and adults who have been vaccinated with a pertussis vaccine.



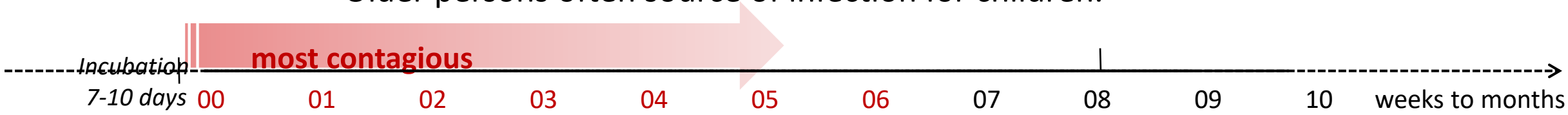
Tozzi A.E.; Diagnosis and management of pertussis; CMAJ 2005;172(4):509-15
http://www.cdc.gov/vaccines/pubs/pinkbook/pert.html accessed October 05, 2013

- The whoop is often absent in adults and in infants less than 6 months old. Initially dry, the cough becomes productive of a clear tenacious mucus
- Paroxysms are sometimes associated with episodes of syncope and vomiting. The paroxysmal stage is followed by up to 2 months of coughing episodes, probably secondary to damage to the epithelial cells of the upper respiratory tract and from toxins produced by the bacillus.

Pertussis: Contagious* Period

- Pertussis is most contagious during the first 2 weeks when symptoms resemble those of a common cold.
- Contagiousness declines rapidly after that, but may last up to three weeks.
- Patients are no longer infectious after 5 days of treatment with appropriate antibiotics.

*Older persons often source of infection for children.



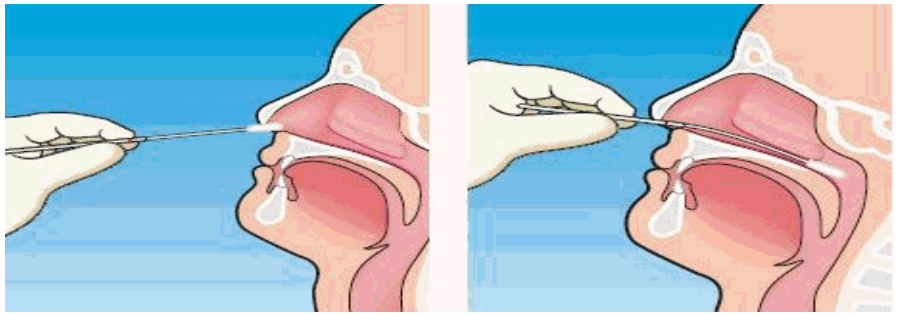
Tozzi A.E.; Diagnosis and management of pertussis; CMAJ 2005;172(4):509-15
http://www.phac-aspc.gc.ca/id-mi/pertussis-coqueluche-eng.php 2013 October 02

Pertussis: Nasopharyngeal Swab*

not cotton

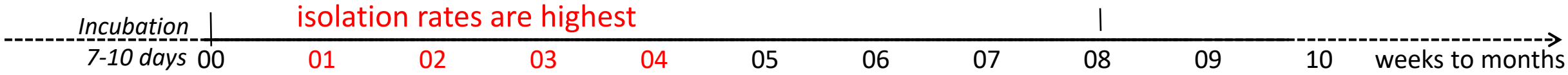
posterior nasopharynx - not the throat

Dacron or
calcium alginate



plated directly on selective media.

*Isolation rates are highest during the first 3 to 4 weeks of illness (catarrhal and early paroxysmal stages).



Tozzi A.E.; Diagnosis and management of pertussis; CMAJ 2005;172(4):509-15
http://www.cdc.gov/vaccines/pubs/pinkbook/pert.html 2013 October 02

Pertussis:Treatment

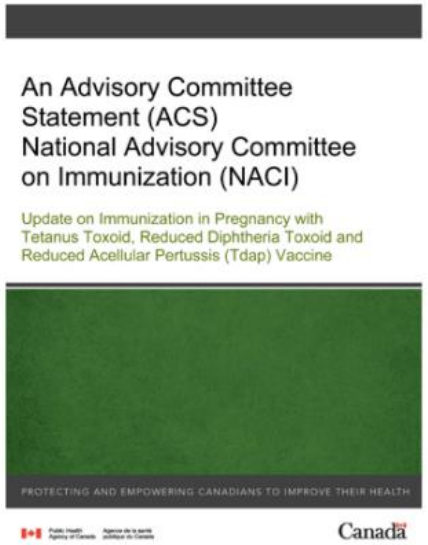
Antibiotic Therapy

Erythromycin
Azithromycin
Clarithromycin
Trimethoprim-sulfamethoxazole

Maintaining high vaccination coverage rates among preschool children, adolescents, **and adults** and minimizing exposures of infants and persons at high risk for pertussis is the most effective way to prevent pertussis.

http://www.cdc.gov/vaccines/pubs/pinkbook/pert.html
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5414a1.htm?s_cid=rr5414a1_e accessed 2013 October03

Dx Pertussis
Treated with Macrolide, but…



Recommendation: NACI recommends that immunization with Tdap vaccine should be offered in <u>every</u> pregnancy, irrespective of previous Tdap immunization history (Strong NACI Recommendation). NACI concludes that there is good evidence to recommend immunization (Grade A Evidence)
Routine maternal Tdap immunization during pregnancy will provide a more robust and complete protection against pertussis in infants compared to immunization during outbreak settings only.

Case 4

- 73 year old woman in Nursing home
- Cough x 8 weeks
- Wet cough, but non-productive
- Fever initially, now intermittent
- Has had two courses of antibiotics

- CXR shows RLL infiltrate
- Speech pathologist did a barium swallow showing aspiration
- Family meeting re G Tube placement?

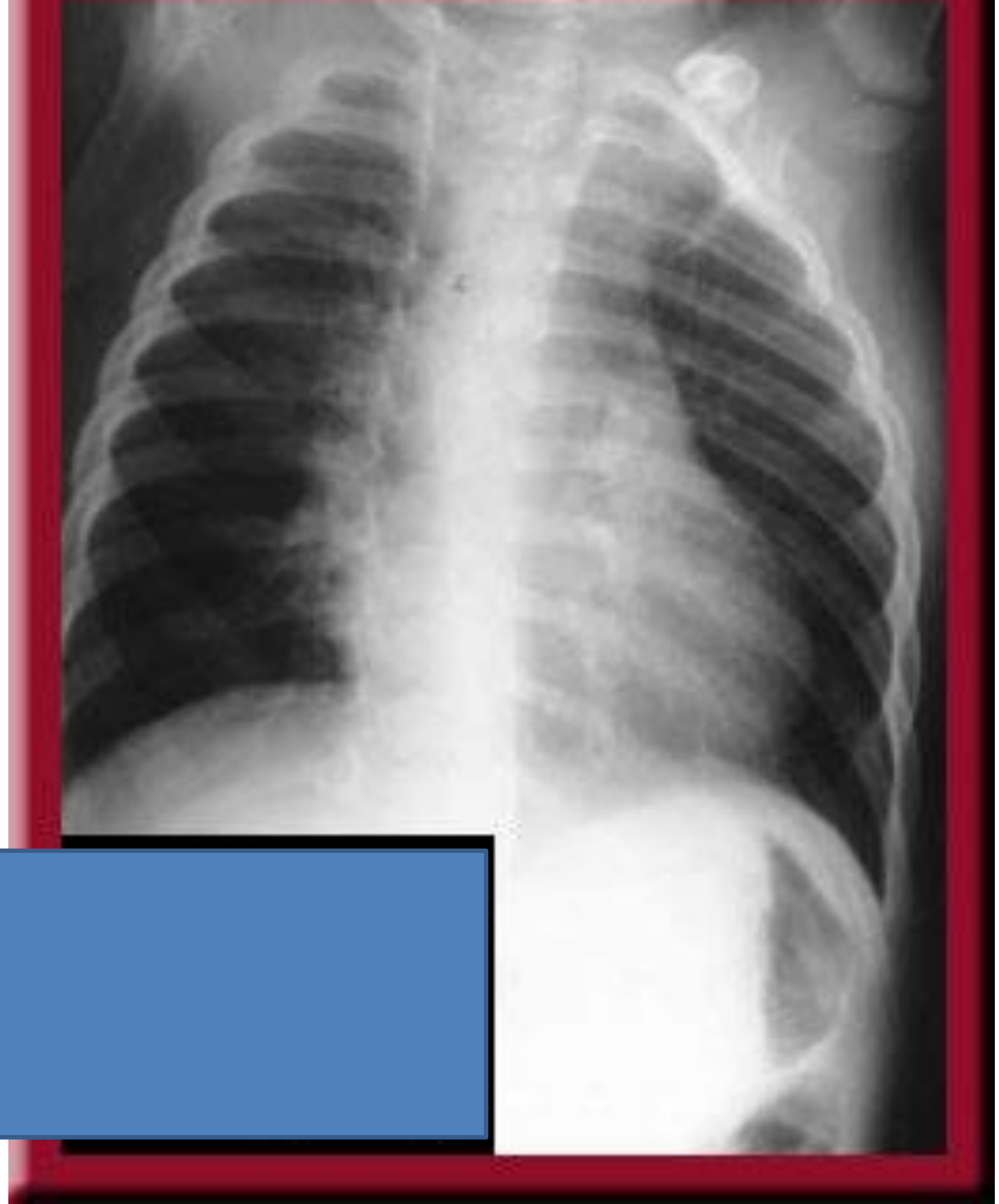
Case 5

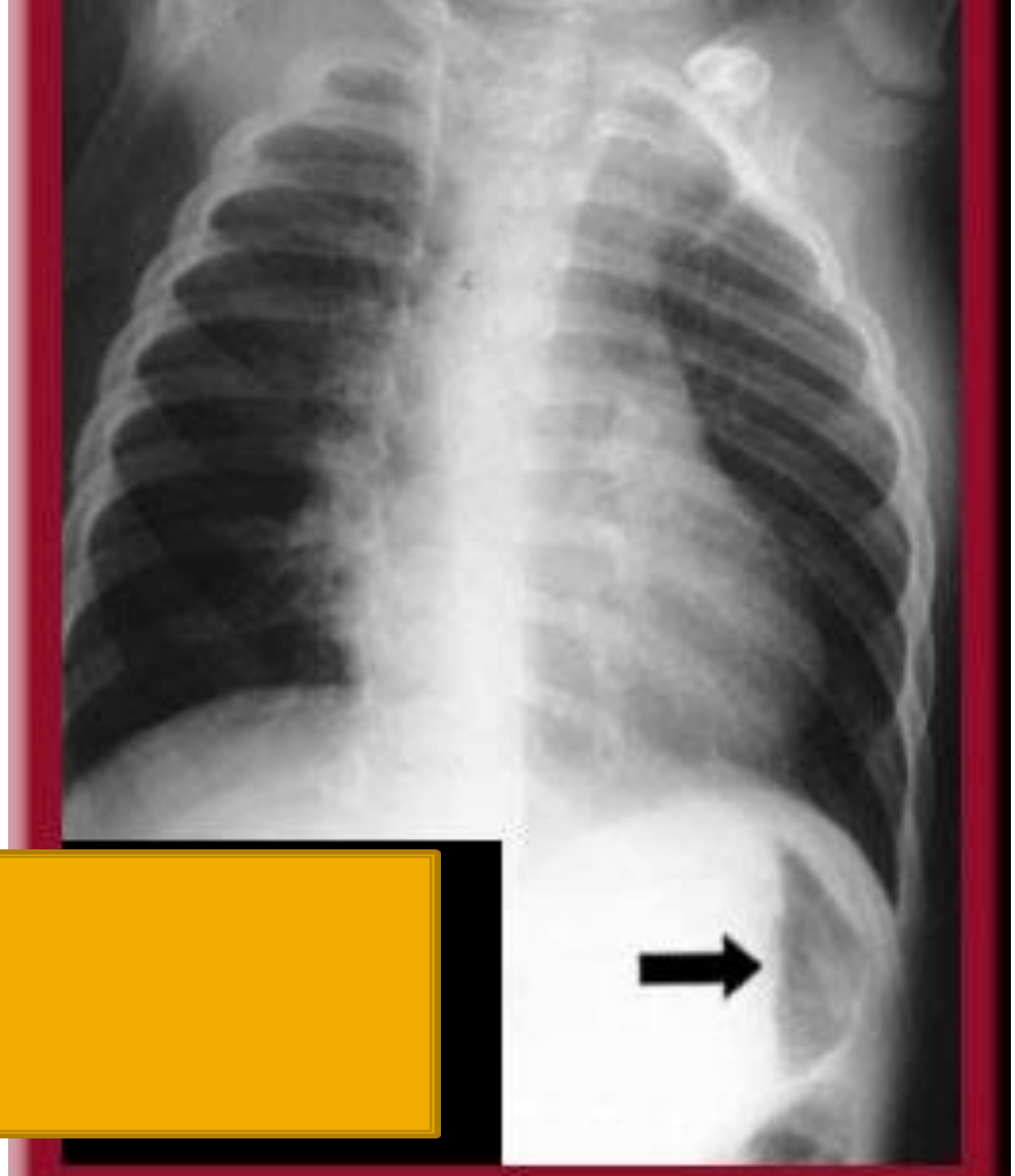
- 68 year old woman
- Widowed, husband passed with brain tumor
- NIDDM, beta thalassemia trait
- Not on ACE or ARB or Beta blocker
- Cough x 8 weeks
- No travel
- CXR, CT, Spirometry/PFTs normal

