COPD

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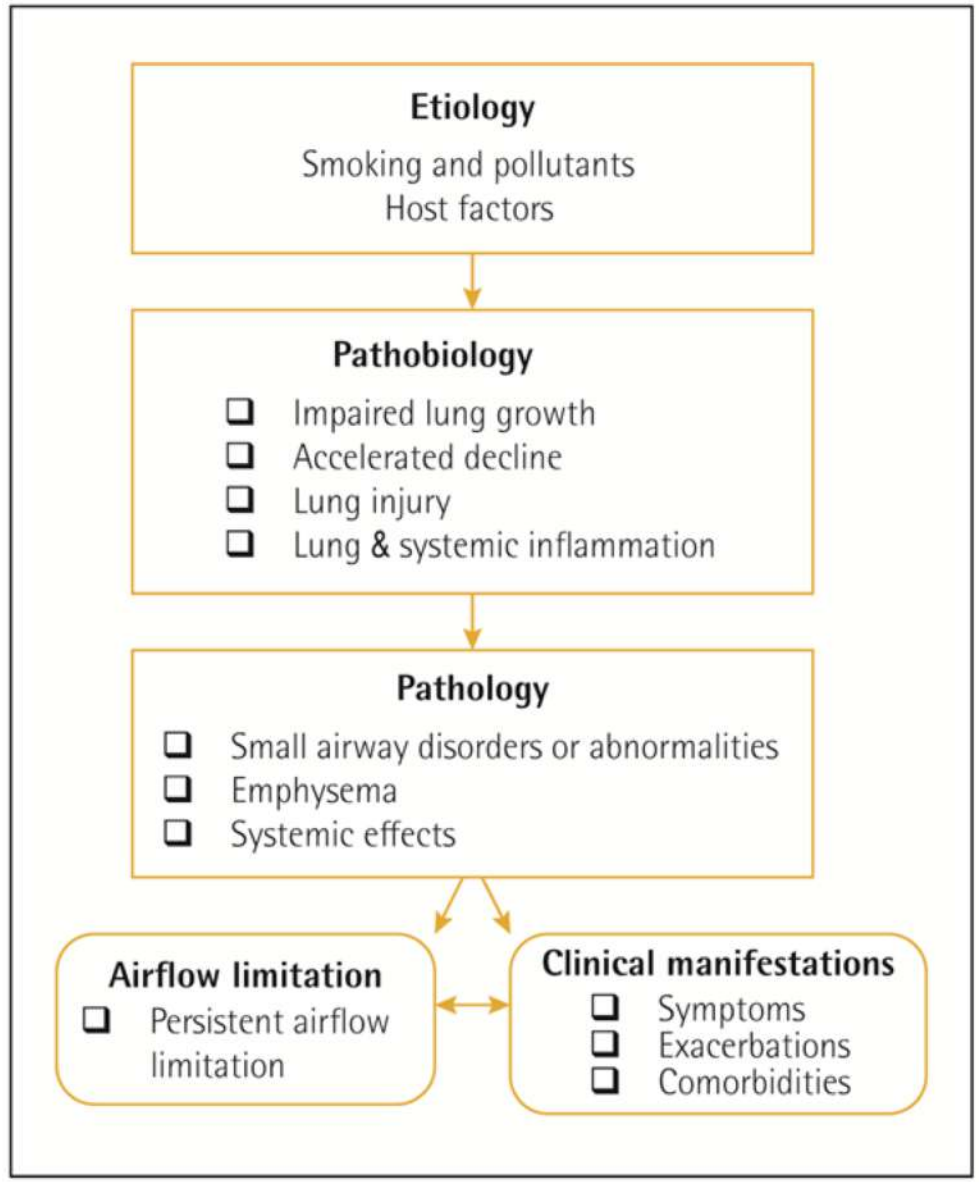
Definition

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Figure 1.1. Etiology, pathobiology and pathology of COPD leading to airflow limitation and clinical manifestations



Chronic Obstructive Pulmonary Disease (COPD)

