Chronic Cough…
and a bit about COPD

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DISCLOSURE

I have no financial relationships that might constitute a conflict of interest.

"The art of medicine is amusing the patient while nature cures the disease."

- Voltaire

Classification

Acute cough

~ maximum of 3 weeks

Subacute cough

~ 3 to 8 weeks

Chronic Cough

~ more than 8 weeks

De Blasio et al. Cough 2011, 7:7

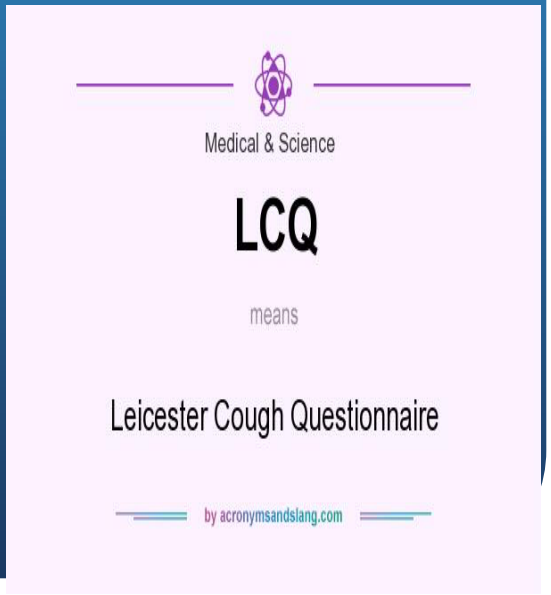
Why is cough important?… To society:

- Most common reason to consult a PCP
- Antitussive drug sales USA >$4billion/yr
- Chronic cough (>8wk): 12% population
- 10-38% of out-patients referrals

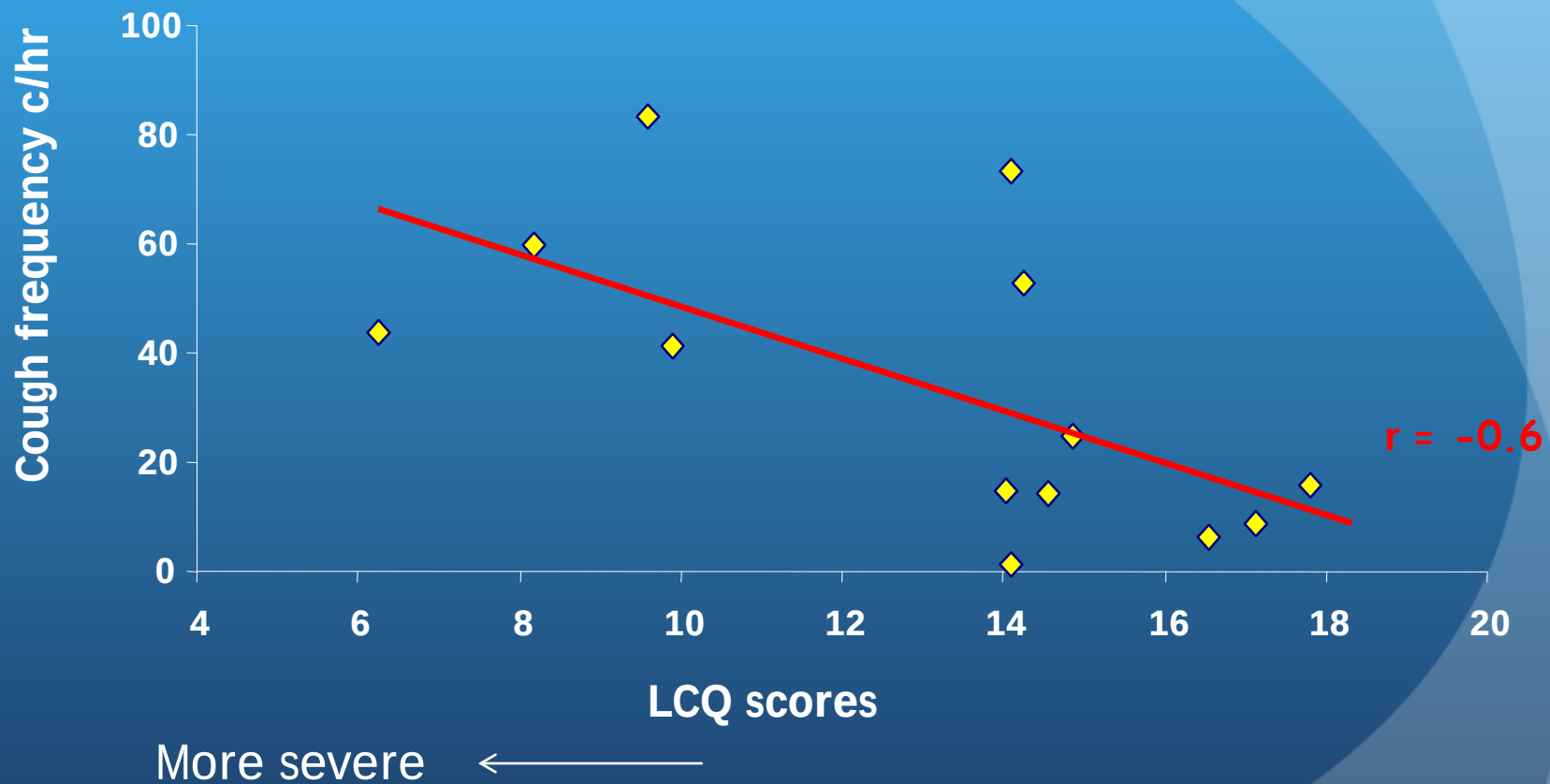
HRQOL: The LCQ

Physical	Psychological	Social
Chest pains	Embarrassed	Conversation
Sputum	Anxious	Annoy family
Tired	In control	Job
Paints/fumes	Frustrated	Enjoyment
Sleep	Fed up	
Frequency	Serious illness	
Hoarse Voice	Other people	
Energy		

Birring S et al, Thorax 2003; 58:339-343

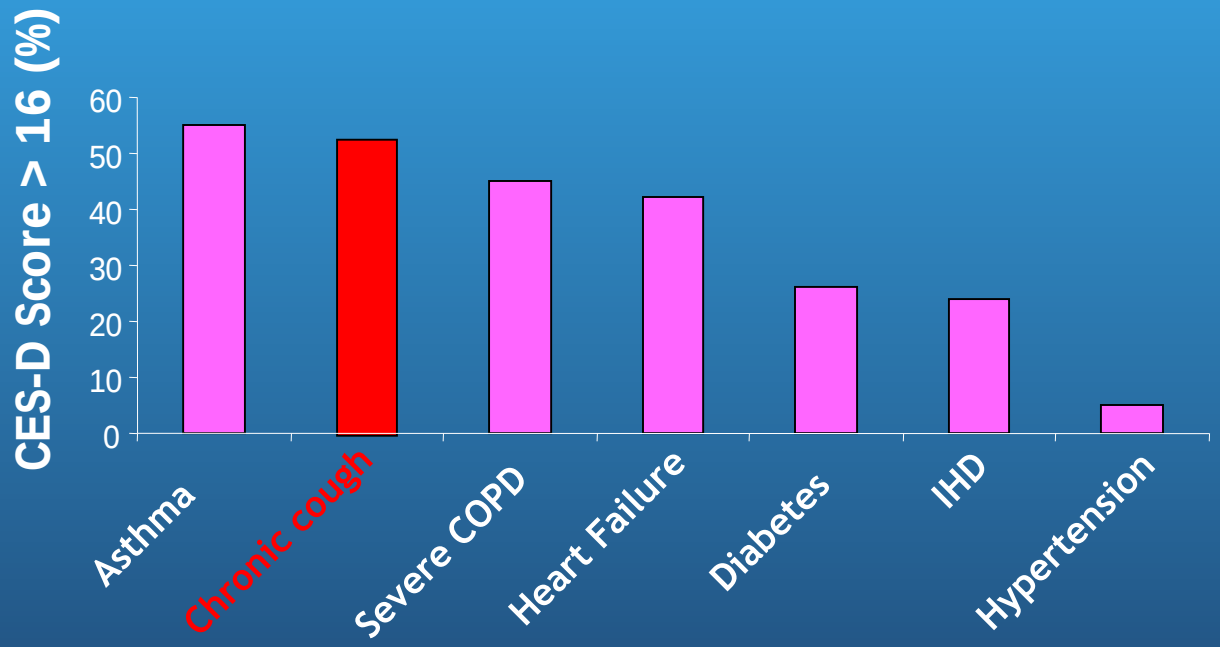


Cough frequency & QOL



Pirrina et al. Respir Med 2006; 100:1105

Depressive symptoms in chronic cough



Dicpinigaitis P et al, Chest 2006; 130:1839

Adverse impact of chronic cough

Worried about serious illness	77%
Concerned something is wrong	72%
Frequent nausea	56%
Exhaustion	54%
Others think something is wrong with me	53%
Embarrassment	49%
Self-consciousness	46%
Difficulty speaking on the telephone	39%
Urine incontinence	30%
Absence from work	11%

French C et al, Arch Intern Med 1998; 158:1657

Cough Reflex: Afferent pathway

- Trigeminal , Superior laryngeal nerve (SLN) and Vagus nerves are major afferent pathways
- Stimuli arise from:
  - Ear (Arnold's nerve)
  - Pharynx
  - Larynx (SLN)
  - Tracheobronchial tree
  - Heart
  - Pericardium
  - Esophagus