- Bronchoscopy showed ++ eosinophils on lavage -> NAEB
- Only thing that gets her better when she worsens is Oral Steroid course....messes up her Diabetes!

Case 6

- 73 year old male
- Cough for many weeks,
  which was treated with inhalers.
- Appropriately immunized
- On presentation he had intermittent cough some wheeze and occasional stridor





The gastric bubble

Our Interpretation

Sunflower seed
right main bronchus.

CHRONIC COUGH
(>8 WEEKS)

History, physical exam and chest X-ray

Smoking, use of ACEIs → Discontinue → No response

Possible cause of cough identified → Investigate and treat → Inadequate response to optimal treatment

- **Upper airway cough syndrome (UACS)**: empiric treatment
- **Asthma**: evaluate if possible (spirometry, bronchodilator reversibility test, bronchial provocation test) or treat empirically
- **Non-asthmatic eosinophilic bronchitis (NAEB)**: look for esinophils in sputum; if not present, treat empirically
- **Gastroesophageal reflux disease (GERD)**: empiric treatment

Inadequate response to optimal treatment

COMPLEMENTARY INVESTIGATION OR REFERRAL TO SPECIALIST

OTHER EXAMINATIONS TO CONSIDER:

- 24-hour esophageal pH monitoring
- Endoscopic or videofluoroscopic evaluation of swallowing
- Esophageal transit study
- Sinus imaging
- High-resolution chest CT scan
- Bronchoscopy
- Echocardiogram
- Environmental evaluation
- Consider the possibility of other rare causes

Consider the possibility of several concomitant causes

Important general considerations:

- **Optimize the treatment for each diagnosis**
- **Verify compliance with therapy**
- **Because of the possibility of more than 1 cause, continue all partially effective treatments**

What about Post Covid?

Nature Public Health Emergency Collection

Public Health Emergency COVID-19 Initiative

Lung. 2020 Nov 13 : 1–3.

doi: 10.1007/s00408-020-00406-6 [Epub ahead of print]

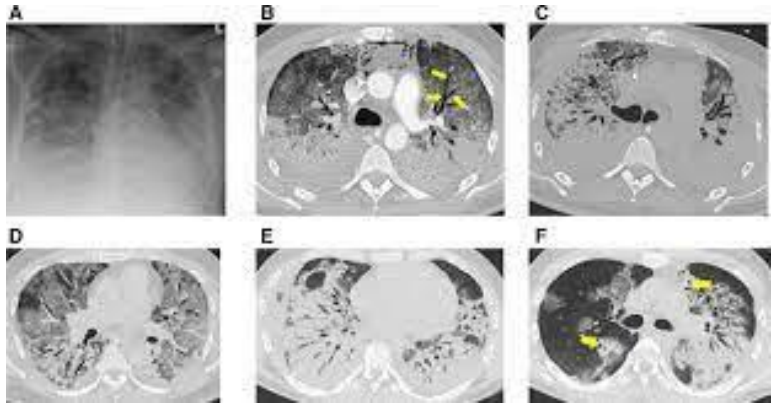
PMCID: PMC7665087

PMID: 33188436

Is There (Will There Be) a Post-COVID-19 Chronic Cough?

Peter V. Dicpinigaitis, MD[✉1] and Brendan J. Canning, PhD[2]

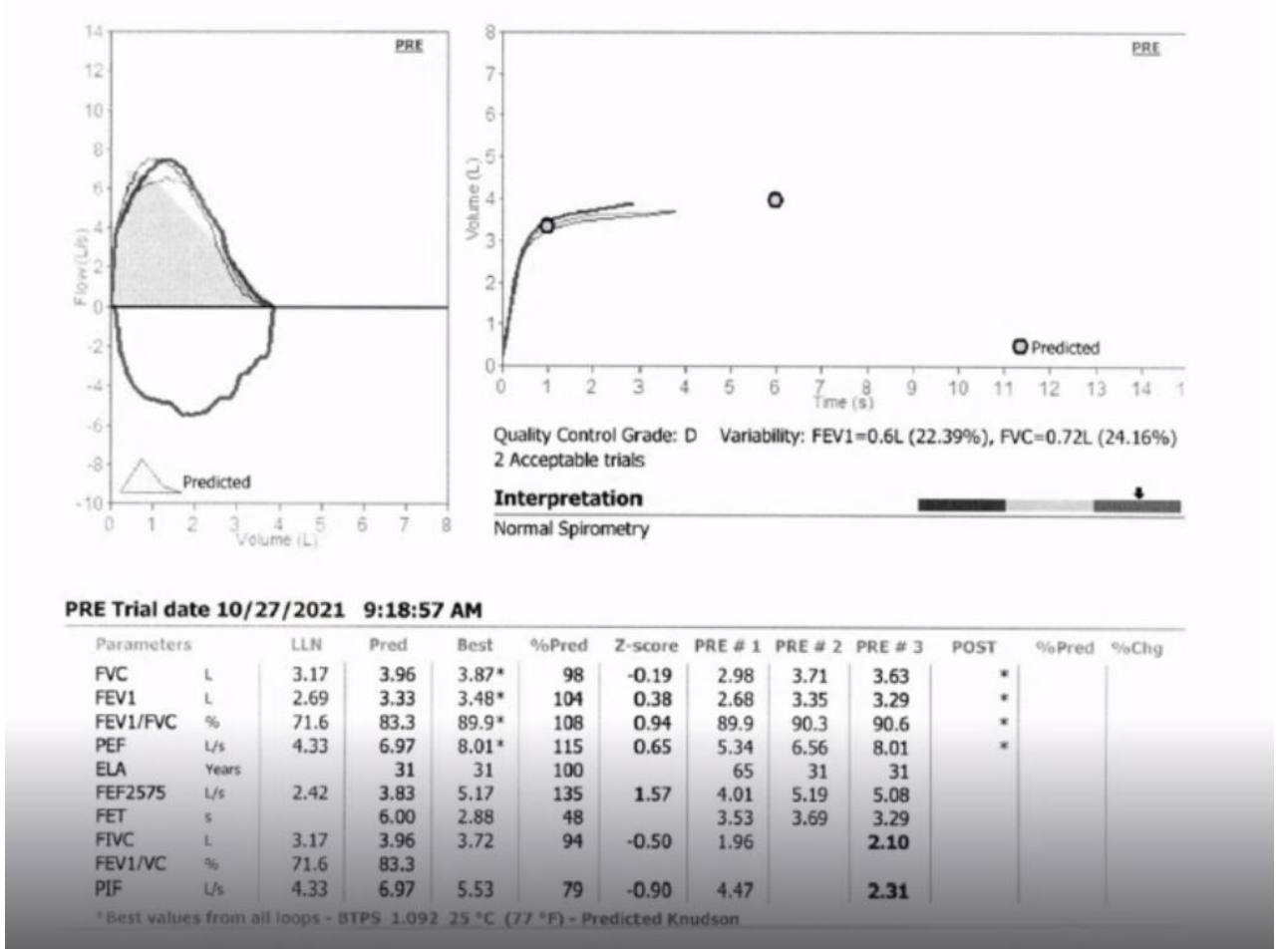
- In summary, clinical experience in the early aftermath of the first wave of the COVID-19 pandemic indicates that postviral chronic cough is neither a frequent nor debilitating residual effect.
- The symptoms of fatigue, dyspnea and chest tightness/discomfort have been reported with significantly greater frequency than cough.



Thankfully, most get better!!

George PM, et al. Thorax 2020;75:1009–1016. doi:10.1136/thoraxjnl-2020-215314

Still symptomatic with dyspnea post Covid



Repeat CT re interstitial fibrosis
Consider CTEPH..do they have persistent Pulmonary emboli?
Dyspnea is subjective:
Could be autonomic dysfunction
Could be fitness
Could be psychologic
May be debilitating even with no pathology!
Send for Pulmonary Rehabilitation!

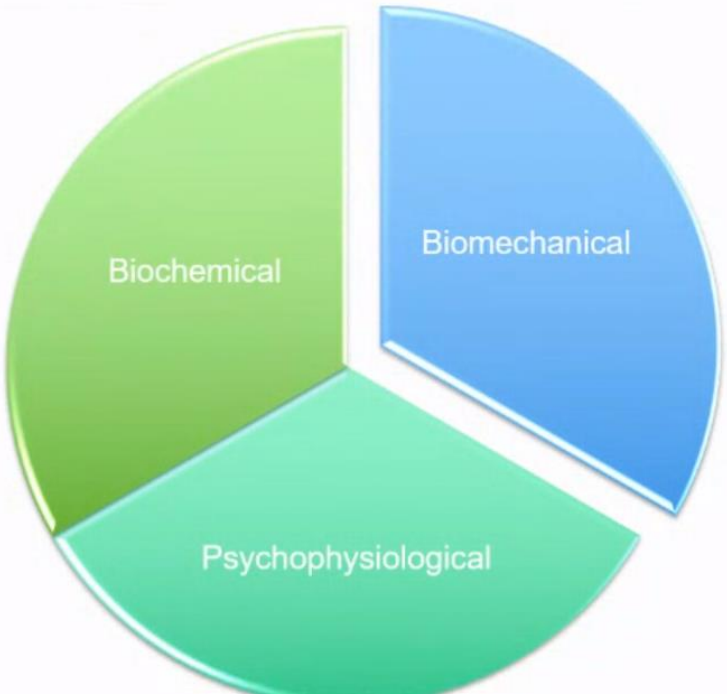
Normal


Hyperventilation: A Possible Explanation for Long-Lasting Exercise Intolerance in Mild COVID-19 Survivors?
Justina Motiejunaite, Pauline Balagny, Florence Arnoult, Laurence Mangin, Catherine Bancal, Marie-Pia d'Ortho and Justine Frija-Masson
Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19
Arno Mohr, Laura Dannerbeck, Tobias J. Lange, Michael Pfeifer, Stefan Blaas, Bernd Salzberger, Florian Hitzenbichler, Myriam Koch
Center for Pneumology, Donaustauf Hospital, Donaustauf
Department of Internal Medicine 2, University Medical Center, Regensburg
Department of Infection Control and Infectious Diseases, University Medical Center Regensburg, Germany
Respiratory rehabilitation for Covid-19 related persistent dyspnoea:
one-year experience
Benoit Bouteleux, Pauline Henrot, Rachel Ernst, Léo Grassion,
Chantal Raherison-Semjen, Fabien Beaufils, Maéva Zysman, Mathieu Delorme
High incidence of hyperventilation syndrome after COVID-19
Jérémie Taverne, Hélène Salvator, Cécile Leboulch, Nicolas Barizien, Marie Ballester,
Etienne Imhaus, Marie-Laure Chabi-Charvillat, Anne Boulin, Céline Goyard, Alexandre Chabrol,
Emilie Catherinot, Claire Givel, Louis-Jean Couderc, Colas Tcherakian
Persistent Exertional Intolerance After COVID-19
Insights From Invasive Cardiopulmonary Exercise Testing
Inderjit Singh, MD; Phillip Joseph, MD; Paul M. Heerdt, MD, PhD; Marjorie Cullinan, RT;
Denyse D. Lutchmansingh, MBBS; Mridu Gulati, MD, MPH; Jennifer D. Possick, MD; David M. Systrom,
and Aaron B. Waxman, MD, PhD
Emerging Breathing Evidence in Long Covid

What is dysfunctional breathing?