Characterized by respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute

Prevalence

Prevalence of COPD was higher in smokers and ex-smokers compared to non-smokers

Higher ≥ 40 year group compared to those < 40

Higher in men than women

Prevalence

- Estimated 384 million COPD cases in 2010.
- Three million deaths annually.
- Increasing smoking
- By 2030 predicted 4.5 million COPD related deaths annually

Pathology, pathogenesis & pathophysiology

Pathology

- Chronic inflammation
- Structural changes

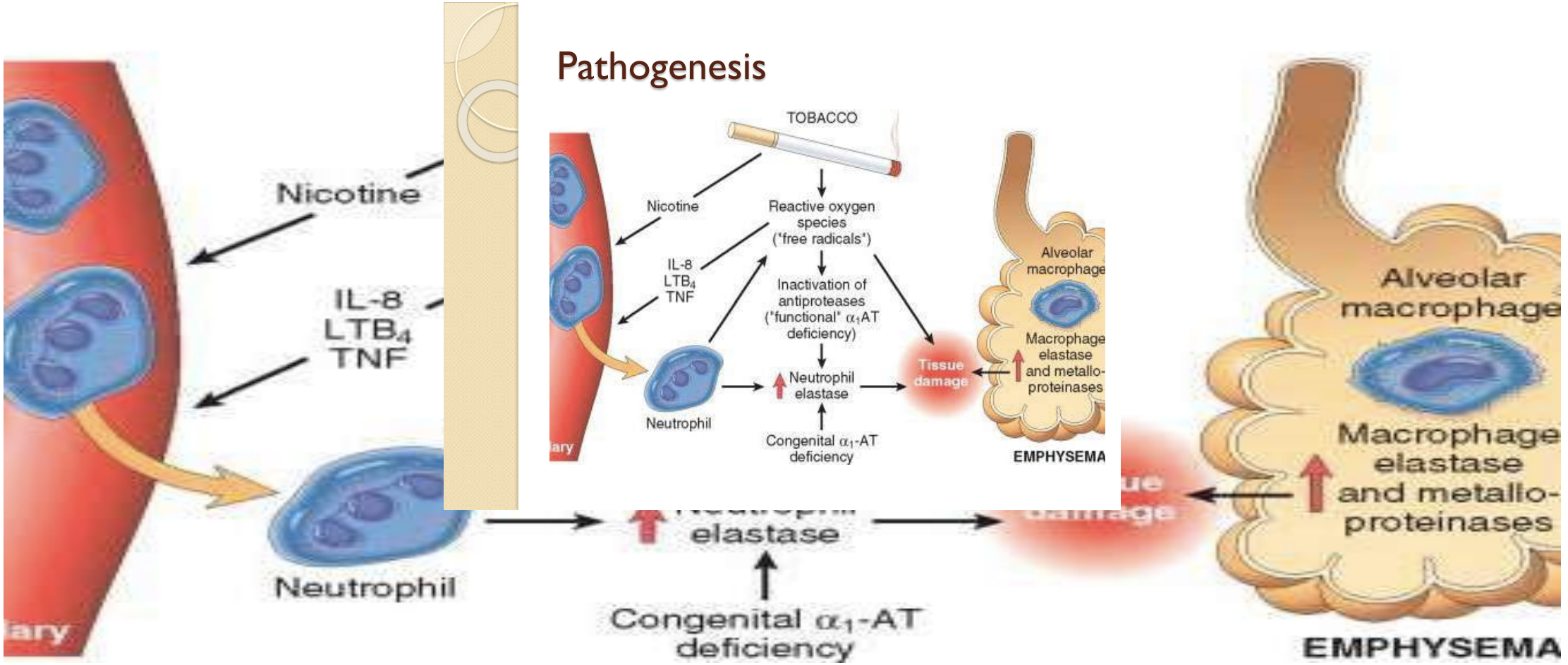
Pathogenesis

- Oxidative stress
- Protease-antiprotease imbalance
- Inflammatory cells
- Inflammatory mediators
- Peribronchiolar and interstitial fibrosis

Pathophysiology

- Airflow limitation and gas trapping
- Gas exchange abnormalities
- Mucus hypersecretion
- Pulmonary hypertension