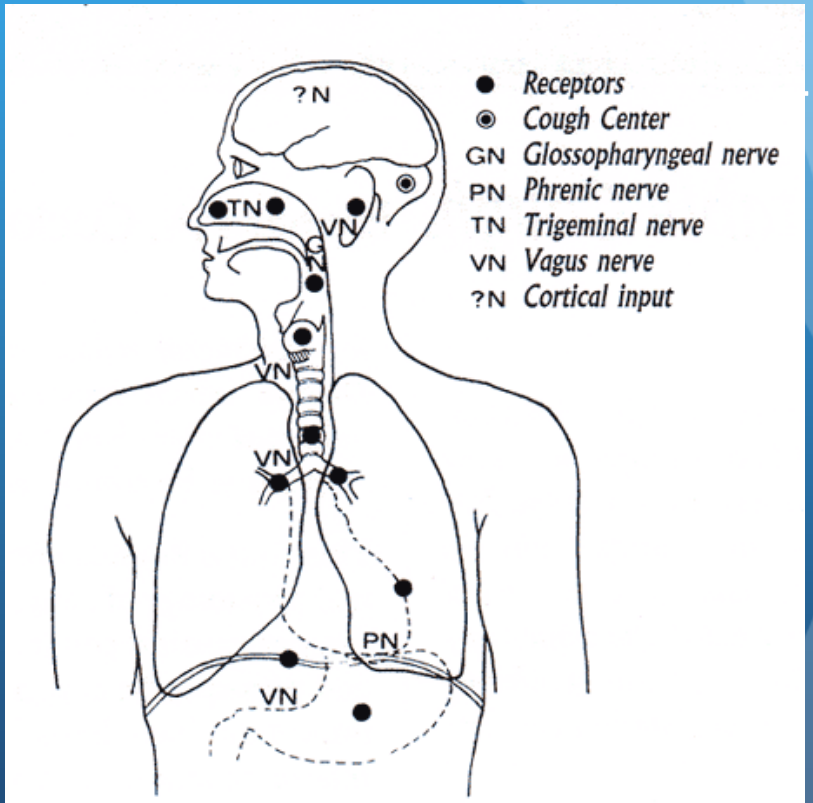
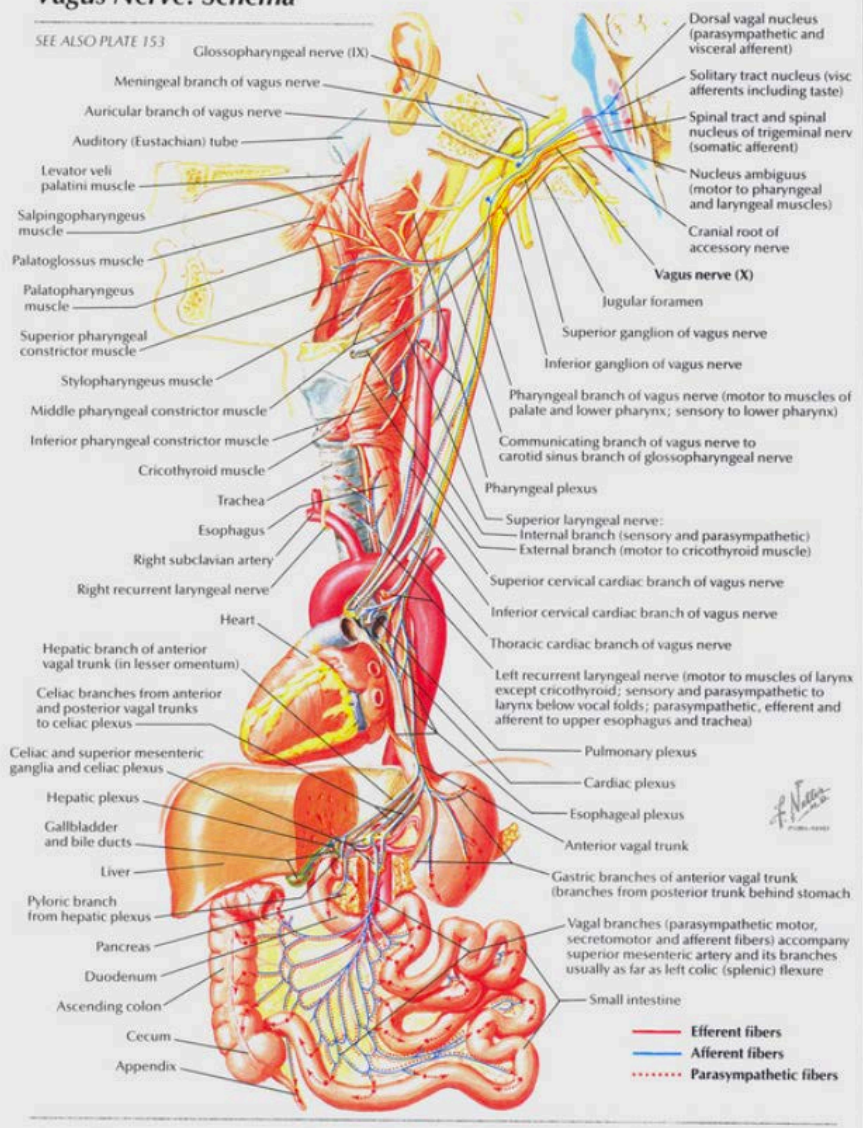


FIGURE 1. Cough Receptors involved in the normal cough mechanism. (From Irwin RS, et al., Cough: A comprehensive review. *Arch Intern Med.* 1977; 137:1186-91)

Vagus Nerve: Schema

SEE ALSO PLATE 153



ACE-Inhibitors: "Déjà vu all over again" (-Yogi Berra)

- Roughly 10% of individuals treated with ACE inhibitors
- May be more common in women and Asians (50%)
- Accumulation of bradykinins and Substance P.
- Maybe also accumulation of bronchoconstrictive thromboxane
- Onset usually 1-2 weeks, but may be delayed (6-12 months)
- Usually resolves in about a week, but may take months

Take Home Message…

"In patients with chronic cough and a normal CXR finding who are nonsmokers and are not receiving therapy with an ACE inhibitor,

the diagnostic approach should focus on the detection and treatment of UACS (formerly called PNDS), asthma, NAEB, or GERD, alone or in combination.

This approach is most likely to result in a high rate of success in achieving cough resolution."

ACCP Evidence-Based Clinical Practice Guidelines

Causes of Chronic Cough (90-95%)

- Upper airway cough syndrome (UACS)
- Asthma
- Gastroesophageal reflux (GERD)
- Nonasthmatic eosinophilic bronchitis (NEAB)

92-100% immunocompetent non-smokers with normal chest X-ray

Upper Airway Cough Syndrome

- "Post-nasal drip syndrome (PNDS) plus"
- Most common cause in adults
- May also be associated with
  - Wheeze
  - Dyspnea

UACS:
Myriad of rhinosinus conditions

- PNDS
- Allergic rhinitis
- Nonallergic rhinitis
  - Vasomotor rhinitis
  - Nonallergic rhinitis with eosinophilia (NARES)
  - Occupational
  - Postinfectious
  - Pregnancy
  - Rhinitis medicamentosa (topical decongestant overuse)
- Sinusitis (bacterial and fungal)

Upper Airway Cough Syndrome

- History:
  - Need to frequently clear throat
  - Tickle in throat
  - Sensation of dripping into throat
  - Nasal symptoms

– Physical Exam:

  - Secretions in nose or oropharynx
  - Cobblestone of mucosa

Treatment

- Oral (1st generation) antihistamine/decongestant x 3-5 weeks
- +/- Intranasal decongestant for maximum of 5 days: e.g. oxymetazoline 2 sprays each nostril bid x 3 days only
- Antibiotics selectively, for sinusitis
- Can often convert to more standard/less expensive/more conventient therapy (newer antihitamine alone, nasal CS, allergy shots)

Asthma

- Second most common cause of cough in adults
- Clues that chronic cough is due to asthma:
  - Episodic wheezing, dyspnea , cold or exercise induced
  - Reversible airflow obstruction
  - Bronchial hyperresponsiveness (test only if needed)
- "Confirmed" by resolution of cough with asthma treatment

Cough Variant Asthma

• 30-60% of patients presenting with chronic cough that was due to asthma had cough as their ONLY symptom

- Clues:

  - nocturnal cough, exercise induced, after allergen exposure

- Bronchoprovocation test: positive
  - Negative test exclude asthma but does not rule out steroid-responsive cough (NAEB)

ASTHMA/Cough Variant Asthma

Treatment

- Inhaled corticosteroid
- ICS/LABA combination > 8 weeks
- Leukotriene receptor antagonist

GERD-associated cough

Two mechanisms:

- Distal esophageal acid stimulates vagus nerve
- Laryngopharyngeal reflux (LPR)
  - Microaspiration of esophageal contents into the laryngopharynx and tracheobronchial tree
  - No heartburn
  - Usually when upright

GERD

- Suspect GERD when…
  - Heartburn or
  - Sour taste in mouth (Waterbrash)
  - Globus or tickle (LPV)

  – Reflux can be demonstrated by:

    - 24-hour pH-impedance monitoring
    - Barium x-ray
- Cough is only symptom in 40-75% of patients

GERD: Life-style modifications

- Stop smoking
- Avoid alcohol
- Lose weight
- Elevate HOB
- Small meals
- Avoid fatty/acidic foods
- Avoid caffeine
- Avoid – tight clothes, eating < 4 hrs pre-bed, recumbency 3 hrs post meal

Treatment

- Antacid therapy ≥ 2 months :
  - Proton pump inhibitor (high dose)
  - H2 blockers less effective
- Motility therapy:
  - Metoclopromide

Surgery is last resort

Non-Asthmatic Eosinophilic Bronchitis (NAEB)

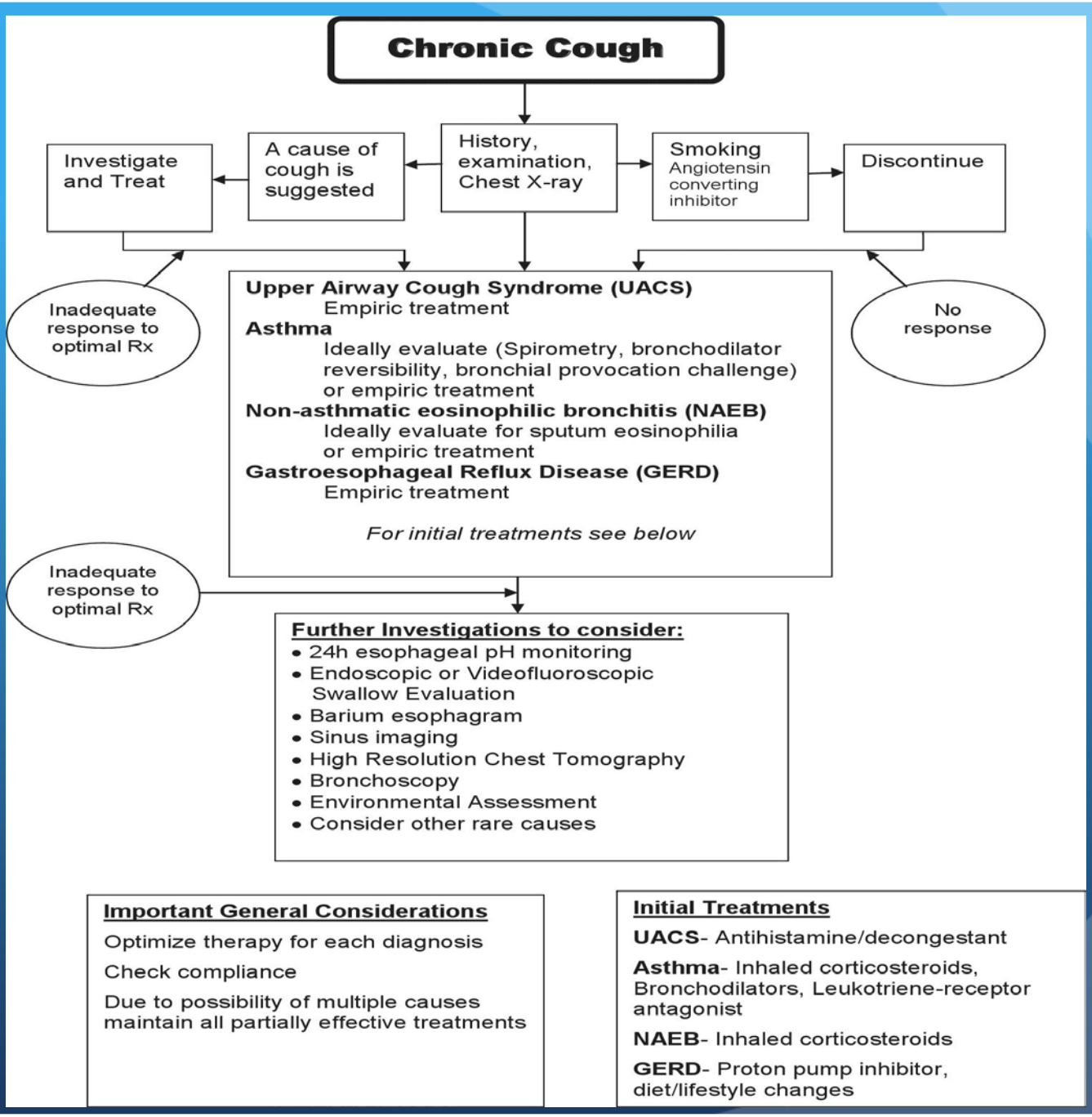
- Eosinophilic airway inflammation WITHOUT variable airflow obstruction or airway hyperresponsiveness