An alteration in the normal biomechanical patterns of breathing that result in intermittent or chronic symptoms which may be respiratory and/or non-respiratory

(Barker & Evard, 2014)



Questionnaire to assist diagnosis

Nijmegen Questionnaire

A score of over 23 out of 64 suggest a positive diagnosis of hyperventilation syndrome.

	Never 0	Rarely 1	Sometimes 2	Often 3	Very Often 4
Chest pain					
Feeling tense					
Blurred vision					
Dizzy spells					
Feeling confused					
Faster or deeper breathing					
Short of breath					
Tight feelings in chest					
Bloated feeling in stomach					
Tingling fingers					
Unable to breathe deeply					
Stiff fingers or arms					
Tight feelings round mouth					
Cold hands or feet					
Palpitations					
Feeling of anxiety					

Management of DB

Patient Education: awareness, breathing, ANS

Breathing Pattern Re-training

- Correct hyperinflation
- Nose breathing
- Abdominal pattern

Biofeedback – HR

Relaxation Training

Stress management

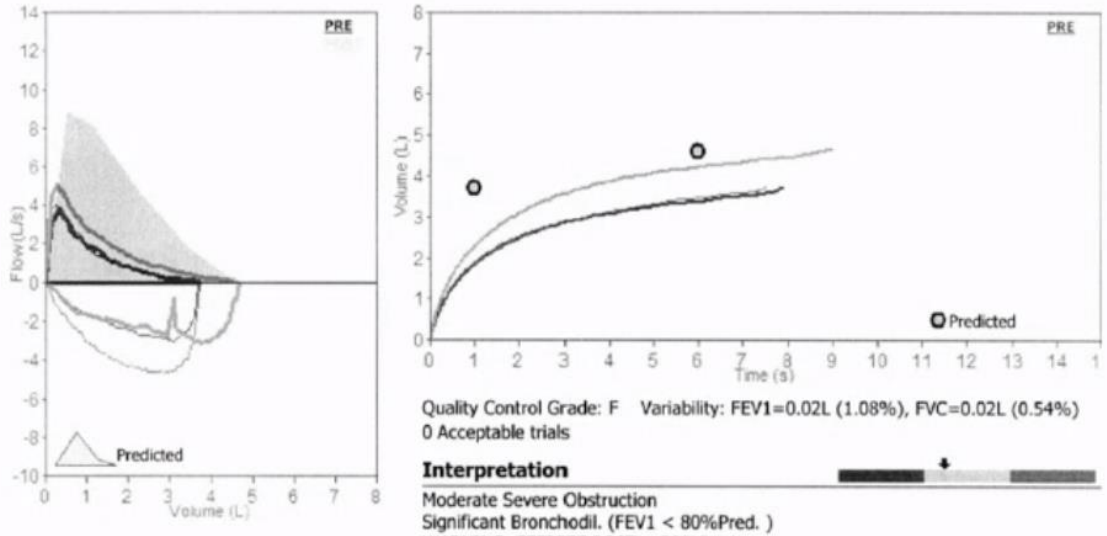
Inspiratory Muscle Training

Nutrition and sleep advice

Postural Correction/Exercises

Breathing with movement and activity

Spiro post Covid in symptomatic woman



Quality Control Grade: F Variability: FEV1=0.02L (1.08%), FVC=0.02L (0.54%)
0 Acceptable trials

Interpretation

Moderate Severe Obstruction
Significant Bronchodil. (FEV1 < 80%Pred.)
WARNING: FEF2575 POST = 39%Pred.

PRE Trial date 8/3/2021 9:33:17 AM **POST Bronchodilation with Generic Drug - 10:30:22**

Parameters		LLN	Pred	Best	%Pred	Z-score	PRE # 1	PRE # 2	PRE # 3	POST	%Pred	%Chg
FVC	L	3.55	4.60	3.74*	81	-1.35	3.74	3.72	3.69	4.69 *	102	25
FEV1	L	2.85	3.72	1.88*	51	-3.50	1.88	**1.85**	**1.86**	2.33 *	63	24
FEV1/FVC	%	70.4	80.5	50.3*	62	-4.89	50.3	**49.7**	**50.4**	49.7 *	62	-1
PEF	L/s	5.40	8.81	4.19*	48	-2.23	3.85	**3.94**	**4.19**	5.12 *	58	22
ELA	Years		55	118	215		118	119	119	102	185	-14
FEF2575	L/s	2.01	3.79	0.79	21	-2.77	0.79	**0.81**	**0.82**	1.46	39	85
FET	s		6.00	7.87	131		7.87	7.52	7.35	8.96	149	14
FIVC	L	3.55	4.60					3.68	**3.50**	4.58	100	
FEV1/VC	%	70.4	80.5									
PIF	L/s	5.40	8.81					**4.73**	**3.03**	3.10	35	

*Best values from all loops - BTPS 1.092 25 °C (77 °F) - Predicted Knudson

NO symptoms pre Covid
Clear airway obstruction
With reversibility
Underlying Asthma!!
Treat the asthma!!

Case 7

- 64 year old man with lung cancer
- Cough is bothersome symptom
- Cannot sleep
- Now what?

What is not a treatment options for cancer related cough?

1) Oral steroids
2) Neuropathic treatments like Gabapentin/ nebulzied Lidocaine
3) Treat the comorbidities (eg. COPD)
4) Opioids
5) Expectorant

CHEST

Symptomat ng Adult Patie
CHEST Guideli

Alex Molassiotis, RN, PhD, lackhall, MD, PhD; and Richard S. Irwin, MD,

TABLE 2] Causes of Cough Among Patients With Cancer[a]

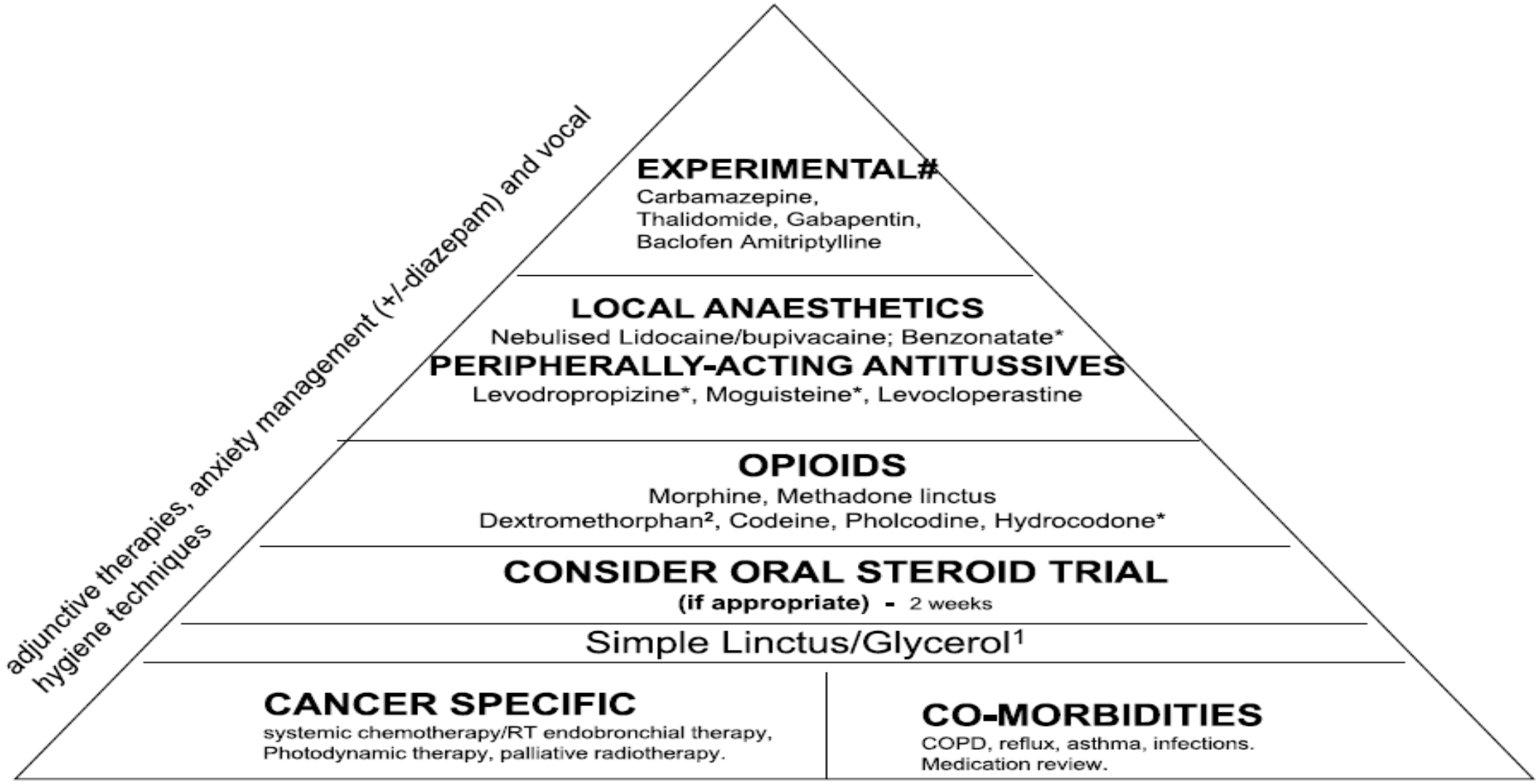
Pleural disease-effusion, tumor
Lung parenchyma infiltration
Major airway or endobronchial tumor
Cough after radiation or after chemotherapy
COPD; chronic bronchitis
Bronchiectasis
Pericardial effusion
Upper airway cough syndrome due to a variety of rhinosinus conditions
Gastroesophageal reflux disease
Asthma
Lymphangitis carcinomatosis
Chest infection
Microembolism
Tracheoesophageal fistula
Vocal cord paralysis
Congestive heart failure
Postinfectious cough
Eosinophilic bronchitis
Angiotensin-converting enzyme inhibitor

Molassiotis A. Chest 2017; 151: 861-874.

Molassiotis *et al. Cough* 2010, 6:9
http://www.coughjournal.com/content/6/1/9

Treatment pyramid for the management of cough in patients with lung cancer

Cough



Molassiotis A. Cough (London, England) 2010; 6: 9.