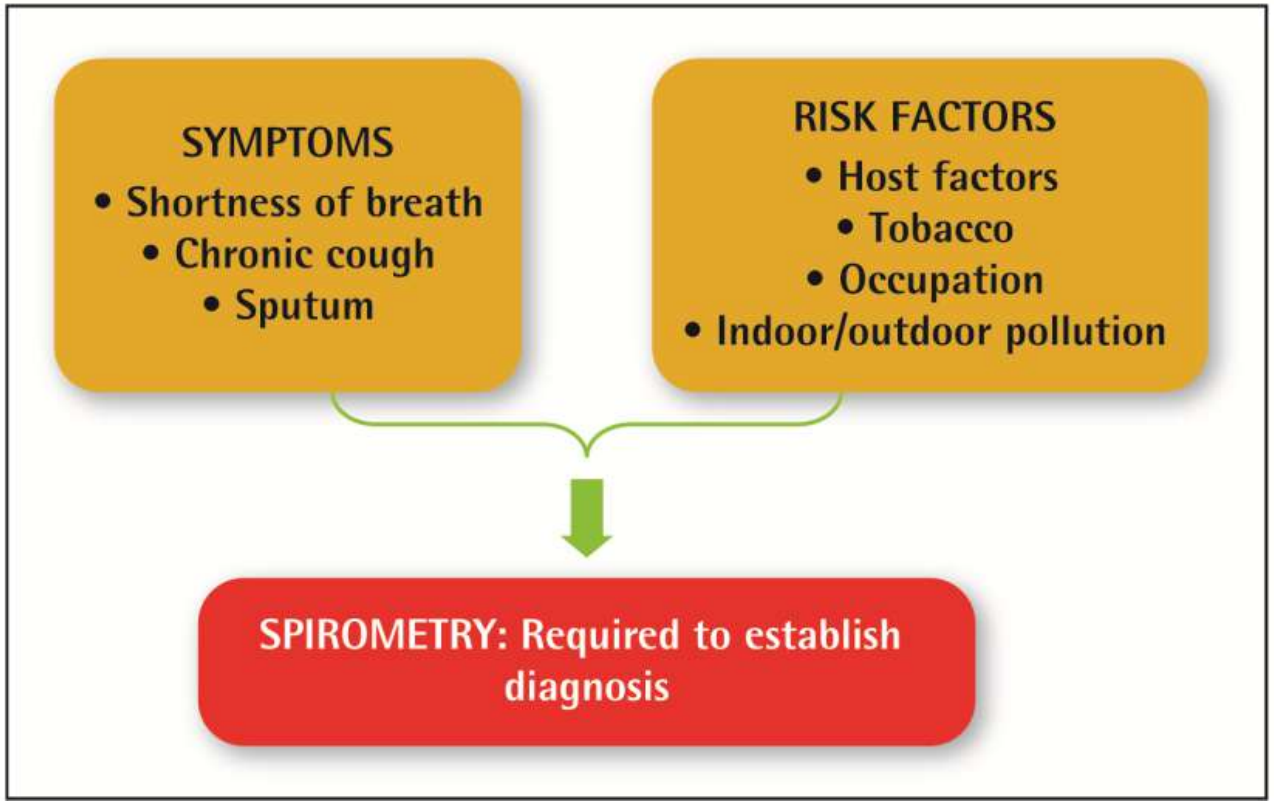
Pathogenesis



Diagnosis and Initial Assessment

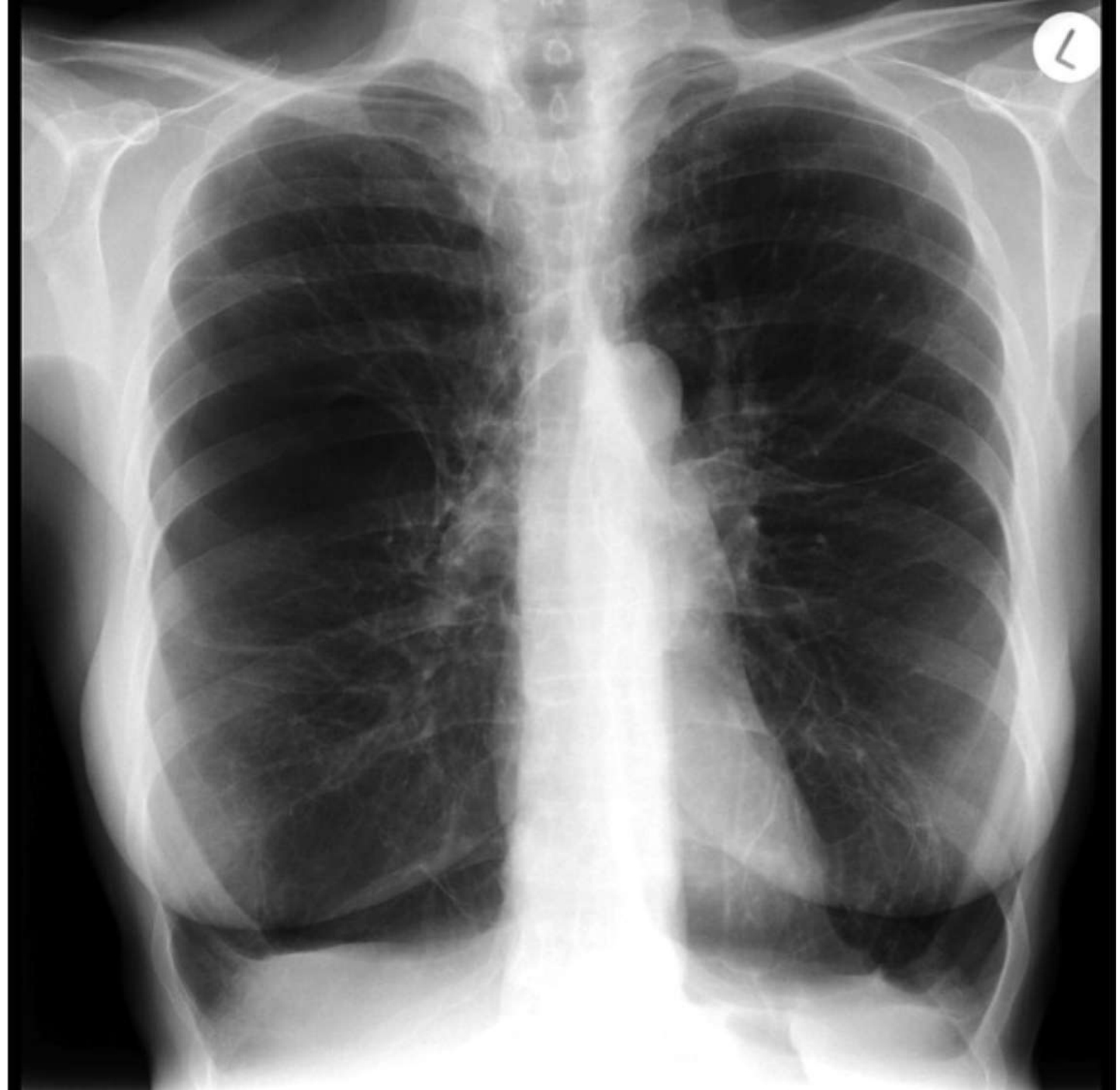
Diagnosis

Figure 2.1. Pathways to the diagnosis of COPD



Symptoms

- Chronic and progressive dyspnea
- Cough
- Sputum production
- Wheezing and chest tightness