- **Diagnostic tests:**
  - Spirometry: normal
  - Methacholine challenge: normal
  - Sputum or BAL eosinophilia: >3% eosinophils

- **Diagnostic/Therapeutic trial**:
  - Characteristically resistant to bronchodilator but responds ICS
  - Confirmed diagnosis if responded to ICS, usually > 4 weeks

Other causes (5-10%)

- Bronchiectasis
- Bronchiolitis
- Bronchogenic carcinoma
- COPD
- Foreign body
- Interstitial Lung Disease
- Neuromuscular disease
- Pertussis
- Psychogenic cough (?)
- Sarcoidosis
- Tracheoesophageal fistula
- Tuberculosis
- Zenker diverticulum
- Chronic Cough Hypersensitivity syndrome


Chronic Cough
History, examination, Chest X-ray
A cause of cough is suggested
Investigate and Treat
Smoking
Angiotensin converting inhibitor
Discontinue
Inadequate response to optimal Rx
No response
Upper Airway Cough Syndrome (UACS)
Empiric treatment
Asthma
Ideally evaluate (Spirometry, bronchodilator reversibility, bronchial provocation challenge) or empiric treatment
Non-asthmatic eosinophilic bronchitis (NAEB)
Ideally evaluate for sputum eosinophilia or empiric treatment
Gastroesophageal Reflux Disease (GERD)
Empiric treatment
For initial treatments see below
Inadequate response to optimal Rx
Further Investigations to consider:
• 24h esophageal pH monitoring
• Endoscopic or Videofluoroscopic Swallow Evaluation
• Barium esophagram
• Sinus imaging
• High Resolution Chest Tomography
• Bronchoscopy
• Environmental Assessment
• Consider other rare causes
Important General Considerations
Optimize therapy for each diagnosis
Check compliance
Due to possibility of multiple causes maintain all partially effective treatments
Initial Treatments
UACS- Antihistamine/decongestant
Asthma- Inhaled corticosteroids, Bronchodilators, Leukotriene-receptor antagonist
NAEB- Inhaled corticosteroids
GERD- Proton pump inhibitor, diet/lifestyle changes

Cough Suppression Physiotherapy

- Education (avoid triggers, no benefit of excessive cough)
- Laryngeal hygiene (reduce alcohol/caffeine, sips water, avoid mouth breathing, correct abnormal breathing pattern+ VCD)
- Cough control (chew sweets, forced swallow, huff, distraction)
- Counselling (reinforcement of techniques, modify behaviour, address adverse symptoms such as incontinence)

Patel A et al; Chronic Resp Dis 2011;8:253-8

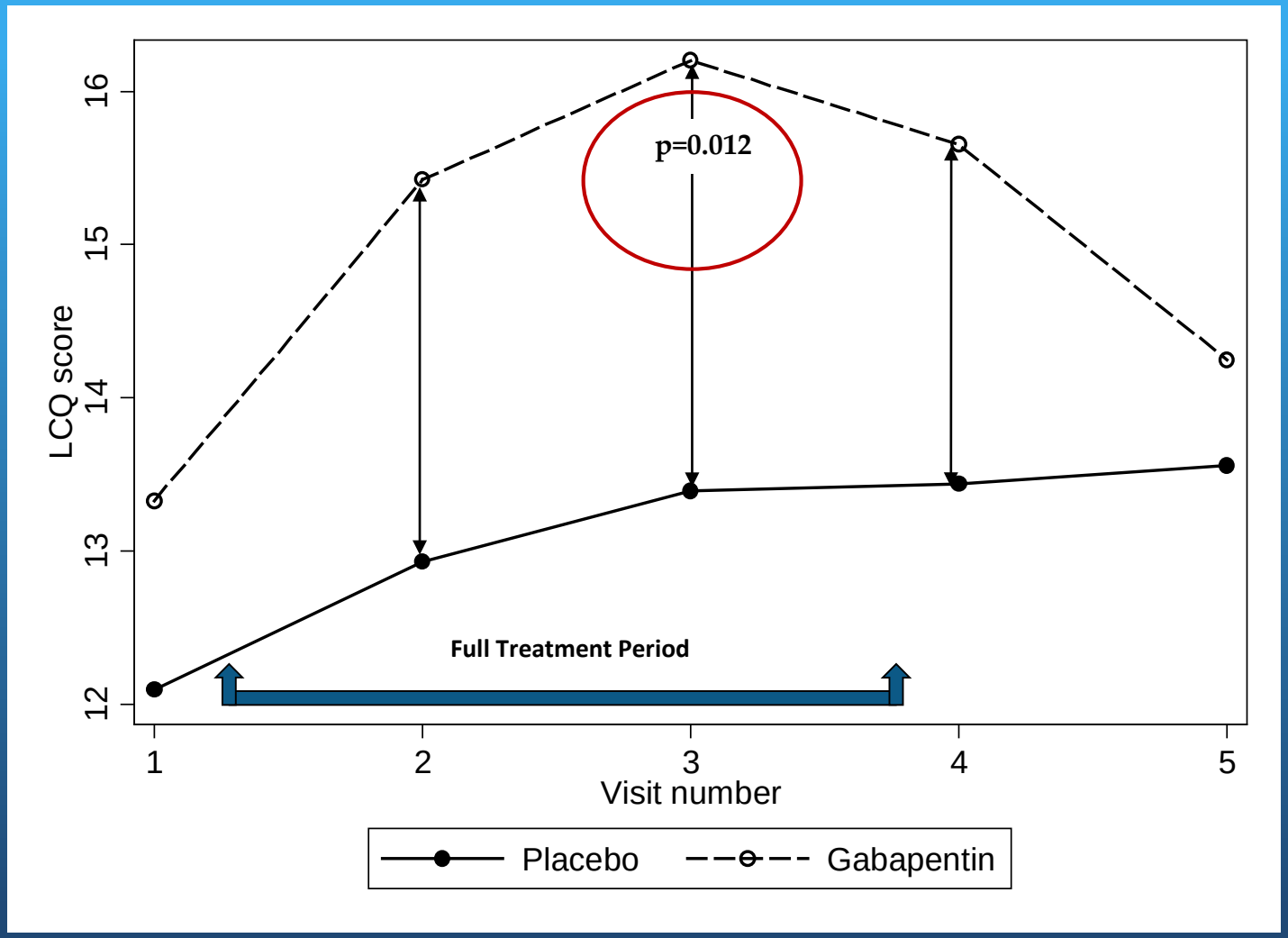
Chronic Cough Hypersensitivity Syndrome
- “psychogenic cough”
- “tic cough”

- **Laryngeal Sensory Neuropathy**
- LN responsible for causing the sensation/urge to cough in affected patients

- SELSAP (Surface Evoked Laryngeal Sensory Action Potential)
- testing of the Superior Laryngeal Nerve

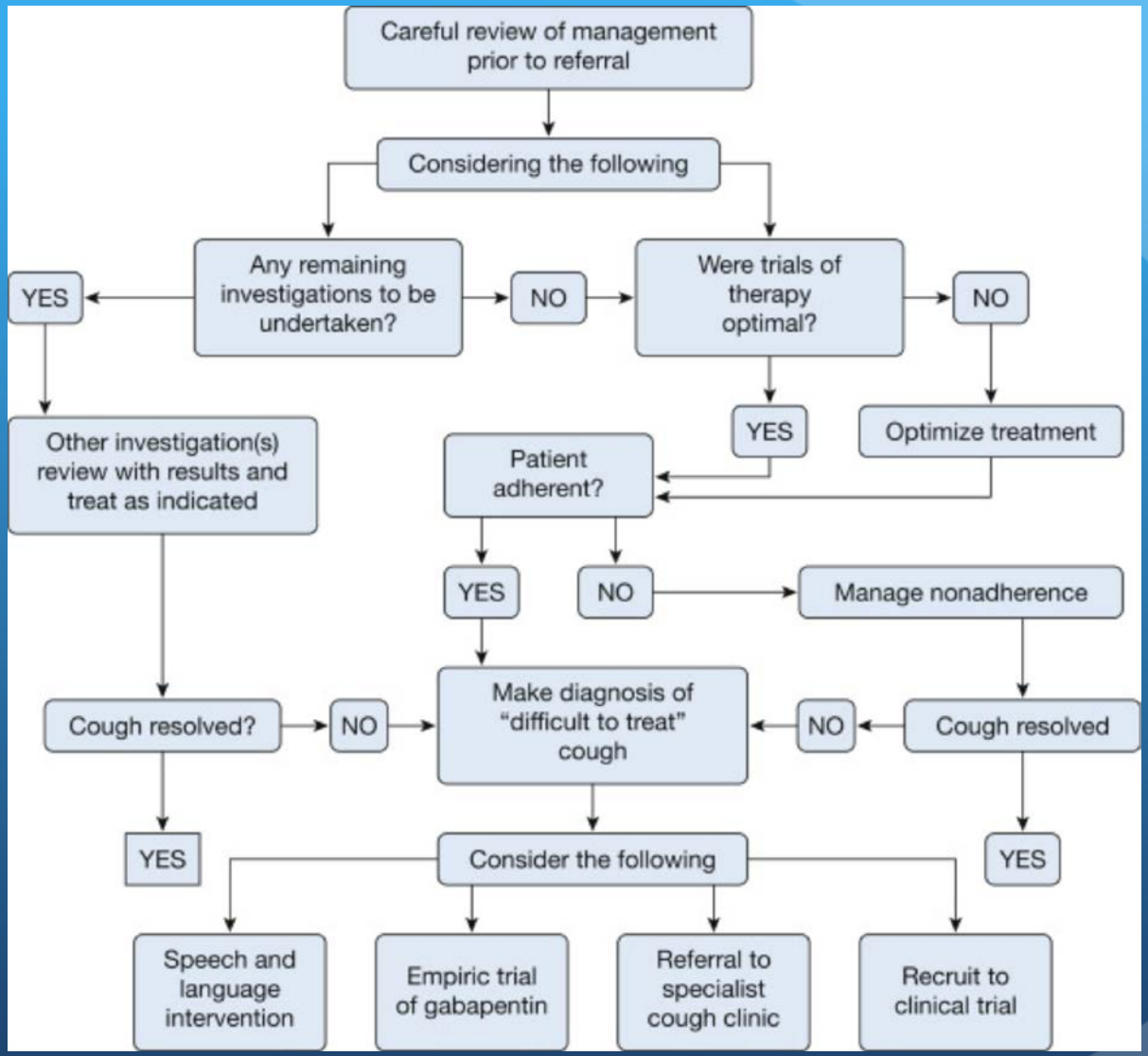
Laryngoscope. 2011 Jan;121(1):158-63. doi: 10.1002/lary.21182.