JOURNAL OF PAIN & PALLIATIVE CARE PHARMACOTHERAPY
2017, VOL. 31, NOS. 3–4, 195–197
https://doi.org/10.1080/15360288.2017.1420120

Taylor & Francis
Taylor & Francis Group

REPORT

Gabapentin for Cough in Cancer

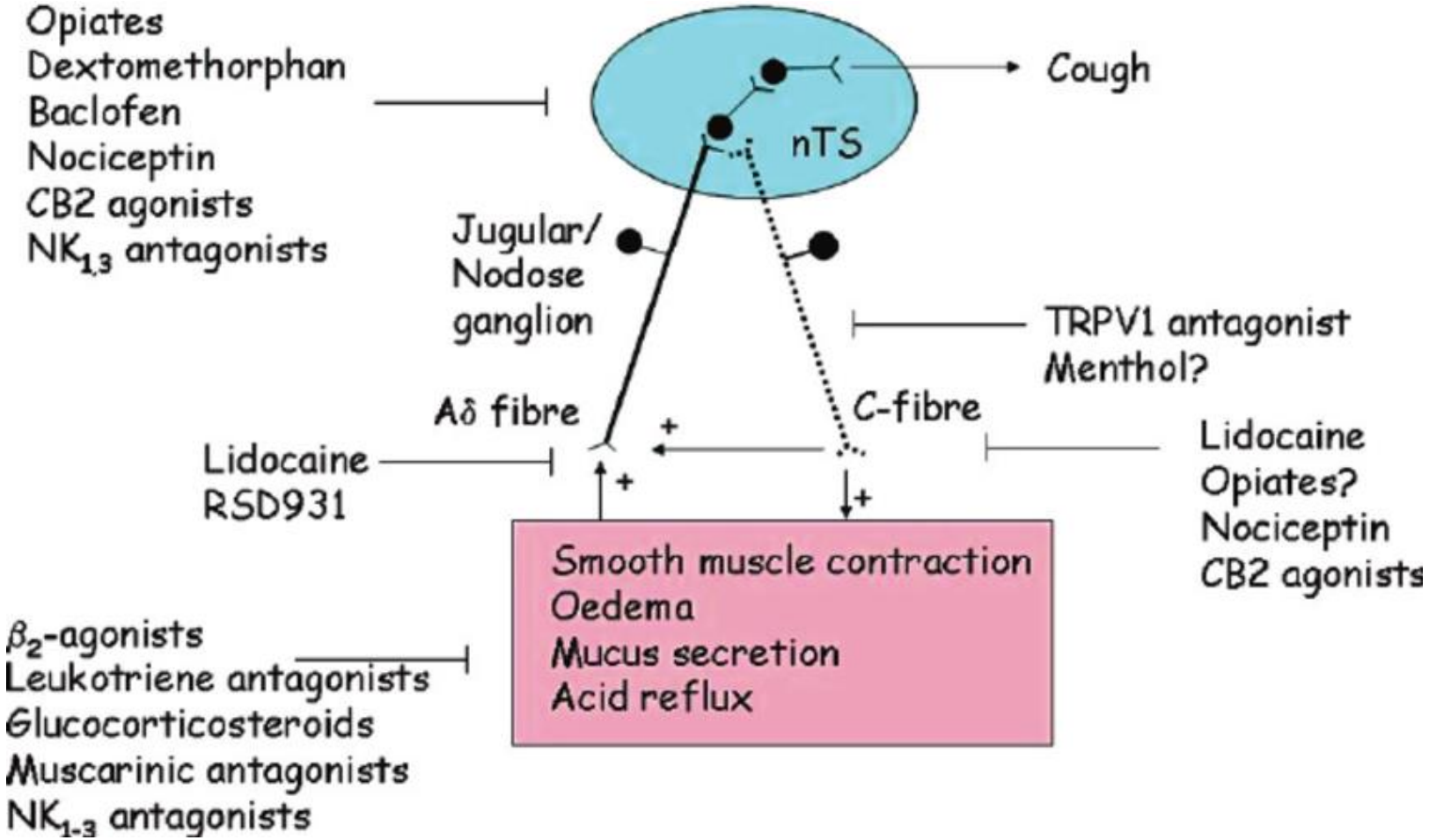
Rab Razzak, Julie M. Waldfogel, Danielle J. Doberman, Josephine L. Feliciano, and Thomas J. Smith

Table 1. Use of gabapentin, doses, and outcomes.

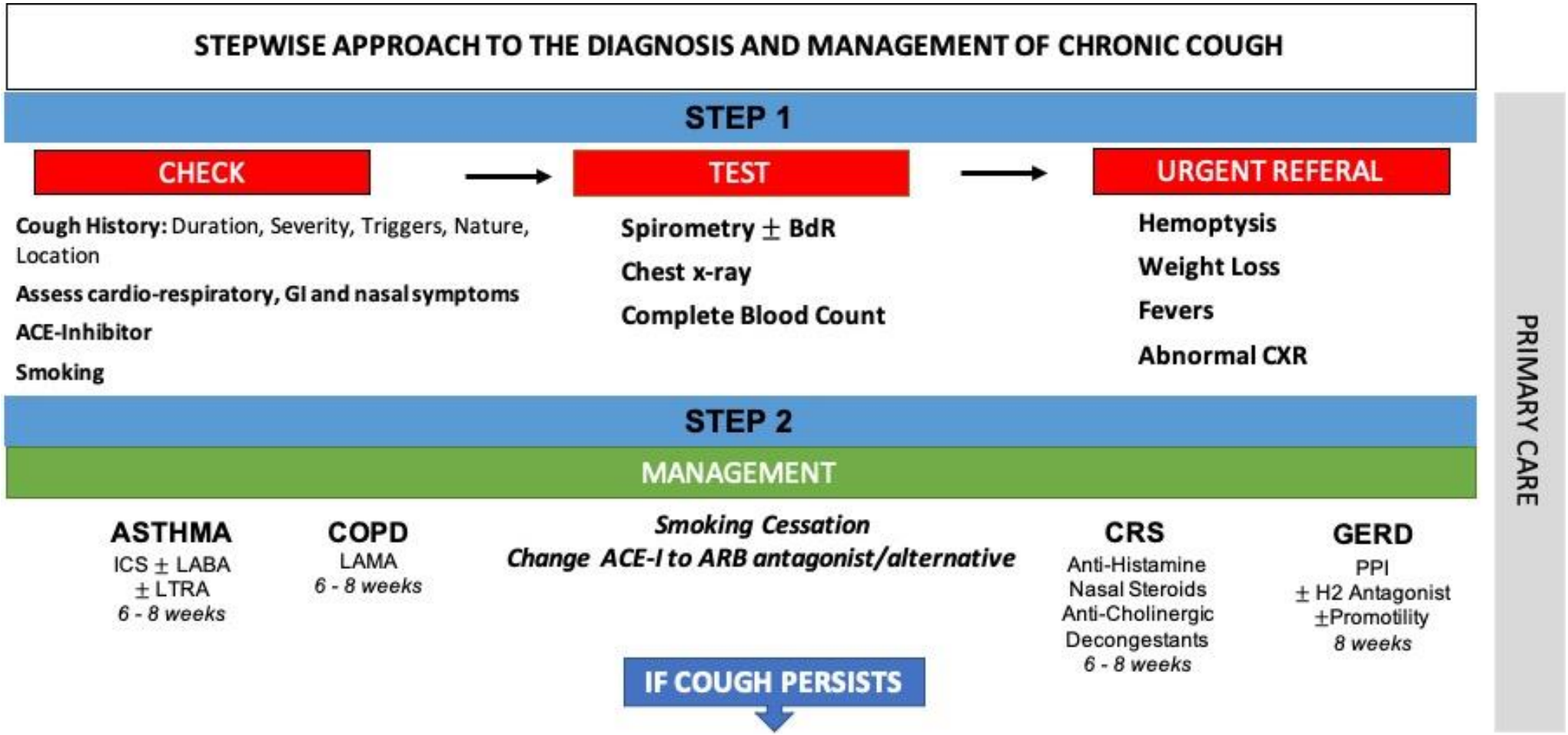
Case	Starting dose	Ending dose	Length of time treated and disposition
1	300 mg hs	300 mg three times a day	Four months; died of progressive disease; took in hospice
2	300 mg hs	400 mg three times a day	Five months; died of progressive disease; took till death
3	300 mg hs	300 mg hs	Lost to follow-up after 1 month

- Successful use of gabapentin at usual doses to treat cough in cancer patients
- With minimal side effects
- Gabapentin may be a useful addition to the symptom management toolbox for palliation of cancer symptoms.

Treat the cause

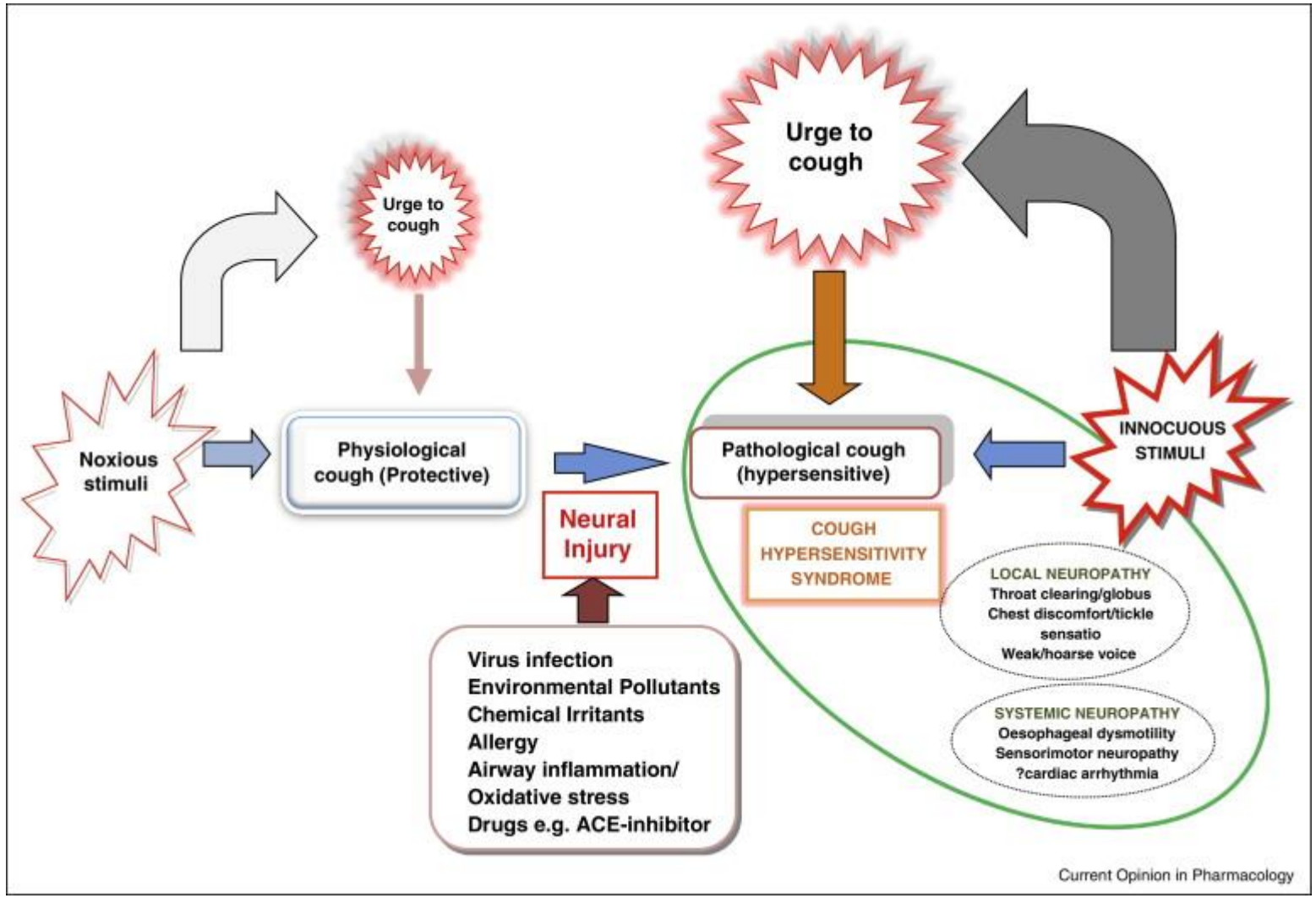


Primary Care steps



Canadian Journal of Respiratory, Sleep and Critical Care Medicine (accepted)