- Others – including fatigue, weight loss, anorexia, syncope, rib fractures, ankle swelling, depression, anxiety.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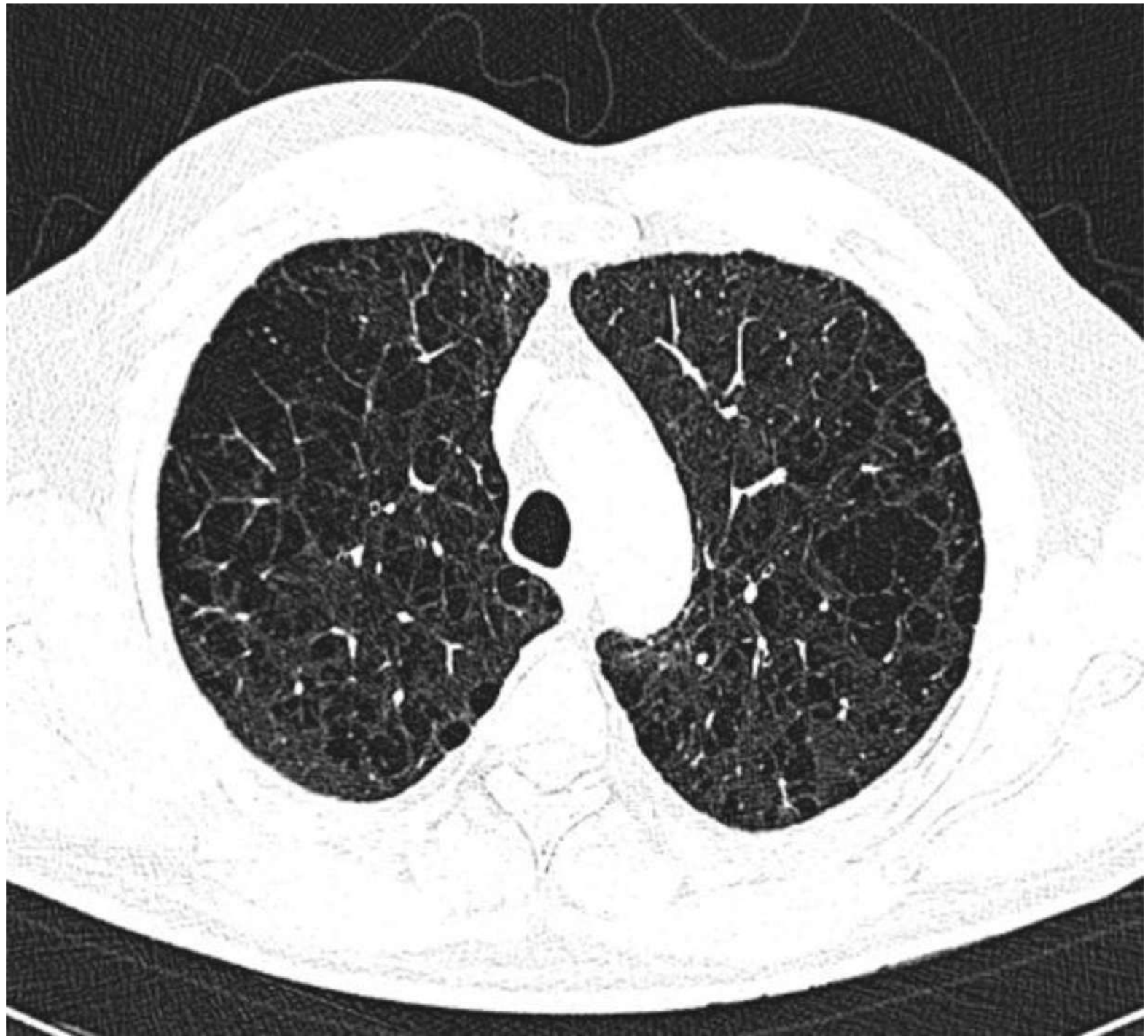


Table 2.2. Other causes of chronic cough
Intrathoracic
• Asthma
• Lung cancer
• Tuberculosis
• Bronchiectasis
• Left heart failure
• Interstitial lung disease
• Cystic fibrosis
• Idiopathic cough
Extrathoracic
• Chronic allergic rhinitis
• Post nasal drip syndrome (PNDS)
• Upper Airway Cough Syndrome (UACS)
• Gastroesophageal reflux
• Medication (e.g. ACE inhibitors)