Gabapentin: randomised controlled trial



Ryan N et al, Lancet 2012:380:1583

“Difficult to treat” unexplained chronic cough

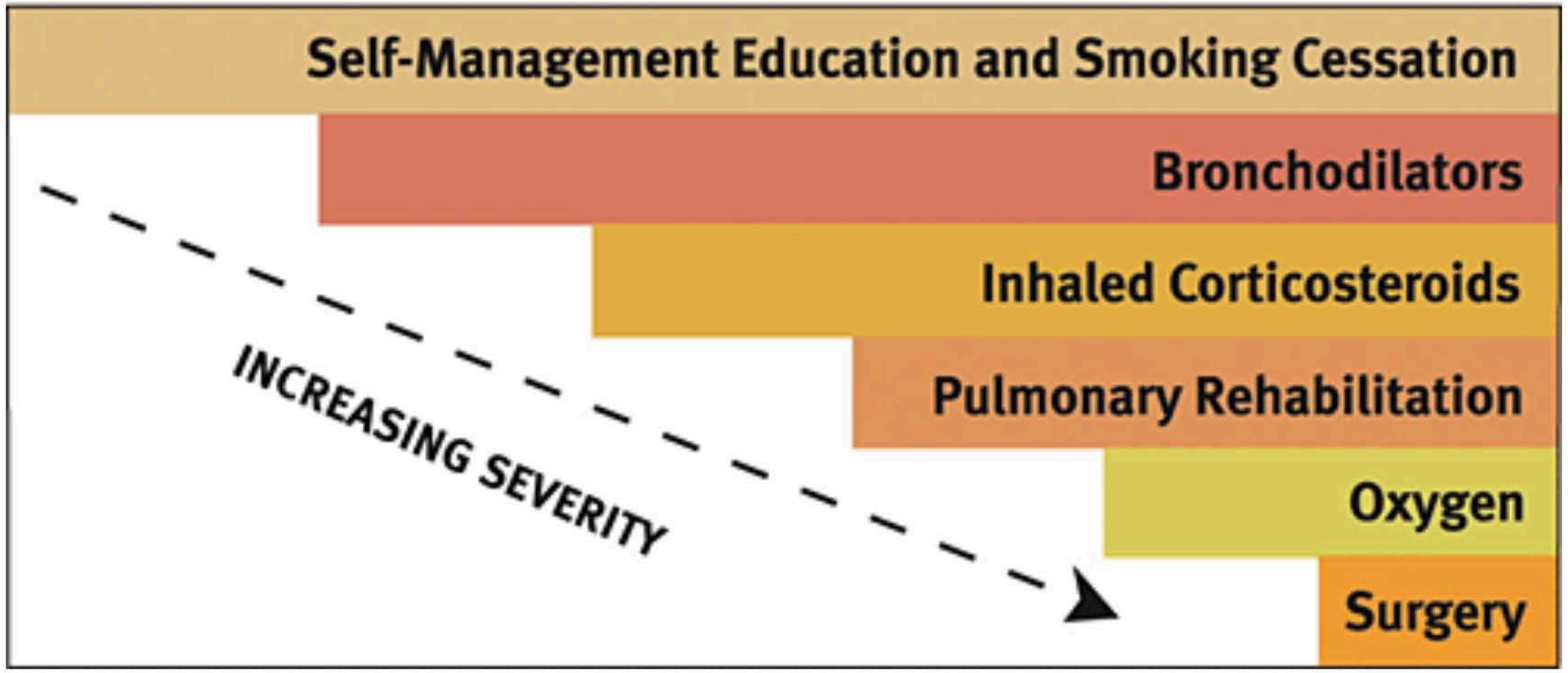


Chest. 2016;149(1):27-44. doi:10.1378/chest.15-1496


AND NOW FOR
SOMETHING
COMPLETELY
DIFFERENT

Is this the making of a 21st Century physician?

TREATMENT OPTIONS FOR COPD



COPD: Treatments that Improve Survival

- **Quit smoking !!!!**
- Use oxygen continuously if:
  - p02 < 55
  - P02 55 – 59 if polycythemia or pulmonary hypertension
- Lung Transplantation
- Lung Volume Reduction
  - If predominantly upper lobe and low exercise capacity
- Lung Cancer Screening

BODE Index

Table. Variables and cutoff values for points 0 to 3 in the BODE index computation.

	Point on BODE index*			
	0	1	2	3
FEV_1 (% of predicted)	≥65	50–64	36–49	≤35
Distance walked in 6 minutes (m)	≥350	250–349	150–249	≤149
Dyspnea scale score	0–1	2	3	4
Body mass index measure	>21	≤21	—	—

*Values range from 0 (best) to 10 (worst)
Source: Adapted from the Body-mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease[1]

- **APPROXIMATE 4 YEAR SURVIVAL INTERPRETATION**
- 0-2 Points: 80%
- 3-4 Points: 67%
- 5-6 Points: 57%
- 7-10 Points: 18%

Celli BR, et al.N Engl J Med 2004; 350:1005-1012

Modified MRC Dyspnoea Scale (mMRC)

Grade 0: Breathless on strenuous exercise

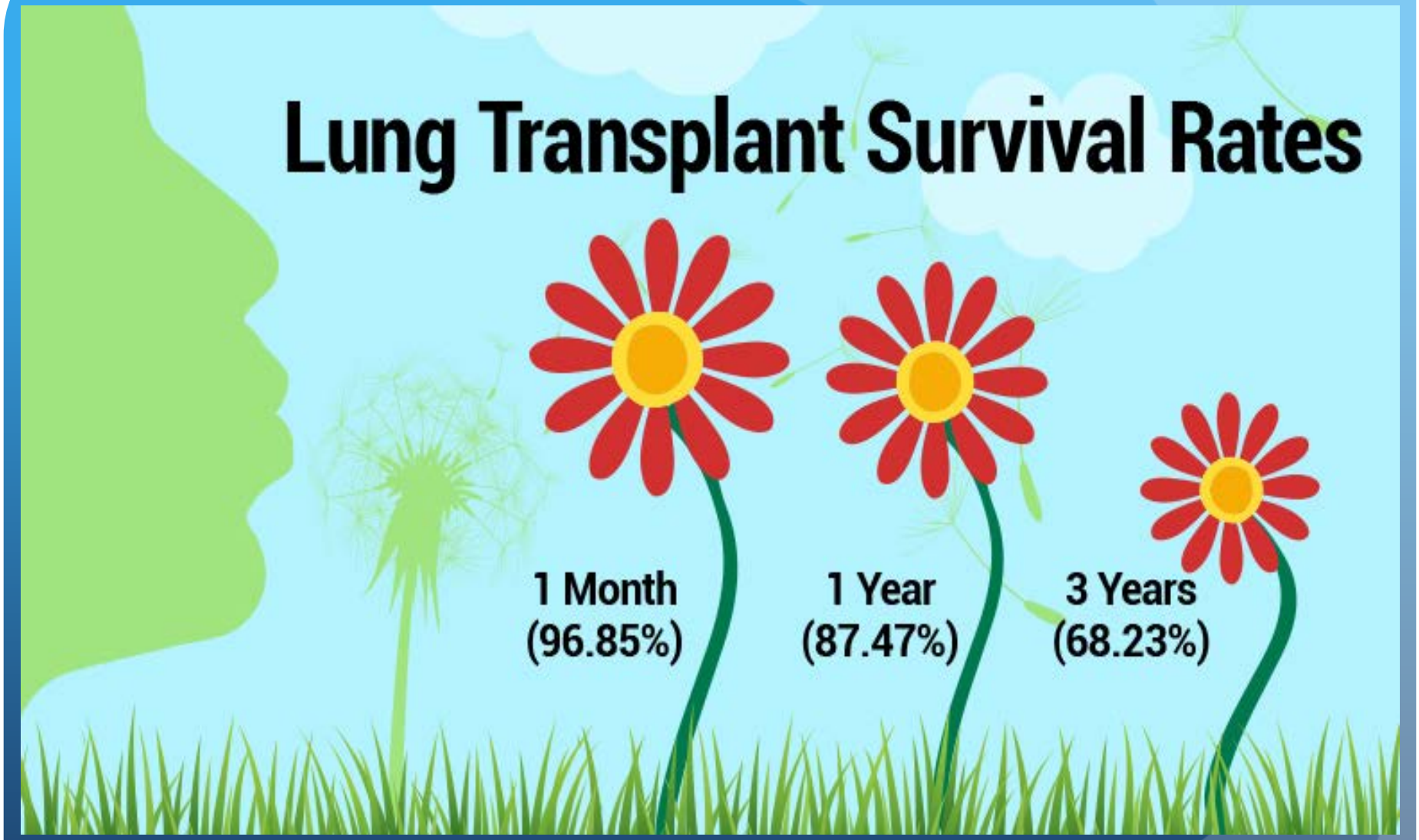
Grade 1: Short of breath when hurrying or walking up a slight hill

Grade 2: Walk slower than others or stop when walking at own pace on level ground

Grade 3: Stop every 100m or after a few minutes

Grade 4: Too breathless to leave the house or breathless on washing/dressing

Am Rev Respir Dis;1987;135(6):1229-33



About 55% at 5 years

Lung Transplantation for COPD: Candidacy

Usually 65 or younger, with progressive disease despite aggressive care, BODE 5-6 and:

- FEV1 < 25% of predicted (without reversibility)
- and/or
  - $PaCO_2$ > 55 mmHg
  - Pulmonary Hypertension with progressive deterioration (cor pulmonale)
- Preference to patients with:
  - Elevated $PaCO_2$, cor pulmonale and 02 dependence

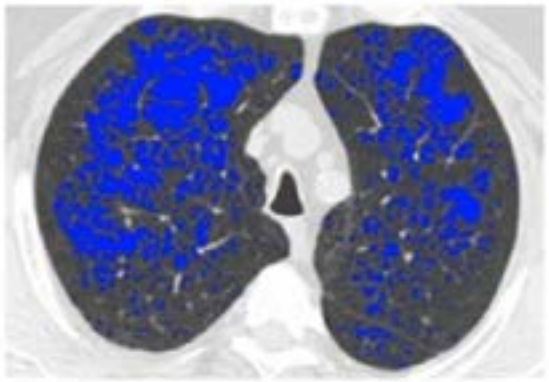
Lung Cancer Screening

- National Lung Screening Trial (NLST)
- Low dose CT chest (LDCT)
- Roughly 1/5th radiation of conventional CT
  - 15 Chest X-rays
  - 50 cross country flights
  - 6 months of natural background radiation

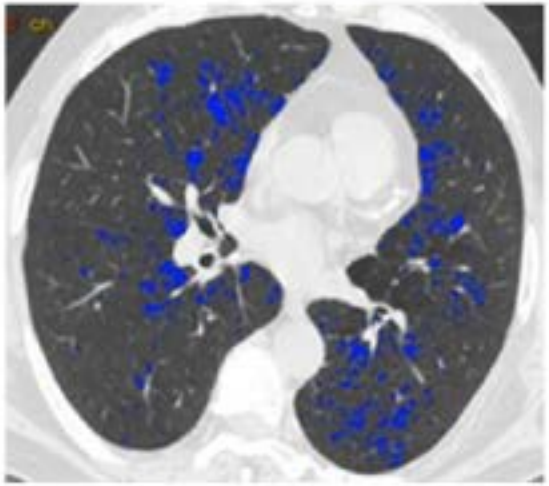
Lung Cancer Screening: CMS approved

- **96% of (+) LDCT findings prove NOT to be cancer
- Reduces lung cancer mortality by 20%
  - 3 fewer deaths/1000 people screened
- Reduces all cause mortality by 6.7%