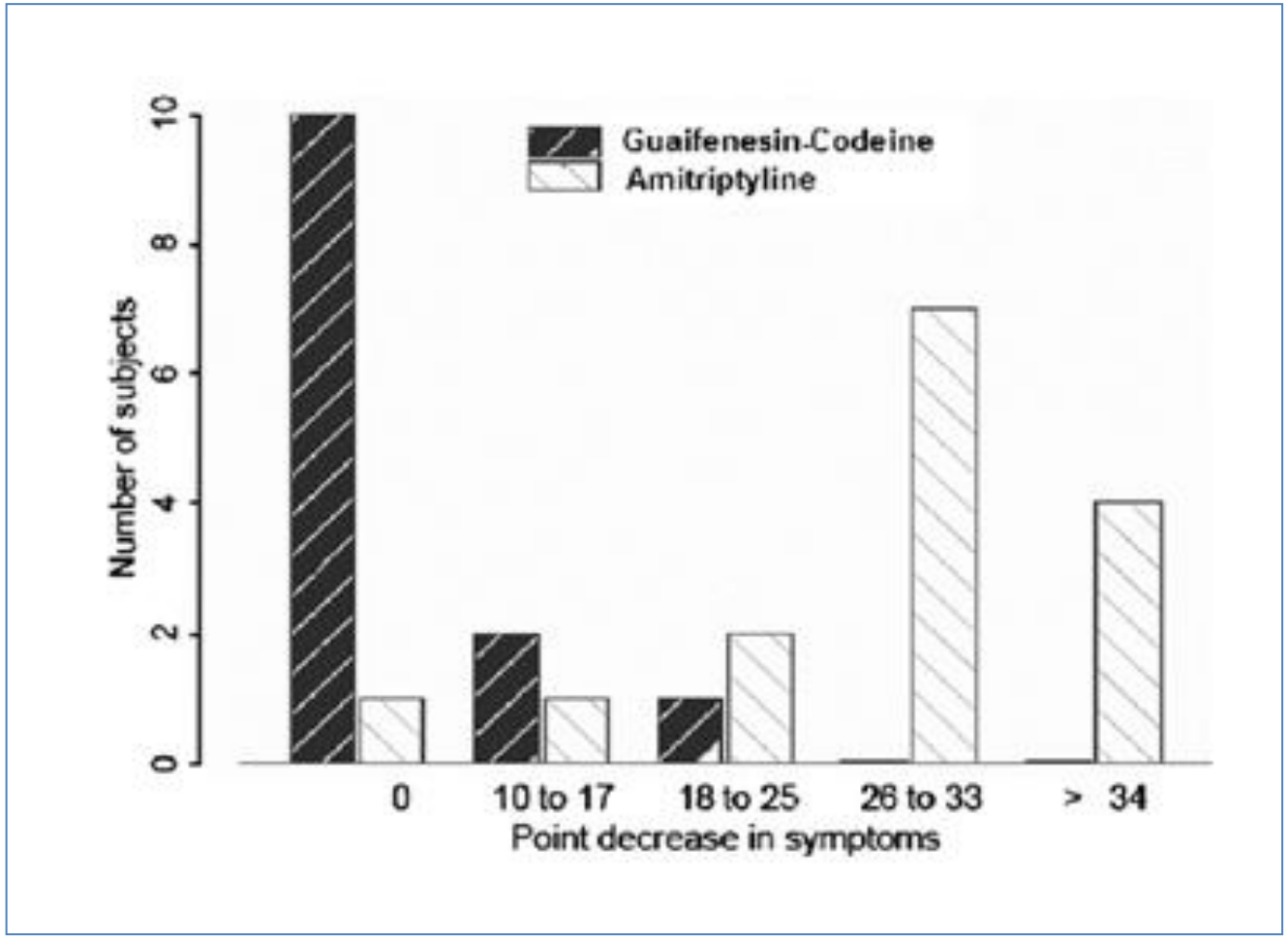
Mechanisms of Cough



It is all about the nervous system!!

- Post Viral **Vagal Neuropathy**
  subsequently called Cough Hypersensitivity Syndrome
- Now other terms:
- RCC: Refractory Chronic Cough
- UCC: Unexplained Chronic Cough

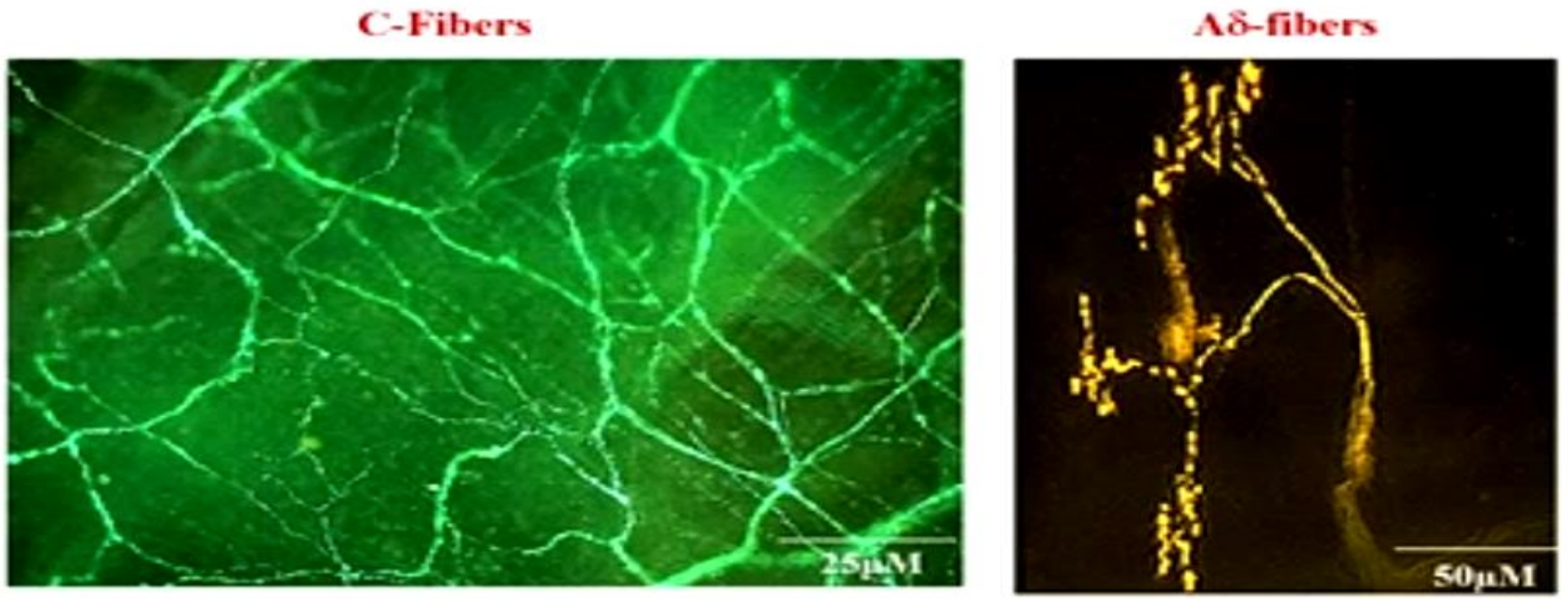
Chronic cough:
Vagal neuropathy??



Jeyakumar et. al. *Laryngoscope* 116: 2108, 2006

Mediated by Vagus nerve
but different sensory nerves

Vagal afferent nerve subtypes regulating the cough reflex



Mazzone et al., 2009

sensory

acid and mechanical

Neuropathic pain and neuropathic cough??

Chronic Pain and Incident Chronic Cough

McMaster University

Table 2: Chronic pain and risk of developing chronic cough (in all eligible participants)

Chronic pain status	Total (n = 2,232)	Incident chronic cough (n=210)	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[c]
No chronic pain	1,116	83	Ref.	Ref.	Ref.
Chronic pain	1,116	127	1.60 (1.20 – 2.14)	1.56 (1.16 – 2.10)	1.47 (1.08 – 1.99)
▪ Weekly/monthly chronic pain	444	48	1.51 (1.04 – 2.19)	1.49 (1.03 – 2.17)	1.43 (0.98 – 2.10)
▪ Daily chronic pain	672	79	1.66 (1.20 – 2.29)	1.61 (1.16 – 2.24)	1.49 (1.06 – 2.11)

a – crude estimate, b – adjusted for age and sex, c – adjusted for age, sex, BMI, smoking, use of ACE inhibitors, chronic rhinosinusitis, gastroesophageal reflux disease, asthma, COPD, lung cancer, heart failure, and CESD score ≥16

Table 3: Chronic pain and risk of developing unexplained chronic cough (in subjects without known risk factors: current smoking, use of ACE inhibitors, chronic rhinosinusitis, gastroesophageal reflux disease, asthma, COPD, or heart failure).

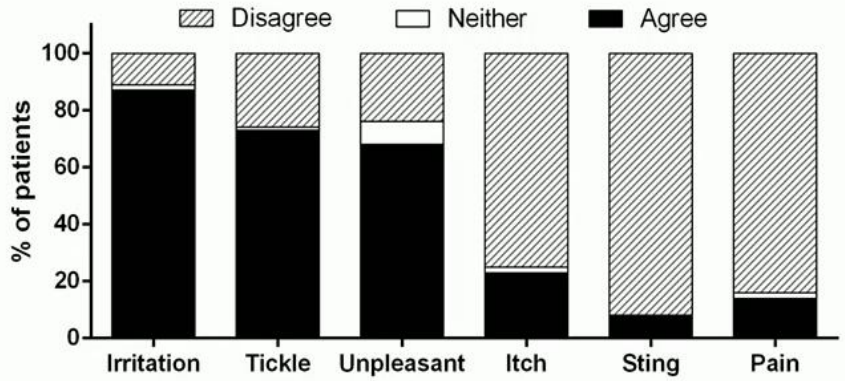
Chronic pain status	Total (n = 1,261)	Incident chronic cough (n=89)	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[d]
No chronic pain	692	38	Ref.	Ref.	Ref.
Chronic pain	569	51	1.69 (1.10 – 2.62)	1.65 (1.06 – 2.57)	1.60 (1.02 – 2.51)

a – crude estimate, b – adjusted for age and sex, d – adjusted for age, sex, BMI, and smoking status (never vs. former and CESD score ≥16

Sensations leading to cough; hint for neuropathic cause??

McMaster University

Sensations Provoking Urge to Cough

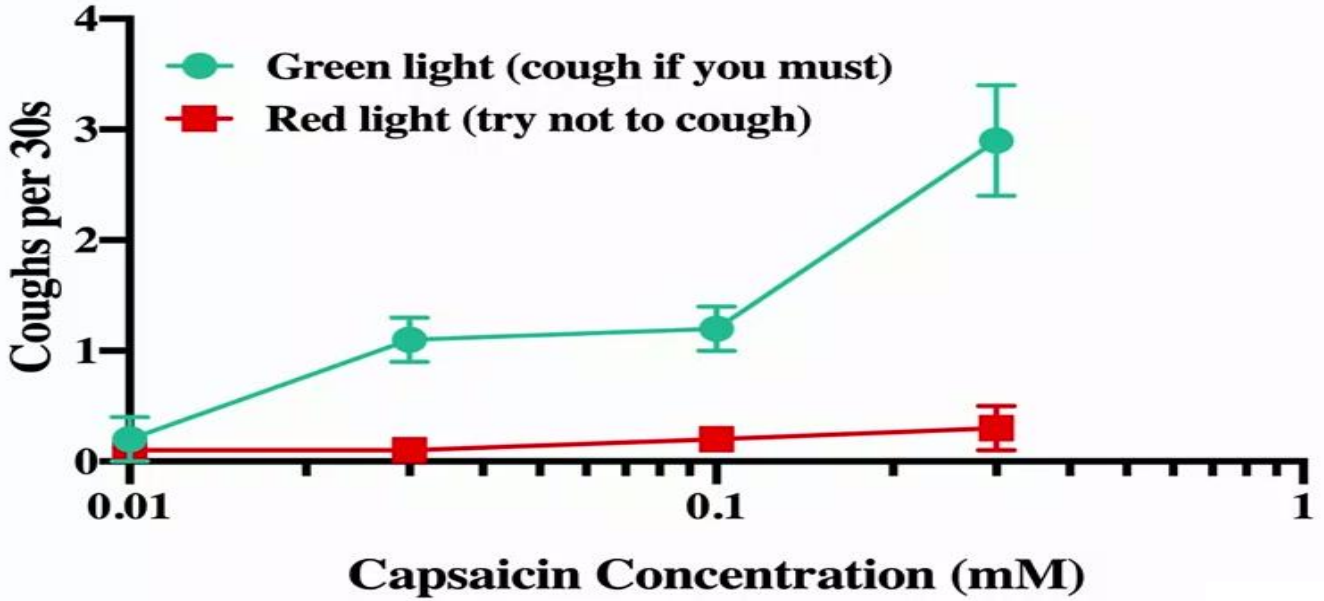


Locations: Neck (75%), Sternum (30%), Chest (23%), Abdomen (5%)

Hilton et al Respir Medicine 2015

Have you ever tried to stop coughing?