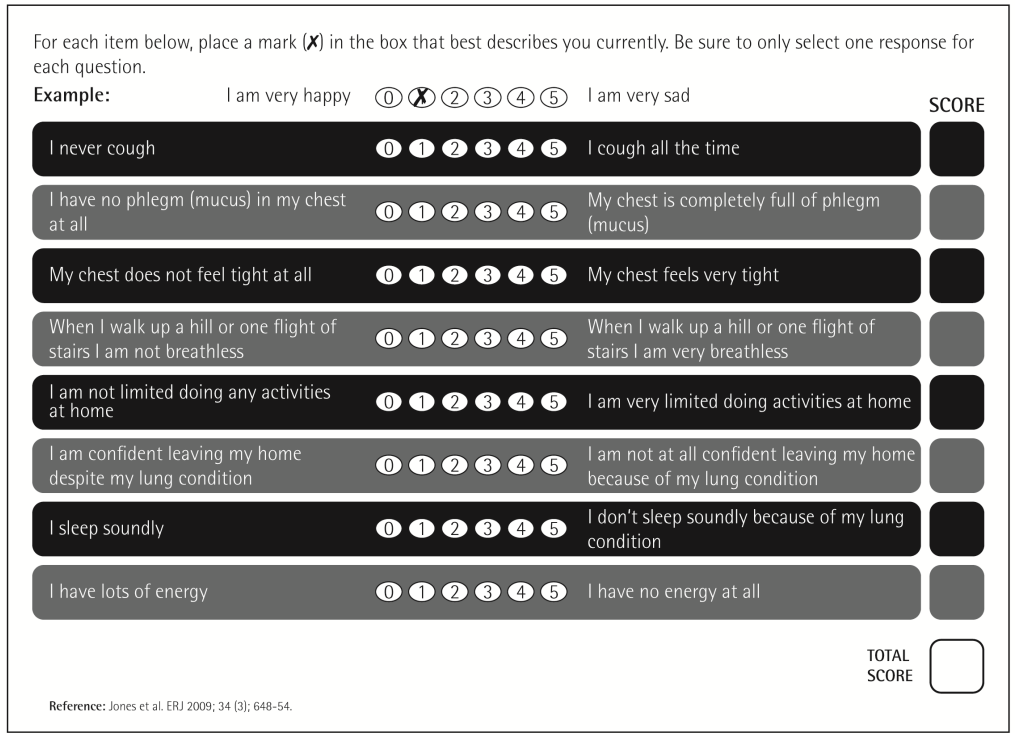
Spirometry

Table 2.4. Classification of airflow limitation severity in COPD (Based on post-bronchodilator FEV_1)		
In patients with $FEV_1/FVC < 0.70$:		
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

Choice of thresholds

- COPD Assessment Test (CAT TM)
- Modified Medical Research Council (mMRC) questionnaire

Figure 2.3. CAT Assessment



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

Example: I am very happy (0) (✗) (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	

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

Table 2.5. Modified MRC dyspnea scale[a]