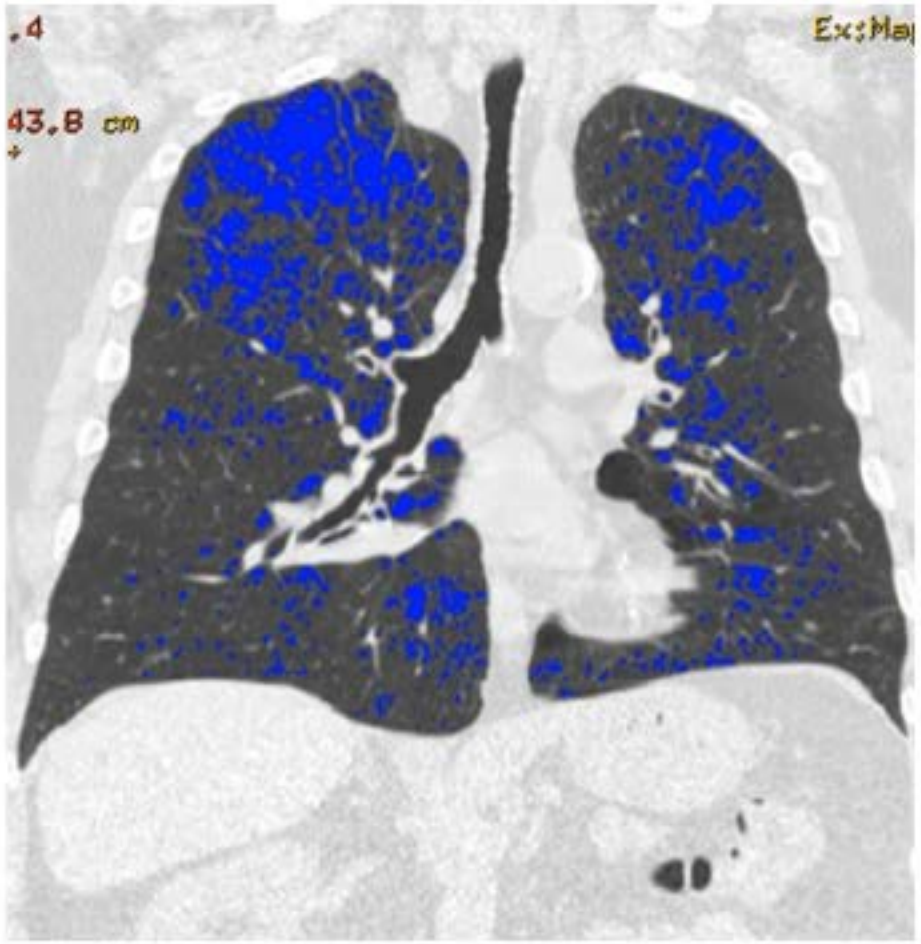
- Current recommendation = Yearly LDCT chest:
  - Age 55-77
  - 30 pack-years or more
  - Smoking within the past 15 years



(a)

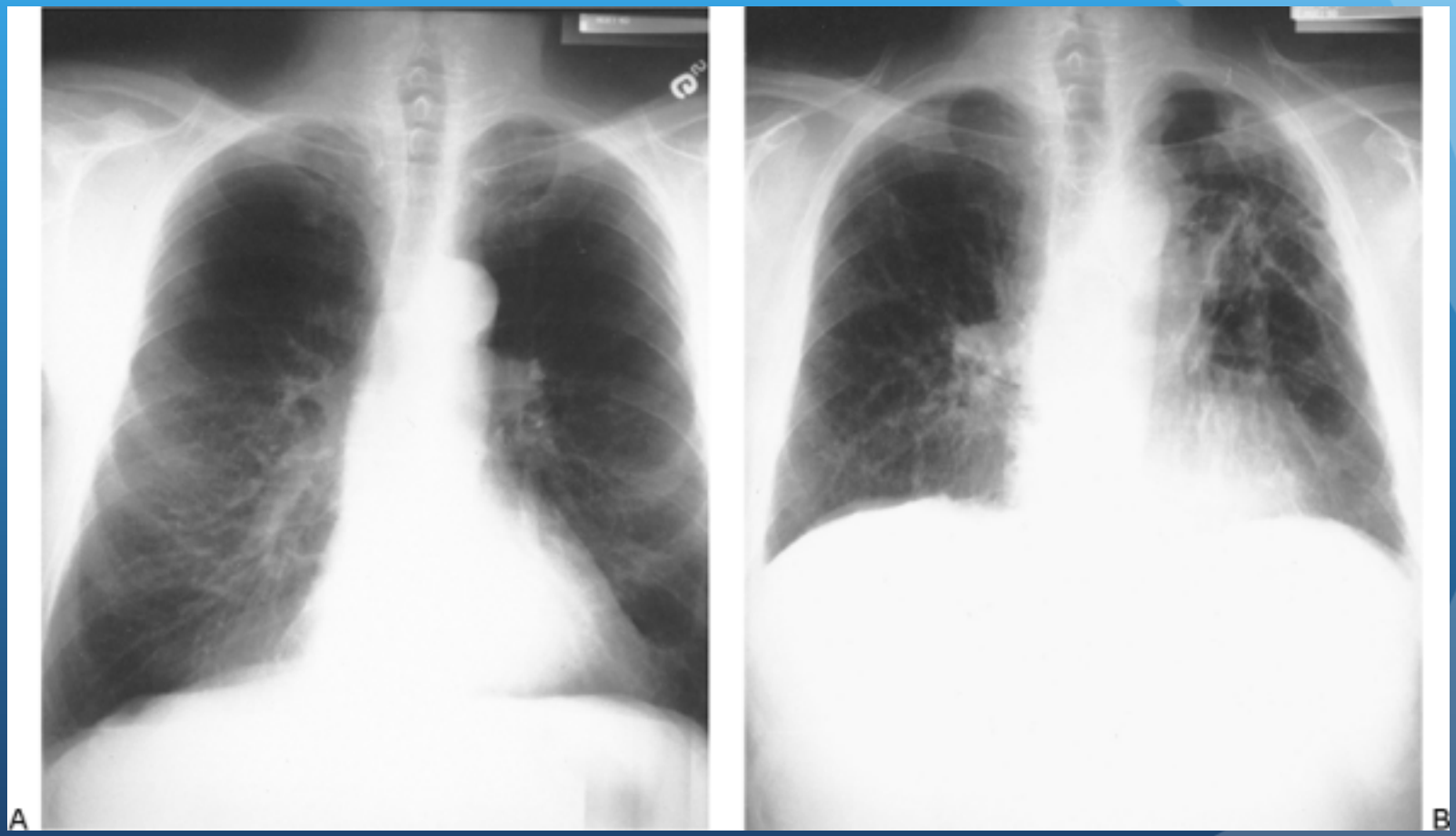


(b)

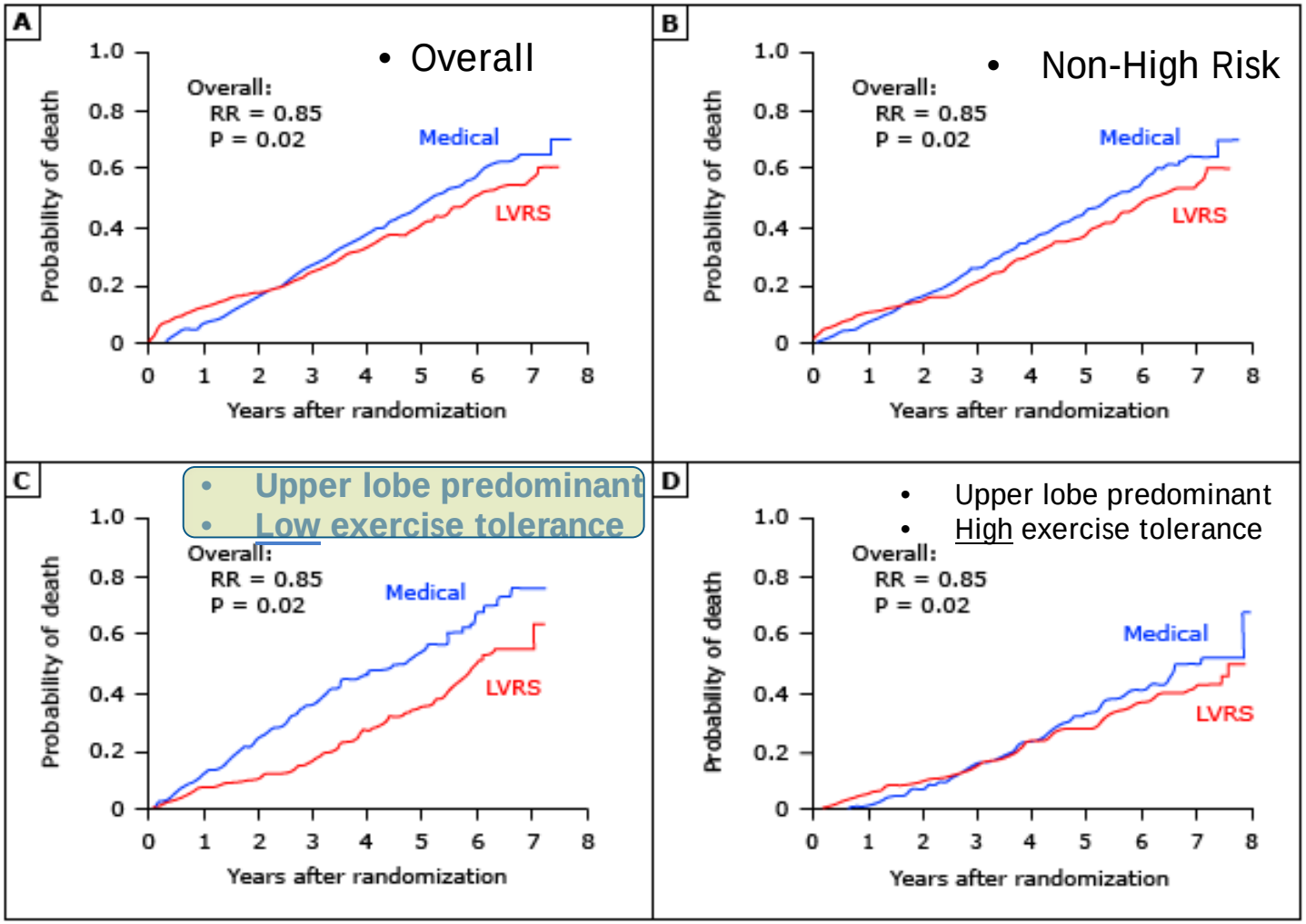


(c)

Lung Volume Reduction Surgery (LVRS)