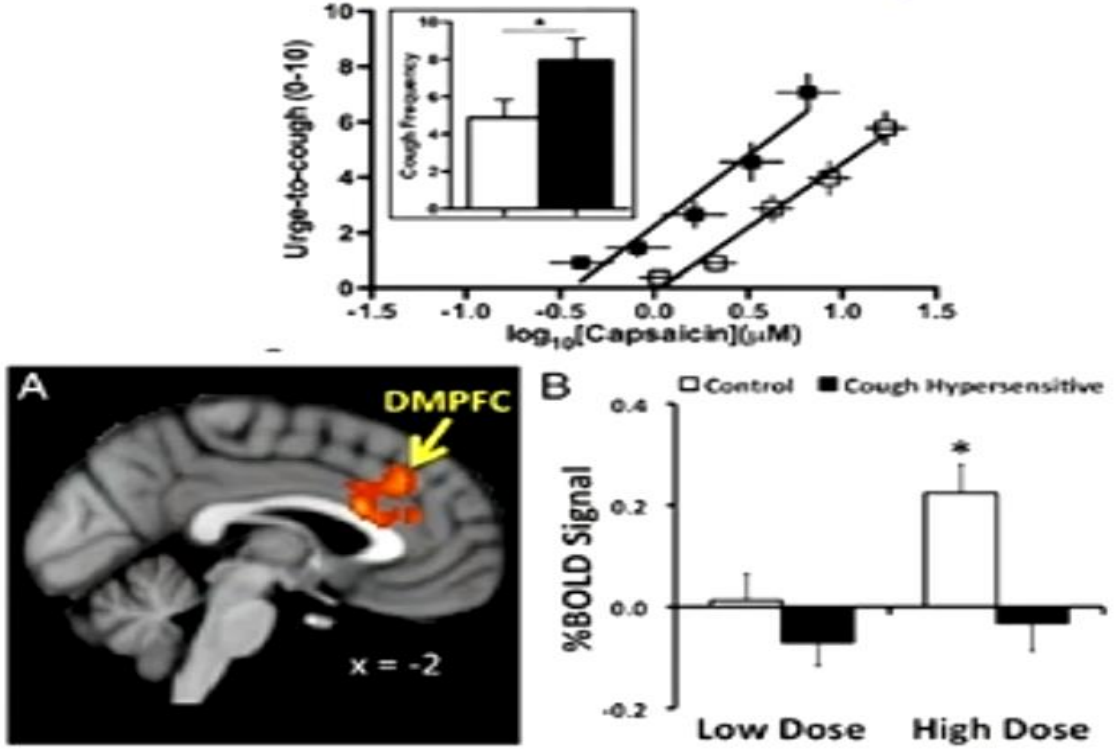
Voluntary suppression of capsaicin-evoked coughing in 24 healthy human volunteers



(modified from Hutchings et al., 1993)

Functional MRI shows changes!

Patients with cough hypersensitivity have a diminished activity in central inhibitory nuclei



(from Ando et al., 2016)

Cough suppression is an issue!

Impaired cough suppression in refractory chronic cough

Peter S.P. Cho [1], Hannah V. Fletcher [2], Richard D. Turner [1,3], Caroline J. Jolley [1] and Surinder S. Birring [1,2]

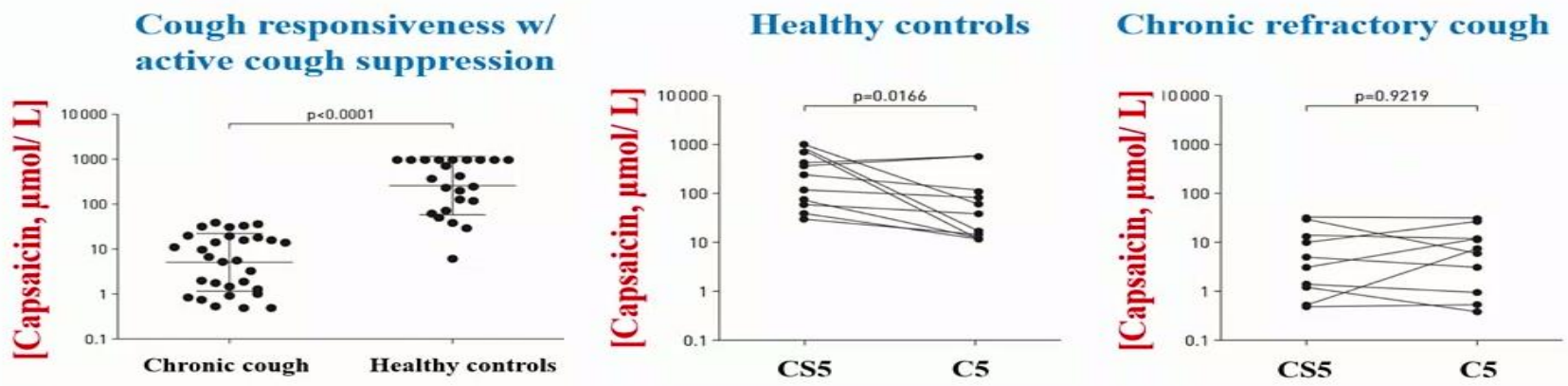


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Figure 2: Central nervous system pathways involved in cough. Schematic illustration of the postulated ascending and descending neuronal pathways which may be modulate cough.
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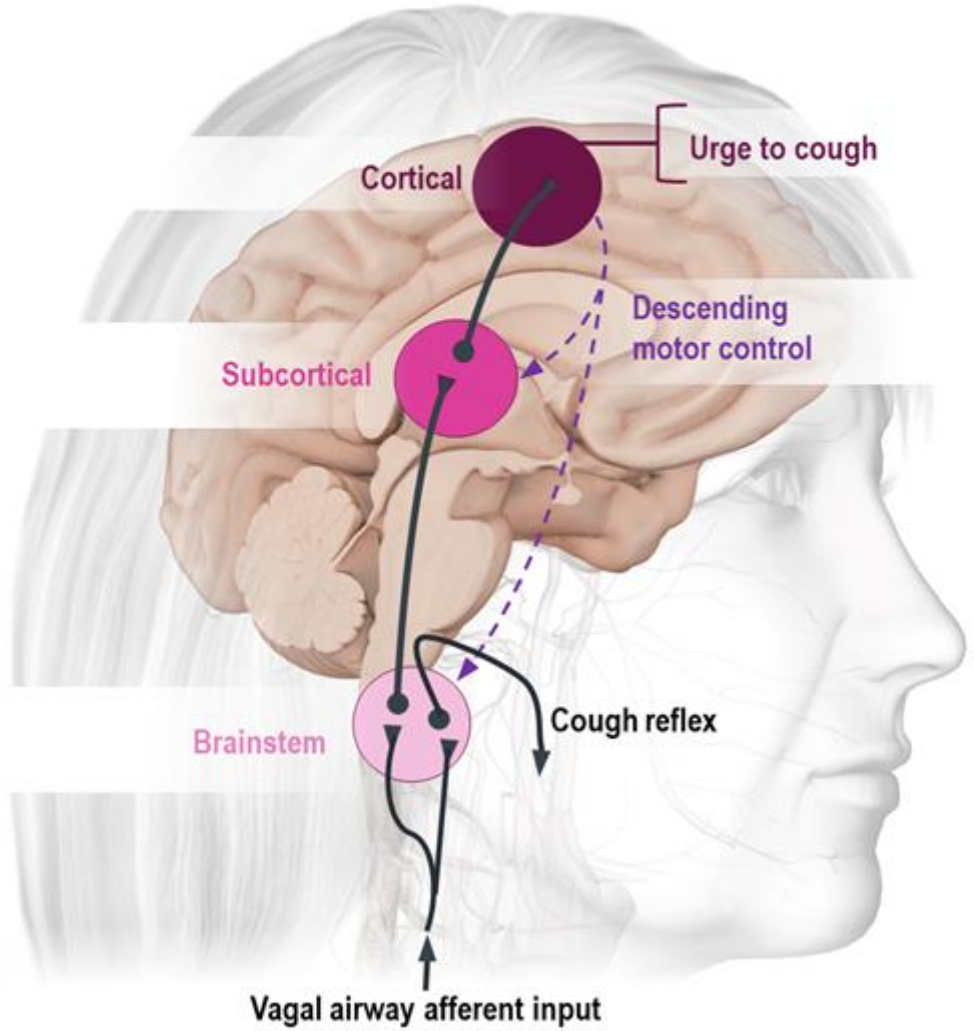
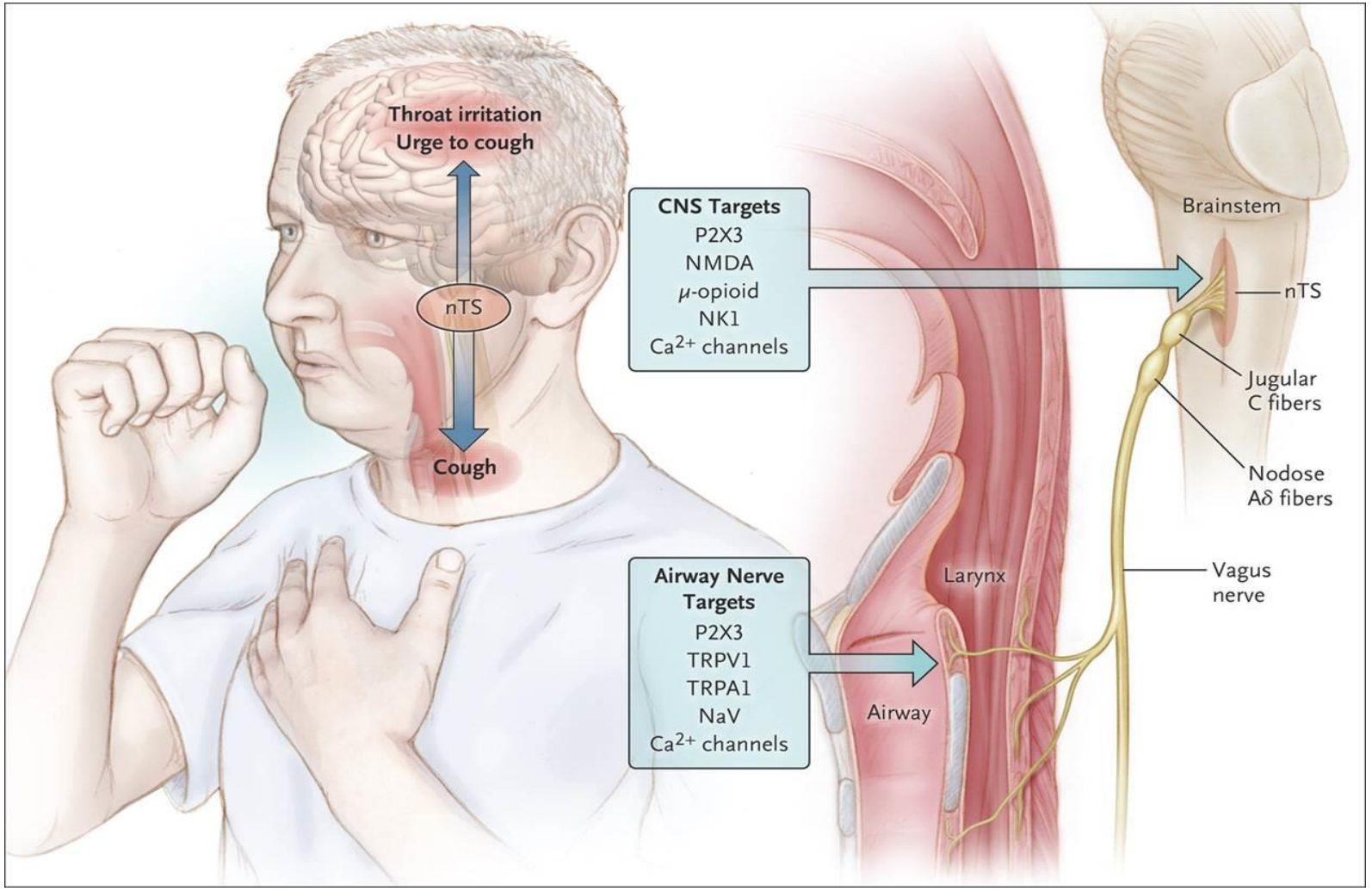


Current Treatment Options for RCC/UCC

Name/Dose	Mechanism	Pros	Cons
Speech Therapy	Teaches cough suppression, avoid triggers, laryngeal exercises	No side effects Patient led	Access, Cost, Requires patient motivation Limited subjective improvement beyond initial 3-4 month treatment period ***1 study of 24-hr cough frequency (LCM)***
Low-Dose Morphine (5-10mg M/R)	delta, kappa, and mu-opioid receptors	Fast onset 1-2 week trial	Nausea, drowsiness, unsteadiness, tolerance, addiction, stigma, constipation ***1 RCT with subjective endpoint***
Pregabalin (max 150mg BID)	α2δ-2 subunit of presynaptic voltage-gated calcium channels	BID Dosing Can start very low doses and titrate up	Drowsiness, hallucinations, suicidal ideation, weight gain, hair loss, difficult weaning off, 150mg BID rarely tolerated ***1 RCT with SPT, no improvement on objective coughs***
Gabapentin Max 300mgTID	α2δ-1 and α2δ-2 (low affinity)	TID Dosing Can start very low doses and titrate up	Unsteadiness, dry mouth, nausea, sleepiness ***1 RCT with subjective endpoint*** ***Cough monitoring for 1-hour only***
Amitriptyline 10mg -25mg OID	TCA, serotonin/noradrenaline re-uptake inhibitor	Might help depression, anxiety	Tremor, dry mouth, weight gain, ***1 uncontrolled study with unvalidated subjective endpoint***

Neuronal Pathways Controlling Cough / Targets: P2X3 New therapy coming



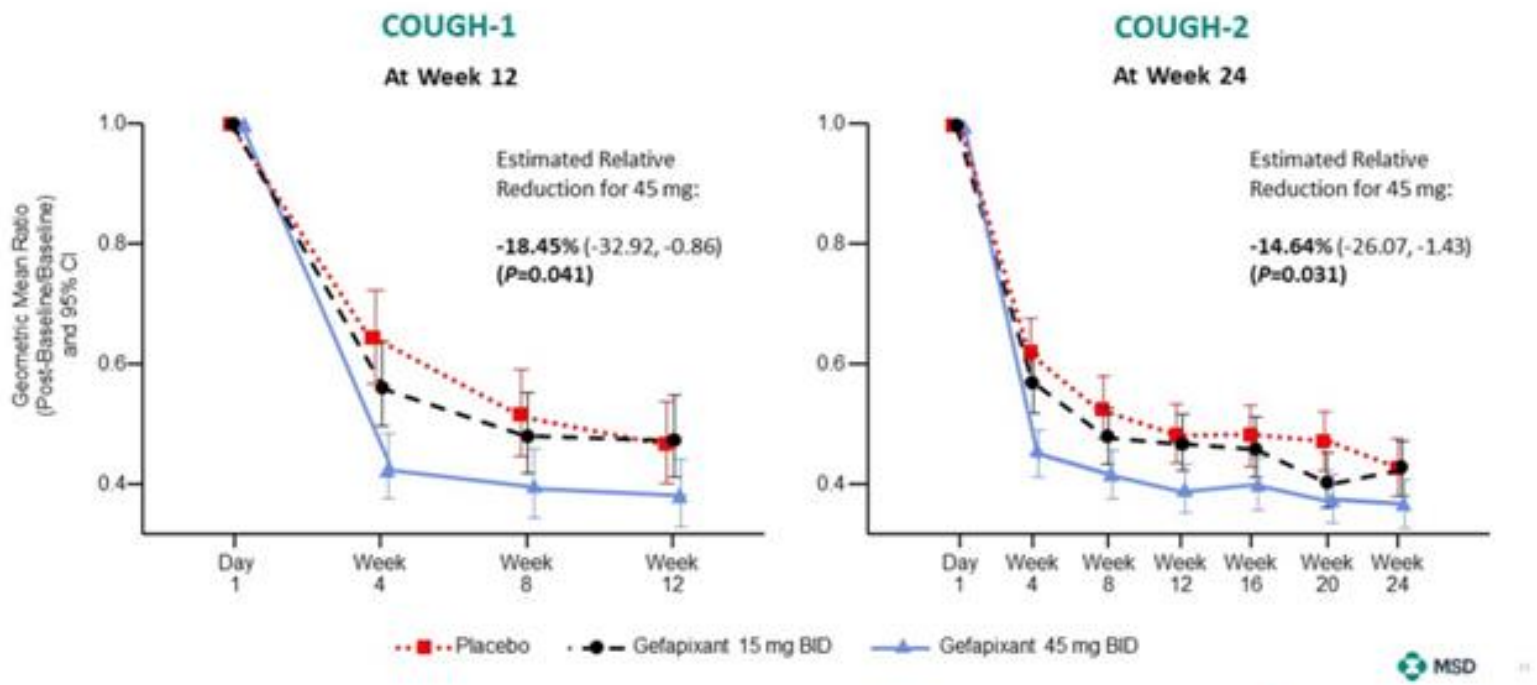
- **P2X3 receptors** are ligand gated ion channels expressed in C-fiber afferent neurons in the lung
- These neurons are activated and sensitized by **ATP**
- Under pathological conditions, C-fiber afferents become **hyper-sensitized** and may fail to return to a quiescent normal state
- MK-7264 (Gefapixant) is a P2X3 antagonist that blocks the activation of these afferents by ATP

N Engl J Med 2016;375:1544-51.

Gefapixant Phase 3 data…drug not yet approved

24-Hour Cough Frequency (Primary Endpoint)

Full Analysis Set



COUGH-2

At Week 24

Treatment	Baseline Geometric Mean	Week 24/ Baseline Geometric Mean Ratio (95% CI) (model-based)
Placebo (N=419)	25.83	0.42 (0.38, 0.47)
Gefapixant 15 mg BID (N=415)	25.56	0.41 (0.37, 0.46)
Gefapixant 45 mg BID (N=409)	24.26	0.36 (0.32, 0.40)

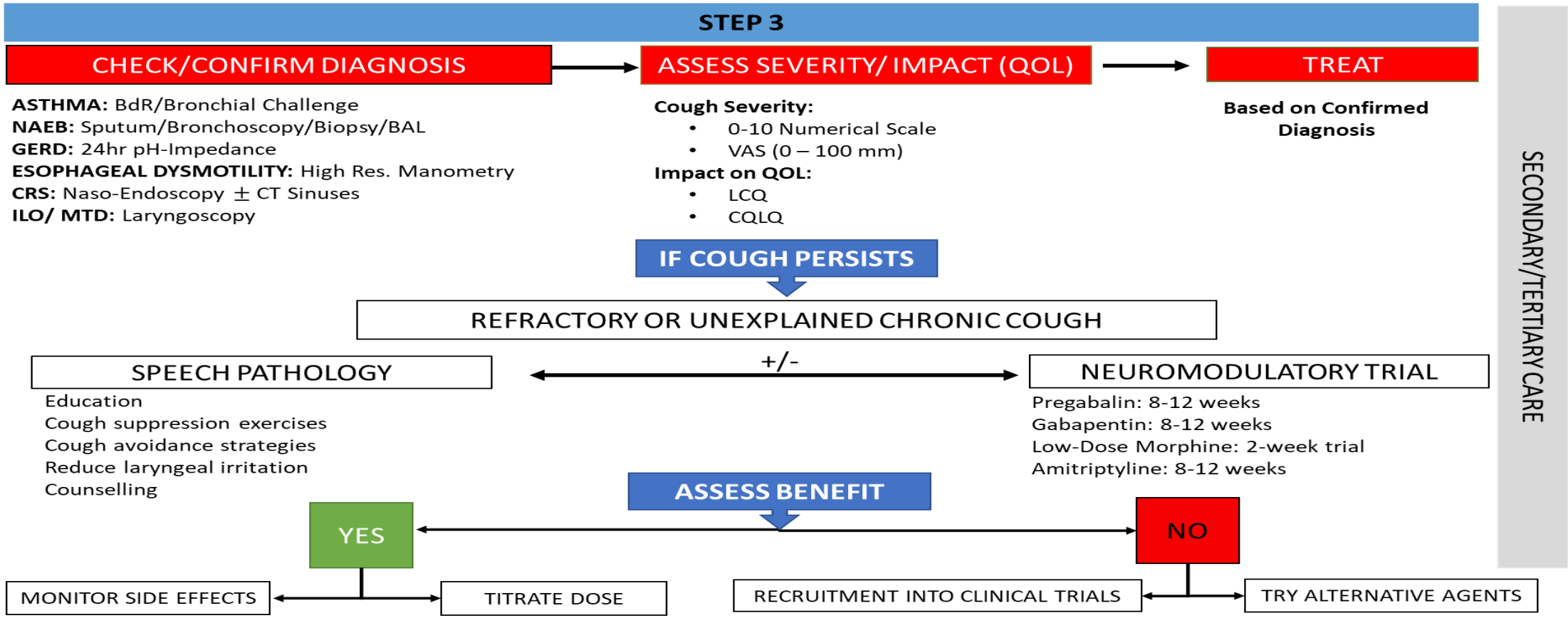
Treatment Comparison	Estimated Relative Reduction (%) and (95% CI)	*P*-value
Gefapixant 15 mg BID vs Placebo	-3.03 (-16.14, 12.12)	0.677
Gefapixant 45 mg BID vs Placebo	**-15.79** (-27.27, -2.50)	**0.022**