LVRS survival curves



National Emphysema Treatment Trial, N Engl J Med 2003; 348:2059-2073

Table 2. Efficacy of Different Approaches to Decreasing Risk for Exacerbations

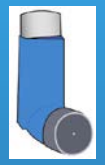
	Efficacy	Support	References
Non-pharmacologic Interventions			
Smoking Cessation	Supported	Large-scale observational study	66
Pulmonary Rehabilitation	Supported	Small-scale clinical studies	68, 69
Vaccination Against Pneumococcal and Influenza Virus Infection	Very strongly supported	Multiple clinical trials and meta-analyses	70-74
Pharmacotherapy			
LABA	Very strongly supported	Meta-analyses and multiple clinical trials	13, 76
LAMA	Very strongly supported	Meta-analyses and multiple clinical trials	57, 79, 80, 82, 83
LABA + LAMA vs. Monotherapy	Supported for LABA + LAMA vs LAMA monotherapy	Clinical trial	132
ICS Monotherapy	Supported	Meta-analysis, benefit limited to patients with FEV_1 <50%	91
ICS + LABA vs ICS or LABA monotherapy	Very strongly supported	Multiple clinical trials	56, 94
Triple Combination Therapy vs. Components	Variable results	Small-scale clinical trials provide conflicting results; meta-analysis indicates no significant benefit; large-scale observational study supports	102-105, 133
Systemic Treatments			
Roflumilast	Very strongly supported as add-on treatment to bronchodilators	Multiple large-scale clinical trials and meta-analysis FEV1 < 50%, chronic bronchitis and > 3 exacerbations/y	106-109
Macrolides/Quinolones	Strongly supported	Supported by large-scale clinical trials	116, 117
Statins	Supported	Supported by multiple observational studies, but no controlled trials to date	121, 122

ICS = inhaled corticosteroid, LABA = long-acting ß2-agonist LAMA = long-acting muscarinic antagonist

Combination Inhalers

SAMA
(Short-Acting Muscarinic Antagonist)

SABA
(Short-Acting Beta2-Agonist)



LAMA
(Long-Acting Muscarinic Antagonist)

LABA
(Long-Acting Beta2-Agonist)

Corticosteroid and LABA

SAMA and SABA

LAMA and LABA

Additional Medications

MDI = Metered Dose Inhaler

Currently FDA approved for COPD

	Mechanism of action	Dosing
Tiotropium	LAMA	Daily
Aclidinium	LAMA	Twice daily
Umeclidinium	LAMA	Daily
Salmeterol	LABA	Twice daily
Formoterol	LABA	Twice daily
Indacaterol	LABA	Daily
Olodaterol	LABA	Daily
Umeclidinium/vilanterol	LAMA/LABA	Daily
Salmeterol/fluticasone	ICS/LABA	Twice daily
Budesonide/formoterol	ICS/LABA	Twice daily
Fluticasone furoate/ vilanterol	ICS/LABA	Daily
Tiotropium/ododaterol	LAMA/LABA	Daily

Global Initiative for Chronic Obstructive Lung Disease

PROGETTO MONDIALE BPCO

STRATEGIA GLOBALE PER LA DIAGNOSI, IL TRATTAMENTO E LA PREVENZIONE DELLA BRONCOPNEUMOPATIA CRONICA OSTRUTTIVA

Revisione 2014

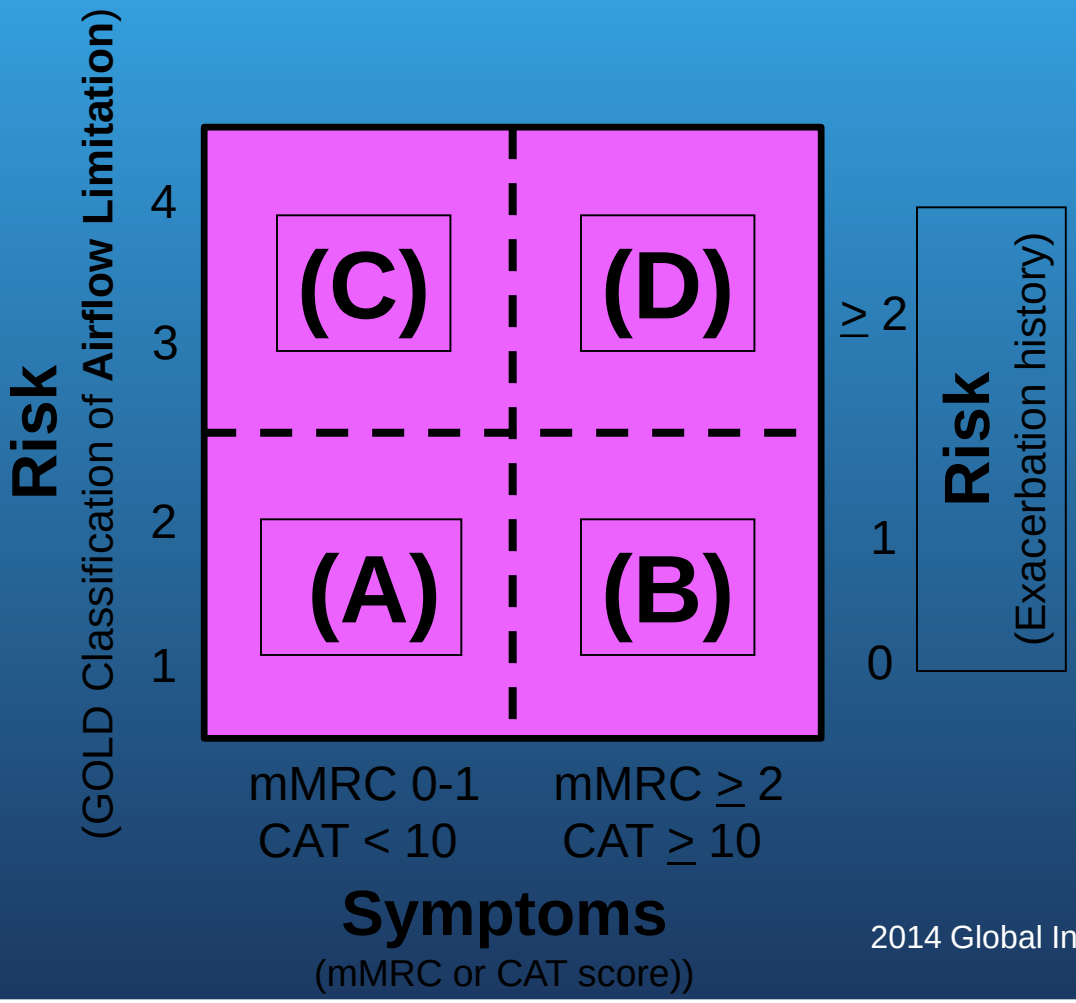
GOLD staging of COPD

Stage 1	**Mild COPD**	FEV_1 at least 80% of normal
Stage 2	**Moderate COPD**	FEV_1 between 50% and 80% of normal
Stage 3	**Severe COPD**	FEV_1 between 30% and 50% of normal
Stage 4	**Very Severe COPD**	FEV_1 below 30% of normal

Global Strategy for Diagnosis, Management and Prevention of COPD

Assessment of COPD
Assess symptoms : CAT, mMRC
Assess degree of airflow limitation using spirometry
Assess risk of exacerbations
Assess comorbidities

Combined Assessment of COPD



Patient is now in one of four categories:

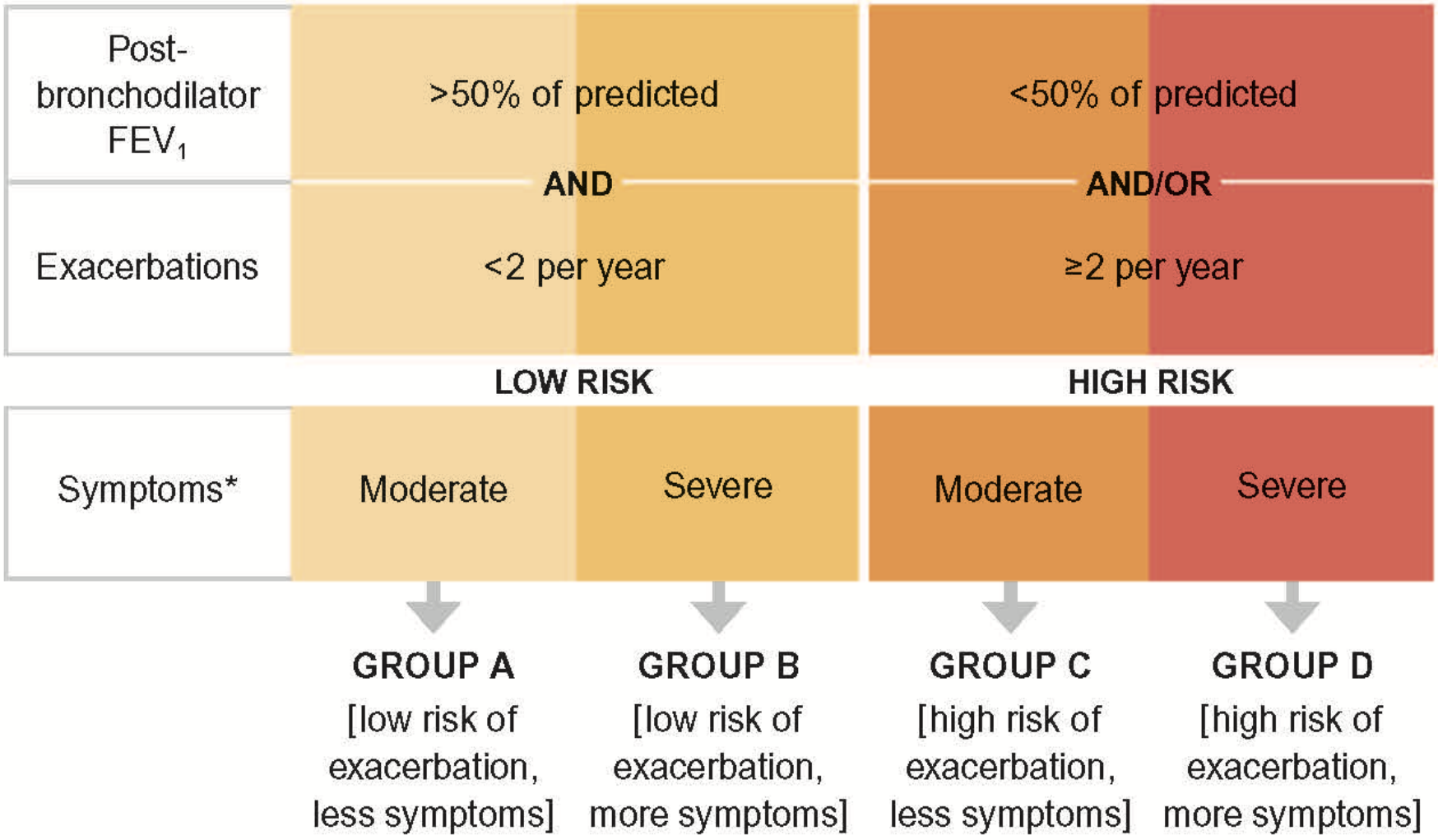
A: Less symptoms, low risk

B: More symptoms, low risk

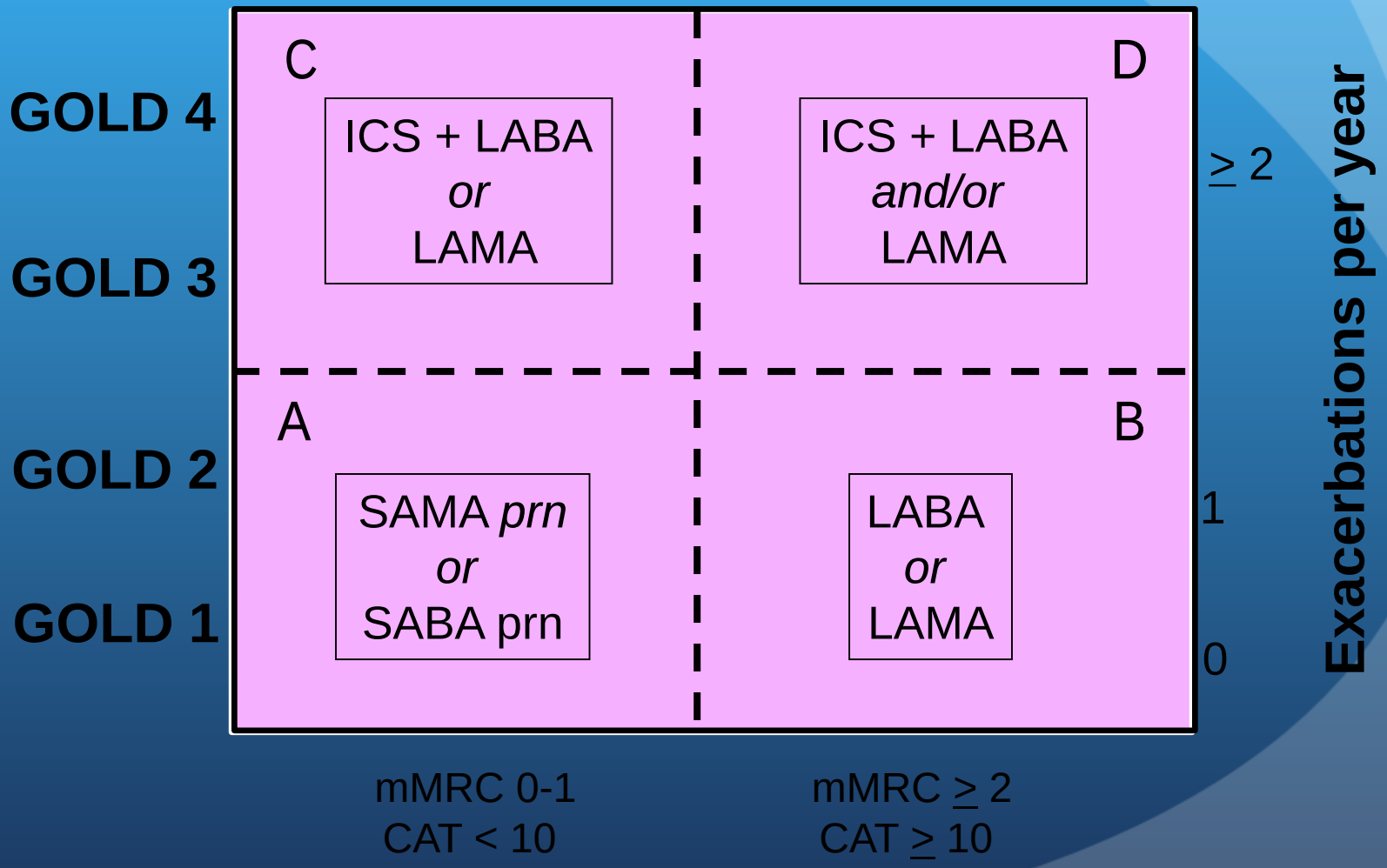
C: Less symptoms, high risk

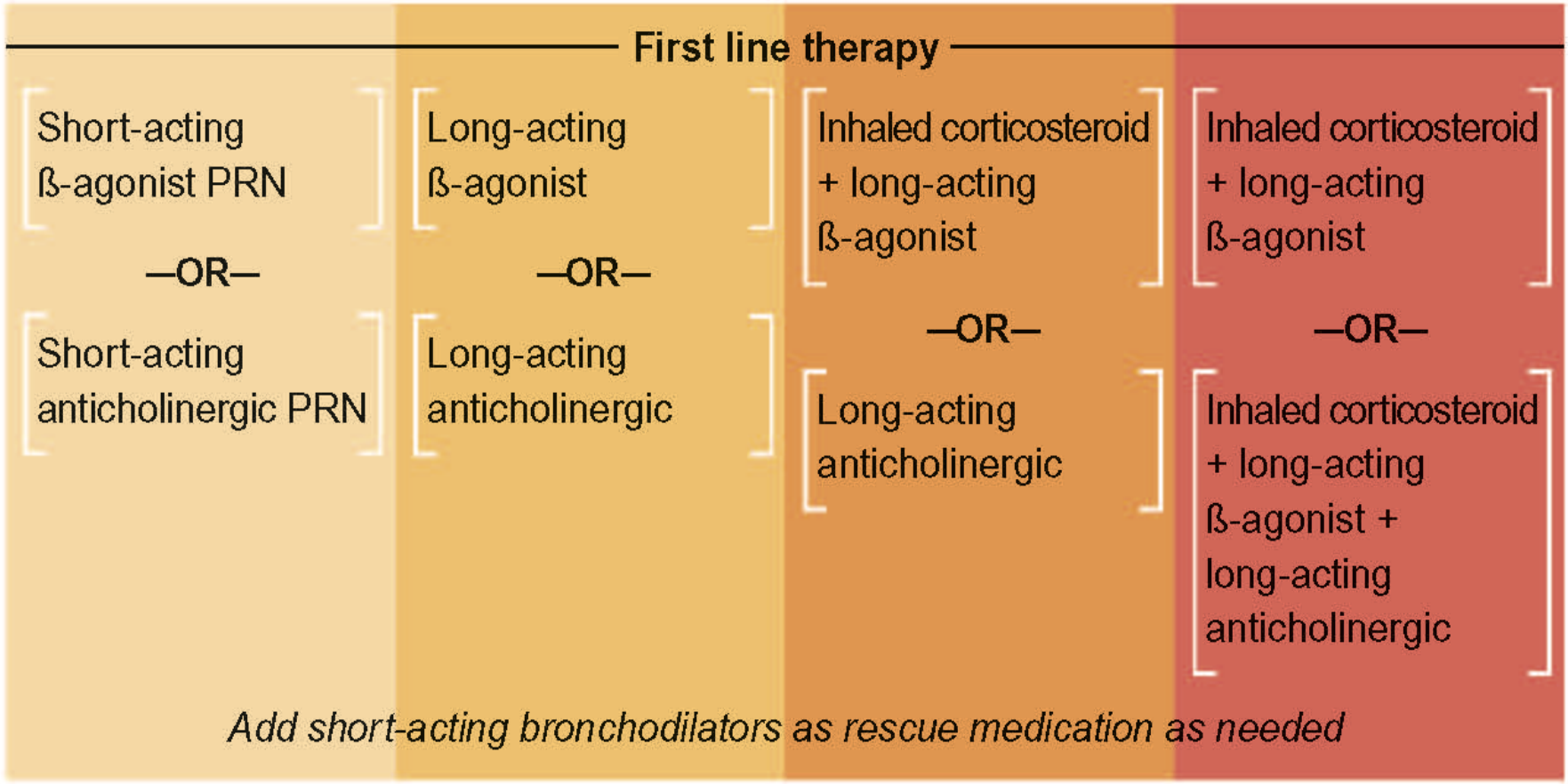
D: More symptoms, high risk

2014 Global Initiative for Chronic Obstructive Lung Disease


Post-bronchodilator FEV_1
>50% of predicted
<50% of predicted
AND
AND/OR
Exacerbations
<2 per year
≥2 per year
LOW RISK
HIGH RISK
Symptoms*
Moderate
Severe
Moderate
Severe
GROUP A
[low risk of exacerbation, less symptoms]
GROUP B
[low risk of exacerbation, more symptoms]
GROUP C
[high risk of exacerbation, less symptoms]
GROUP D
[high risk of exacerbation, more symptoms]

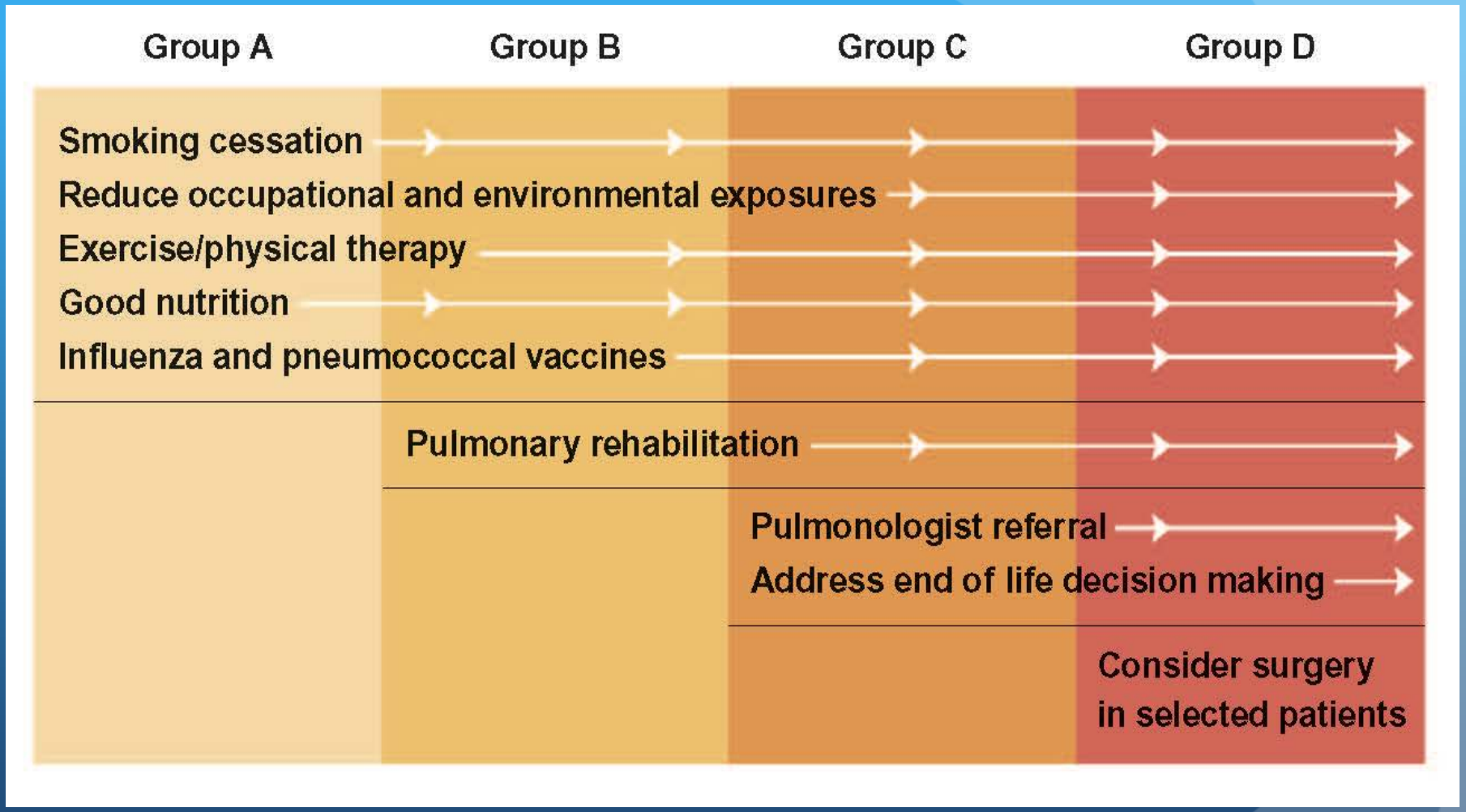
Pharmacologic Therapy
RECOMMENDED FIRST CHOICE





Optional alternative therapies:

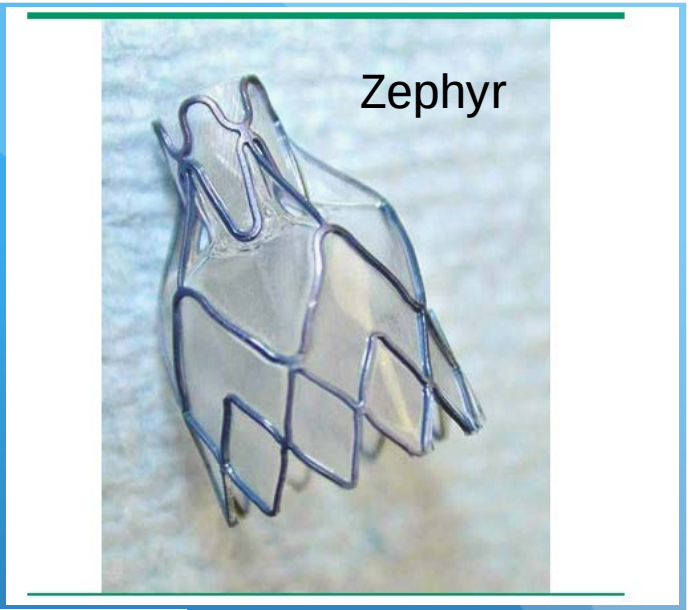
Group A: [Short-acting ß-agonist + short-acting anticholinergic] **or** [long-acting ß-agonist] **or** [long-acting anticholinergic]
Group B: [Long-acting ß-agonist + long-acting anticholinergic]
Group C: [Inhaled corticosteroid + long-acting anticholinergic] **or** [long-acting ß-agonist + long-acting anticholinergic] **or** [long-acting ß-agonist/long-acting anticholinergic + PDE4 inhibitor for chronic bronchitis]
Group D: [PDE4 Inhibitor added to first line therapy for chronic bronchitis]

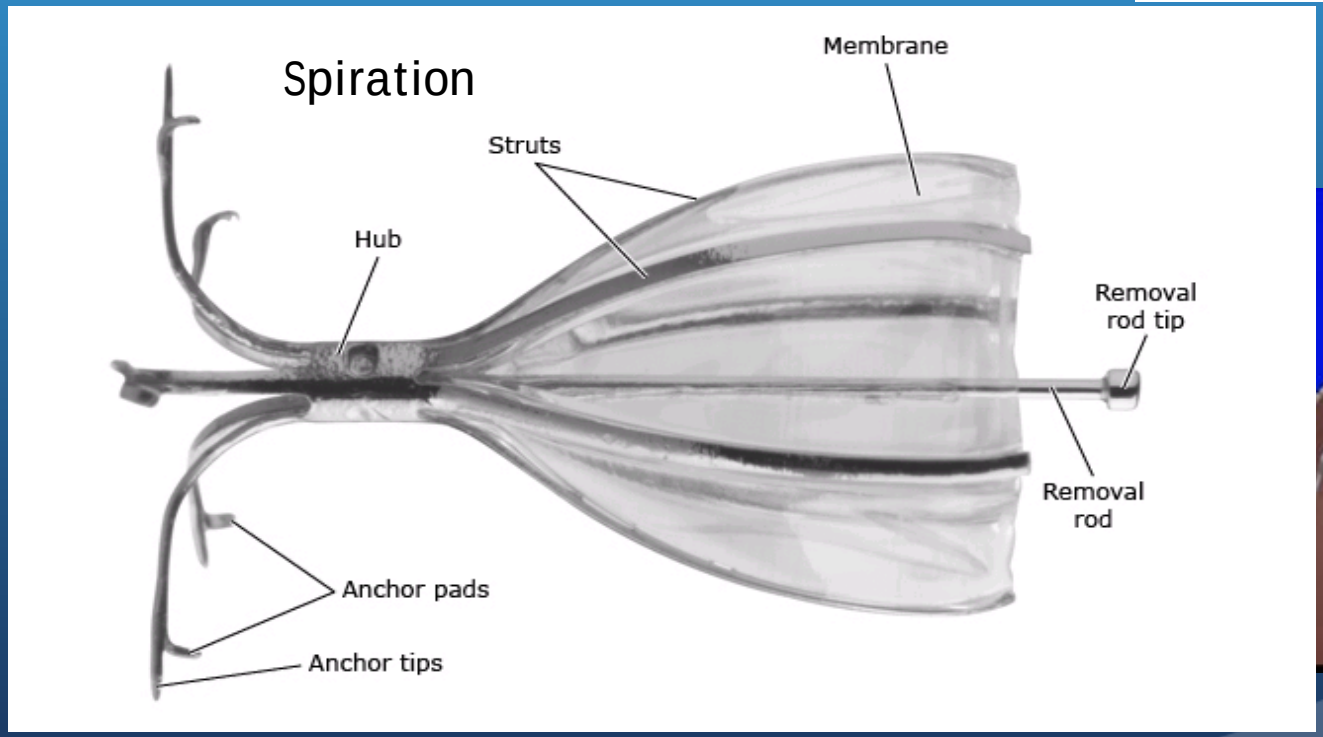

Group A
Group B
Group C
Group D
Smoking cessation
Reduce occupational and environmental exposures
Exercise/physical therapy
Good nutrition
Influenza and pneumococcal vaccines
Pulmonary rehabilitation
Pulmonologist referral
Address end of life decision making
Consider surgery
in selected patients

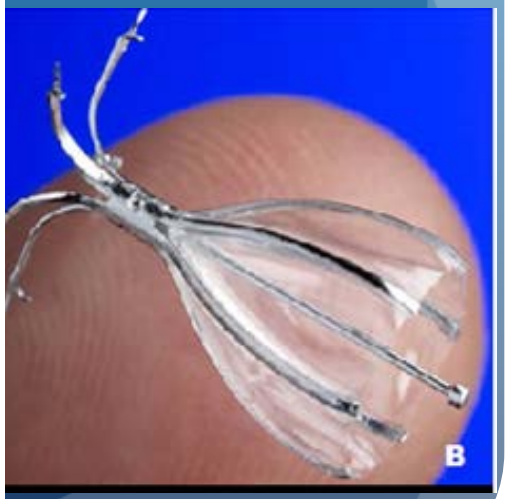
On the horizon……

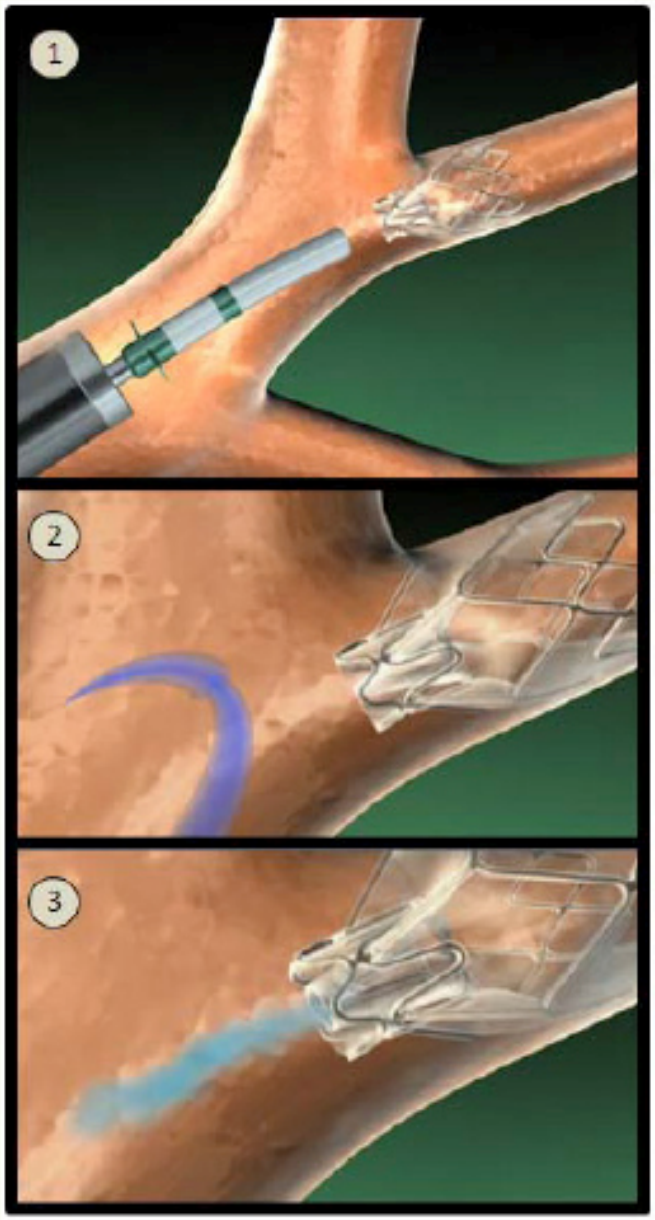
Endobronchial LVRS

- Valves
- Coils
- Biologics (thrombin/fibrin)
- Thermal ablation









Endobronchial Valves are delivered to the target airway via a delivery catheter placed through the working channel of the bronchoscope (Panel 1). Multiple valves are placed to completely isolate the diseased, hyperinflated target lobe.

Upon inspiration, the unidirectional valve at the center of the device blocks air from entering the target lobe (Panel 2).

Upon exhalation, air and fluids escape through the valve (Panel 3).

Art courtesy of the
New England Journal of Medicine

Regenerative therapy for COPD?

- Inducing endogenous stem cells to proliferate and differentiate in situ
  - Retinoids (all-trans-retinoic acid)
  - Others…
- Adding differentiated stem cells
  - Stem cells differentiated to Type II pneumocytes in vitro
    - Embryonic stem cells
    - Autologous (mesechymal) stem cells
      - Adverse effects: Sarcomas and Fibrosis

??????????????

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Select Disease

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- Lung Diseases

THANK YOU

PDF

In Patients with FEV1/FVC < 0.70:

Gold 1:	Mild	$FEV_1 \geq 80\%$ predicted
Gold 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
Gold 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
Gold 4:	Very Severe	$FEV_1 < 30\%$ predicted

Patient	Characteristic	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0 - 1	< 10
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0 - 1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

Patient Group	RECOMMENDED FIRST CHANCE	ALTERNATIVE CHOICE	OTHER POSSIBLE TREATMENTS
A	SA anticholinergic prn *or* SA $beta_2$-agonist prn	LA anticholinergic or La $beta_2$-agonist or SA anticholinergic and SA $beta_2$-agonist	Theophylline
B	LA anticholinergic *or* LA $beta_2$-agonist	LA anticholinergic and LA $beta_2$-agonist	SA $beta_2$-agonist *and/or* SA anticholinergic Theophylline
C	LA anticholinergic *or* ICS + LA $beta_2$-agonist	LA anticholinergic and LA $beta_2$-agonist or LA anticholinergic and PDE-4 Inhibitor or LA $beta_2$-agonist and PDE-4 Inhibitor	SA $beta_2$-agonist *and/or* SA anticholinergic Theophylline
D	LA anticholinergic *and/or* ICS + LA $beta_2$-agonist	LA anticholinergic and ICS + LA $beta_2$-agonist or ICS + LA $beta_2$-agonist and PDE-4 Inhibitor or LA anticholinergic and LA $beta_2$-agonist or LA anticholinergic and PDE-4 Inhibitor	Carbocystine SA $beta_2$-agonist and/or SA anticholinergic Theophylline

PDF

Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy (0) X (2) (3) (4) (5) I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

Last Updated: February 24, 2012