COUGH-2

Adverse Events at 24 Weeks

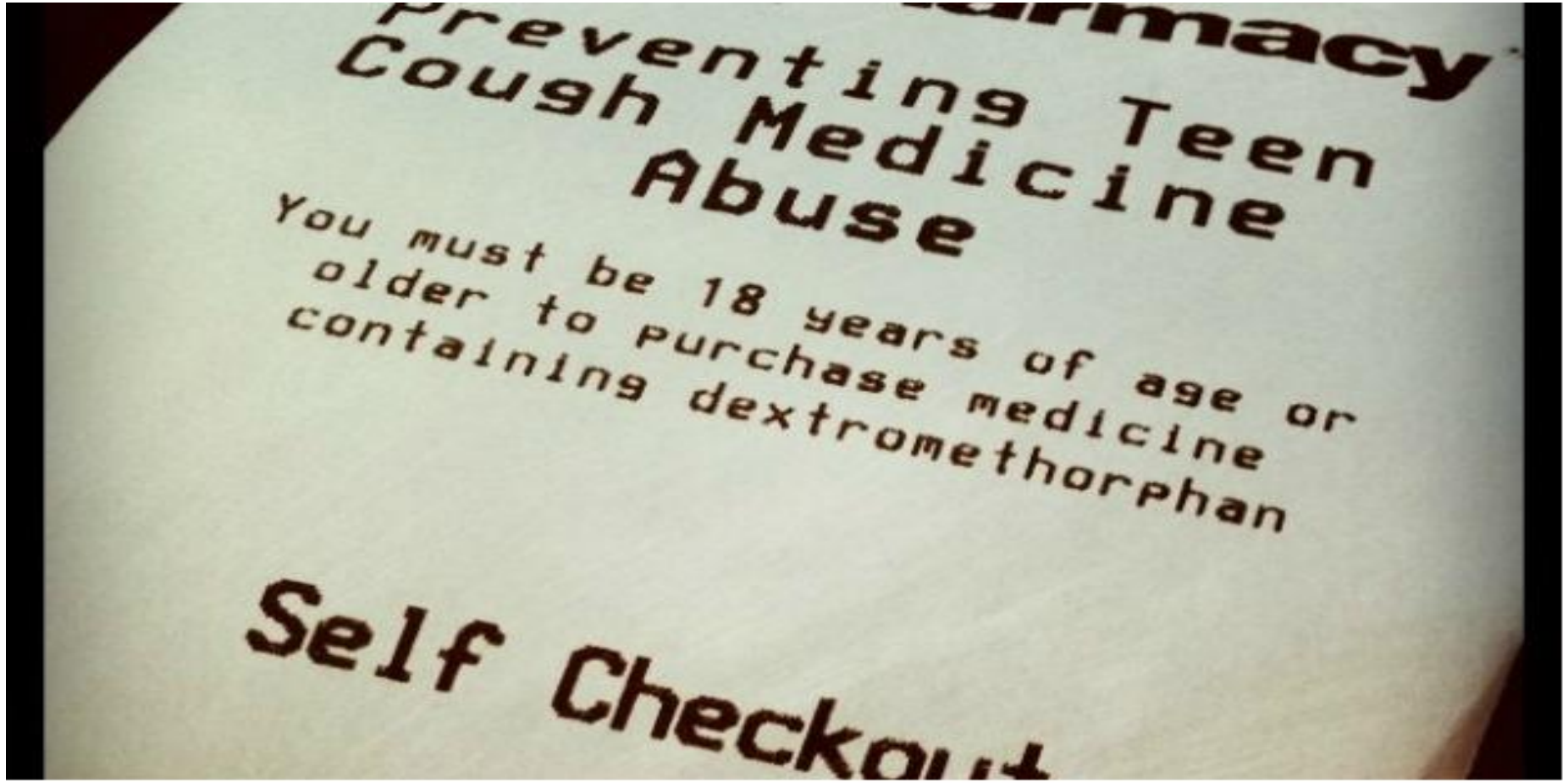
	Placebo N=413	Gefapixant 15 mg N=441	Gefapixant 45 mg N=440
Most Common AEs			
Agerusia	6 (1.4)	12 (2.7)	**70 (15.9)**
Dry mouth	11 (2.5)	15 (3.4)	31 (7.0)
Dysgeusia	28 (6.5)	54 (12.2)	**190 (43.2)**
Headache	**61 (14.1)**	**63 (14.3)**	66 (15.0)
Hypogeusia	3 (0.7)	18 (4.1)	57 (13.0)
Nasopharyngitis	**60 (13.9)**	**74 (16.8)**	58 (13.2)
Nausea	27 (6.2)	25 (5.7)	39 (8.9)

In Specialist Care



Canadian Journal of Respiratory, Sleep and Critical Care Medicine (accepted)

Cough syrups...careful!!



Summary

- Chronic cough is a common miserable condition.
- Approach is history (including meds and travel), physical exam …then..
- CXR, spirometry, FENO? will give you most of the answers!
- Next tests depend on clinical considerations and failure of first line therapies
- Remember, there may be a combination of causes!!

Just give ICS, Right?

- Asthma/eosinophilic airway syndrome are common and generally steroid responsive
- FeNO has value in the clinic (Yi F *et al*. Chest 2016; 149(4): 1042-1051; Price D *et al*. Lancet Respiratory Medicine 2017)
- Negative tests for bronchial hyper-responsiveness and eosinophilia – no steroids!

Resources

- FPAGC tools, cough algorithm at www.fpagc.com

- CTS led by Dr.Louis Phillipe Boulet educational program on cough at:

https://chairecoeurpoumons.learnworlds.com/course?courseid=cough-program

Article worth reviewing!!

Taylor & Francis
Taylor & Francis Group

Canadian Journal of Respiratory, Critical Care, and Sleep Medicine

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Chronic cough: Investigations, management, current and future treatments

I. Satia, M. Wahab, E. Kum, H. Kim, P. Lin, A. Kaplan, P. Hernandez, J. Bourbeau, L. P. Boulet & S. K. Field

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Proposed Primary Care Approach to Assessing Adults with Chronic Cough

Primary Investigations

To aid in diagnosis and/or referral

- ❑ Consider duration of symptoms (chronic cough definition >8 weeks)
- ❑ Review Red Flags (see below)
- ❑ Review medical history, including potential triggers:
  - ❑ Smoking, ACE inhibitors, sitagliptin?
  - ❑ Occupational/environmental issues or travel exposure?
- ❑ Perform physical exam
- ❑ Complete chest radiograph

Cough persists

Work-up for potential underlying conditions (Reassess in 4-6 weeks at least)

Assess for and treat as needed (alone or in combination)

- ❑ **Asthma**
  - ❑ Testing: Spirometry
  - ❑ Exploratory initial treatment per guidelines if indicated
- ❑ **GERD**
  - ❑ Exploratory initial treatment per guidelines if indicated

- Consider initiating referral to secondary care while waiting for testing/treatment results
- Assess if treatment resolved chronic cough

Cough persists

While patient waits to be seen by specialist

To expedite future diagnosis

- ❑ Consider other potential causes / additional investigations
- ❑ Consider possibility of >1 cause
- ❑ Assess adherence to treatment of potential underlying conditions
- ❑ Re-evaluate patient for (subtle) symptoms
- ❑ Continue to support your patient through their journey

Red flags for more severe issues

- Hemoptysis
- Smoker >45 years with new cough, cough change or coexisting voice disturbance
- Age 55-80 years: 30 pack-year smoking history + current smoker *or* quit <15 years ago
- Prominent dyspnea, especially at rest or at night
- Hoarseness
- Systemic symptoms, including fever, weight loss, peripheral edema with weight gain
- Trouble swallowing while eating or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or chest radiograph coinciding with duration of cough

Other potential causes of chronic cough (often assessed in secondary care), including

- UACS
- NAEB
- Bronchiectasis

Additional investigations (depending on access to testing)

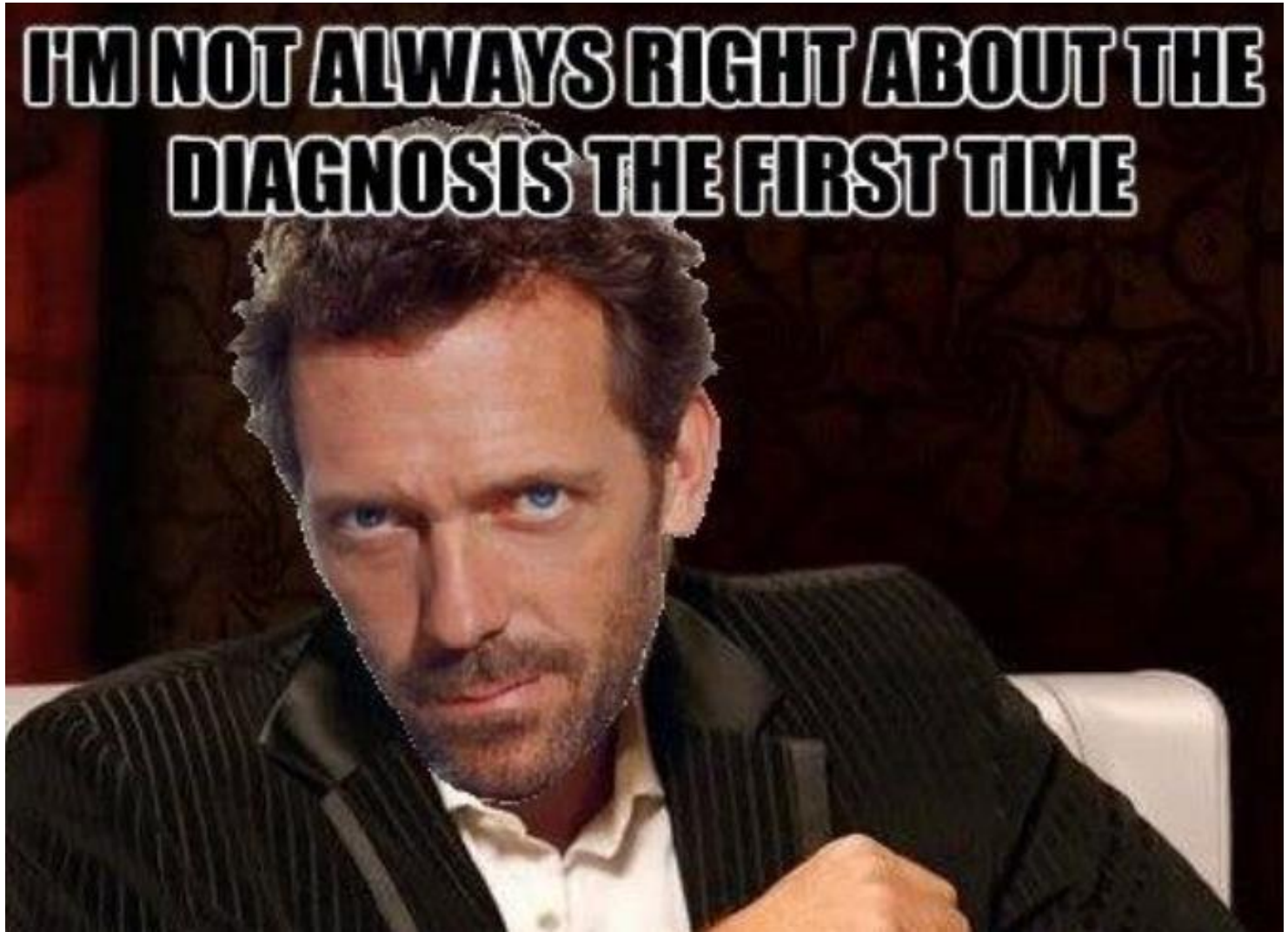
- 24-hour esophageal pH monitoring
- Endoscopic/videofluoroscopic swallow evaluation
- Barium esophagram / modified barium swallow
- Sinus imaging
- HRCT
- Bronchoscopy
- Cardiac workup (ECG, Holter monitoring, Echo)
- Environmental / occupational assessment
- Uncommon causes?

Kaplan A.
Adapted from 2018 ACCP Guidelines
Irwin RS et al. Chest 2018;153(1):196-209

ACE, angiotensin-converting enzyme; ECG, electrocardiogram; HRCCT, high resolution computed tomography; GERD: gastro-esophageal reflux disease, NAEB: non-asthmatic eosinophilic bronchitis, UACS: upper airway cough syndrome, PNDS: post-nasal drip syndrome; UACS, upper airway cough syndrome

Chronic Cough

- Don’t just give ICS!
- Make the diagnosis!



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