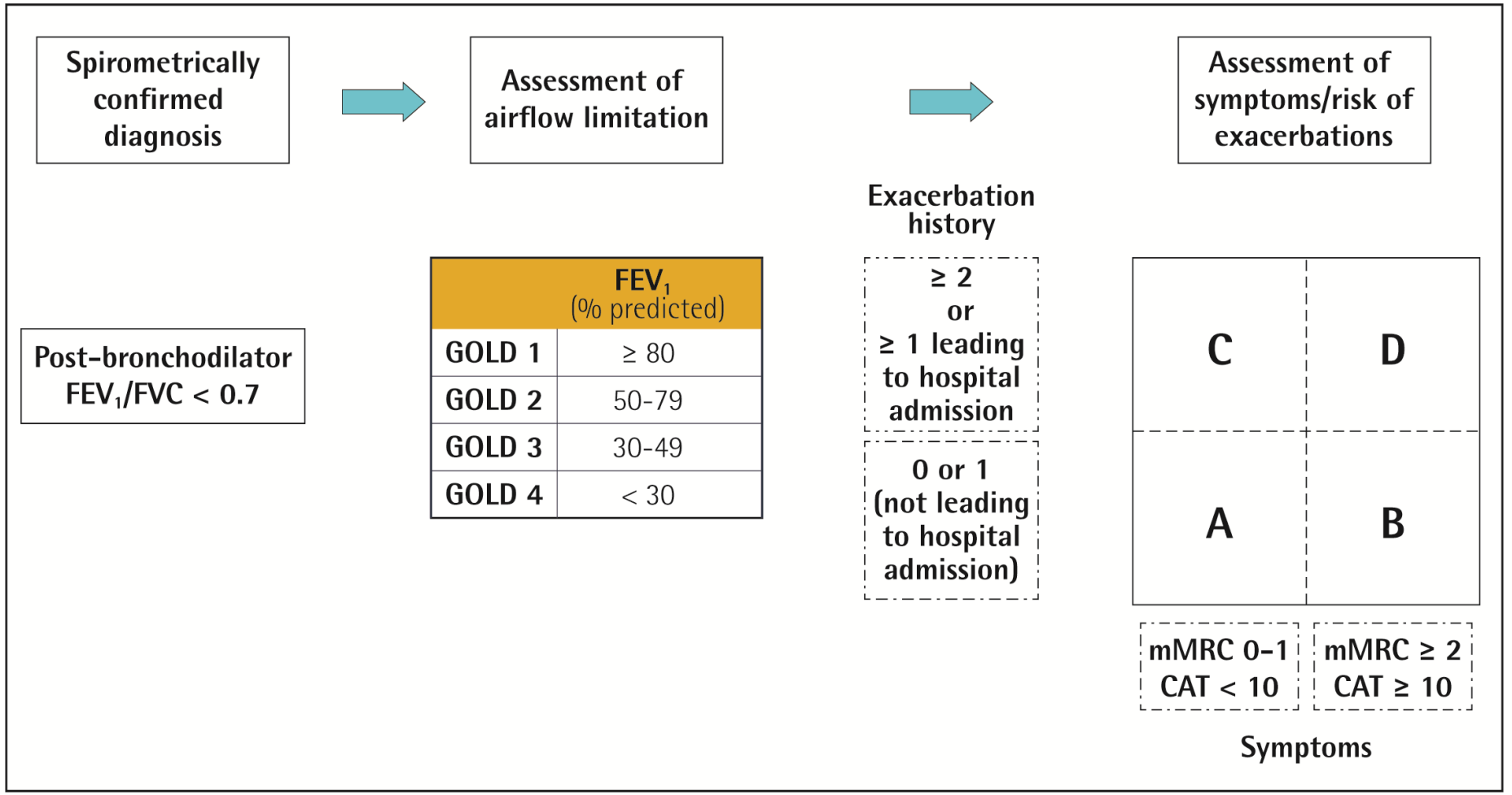
PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY) (Grades 0-4)

mMRC Grade 0. I only get breathless with strenuous exercise.	☐
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

[a] Fletcher CM. BMJ 1960; 2: 1662.

ABCD of COPD

Figure 2.4. The refined ABCD assessment tool



Alpha-1 antitrypsin deficiency (AATD)

- The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once especially in areas with high AATD prevalence.
- AATD patients are typically < 45 years with panlobular basal emphysema
- Delay in diagnosis in older AATD patients presents as more typical distribution of emphysema (centrilobular apical).
- A low concentration (< 20% normal) is highly suggestive of homozygous deficiency.

Differential Diagnosis

Management

Approach

Management of Stable COPD

Once COPD has been diagnosed, effective management should be based on an individualized assessment to reduce both current symptoms and future risks of exacerbations.

Table 4.1. Goals for treatment of stable COPD

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

→ REDUCE SYMPTOMS

and

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

→ REDUCE RISK

Non-Pharmacologic Treatment

- Education and self-management
- Physical activity
- Pulmonary rehabilitation programs
- Exercise training
- Self-management education
- End of life and palliative care
- Nutritional support
- Vaccination

Smoking

- Smoking cessation has the greatest capacity to influence the natural history of COPD.

- If effective resources and time are dedicated to smoking cessation, long-term quit success rates of up to 25% can be achieved.

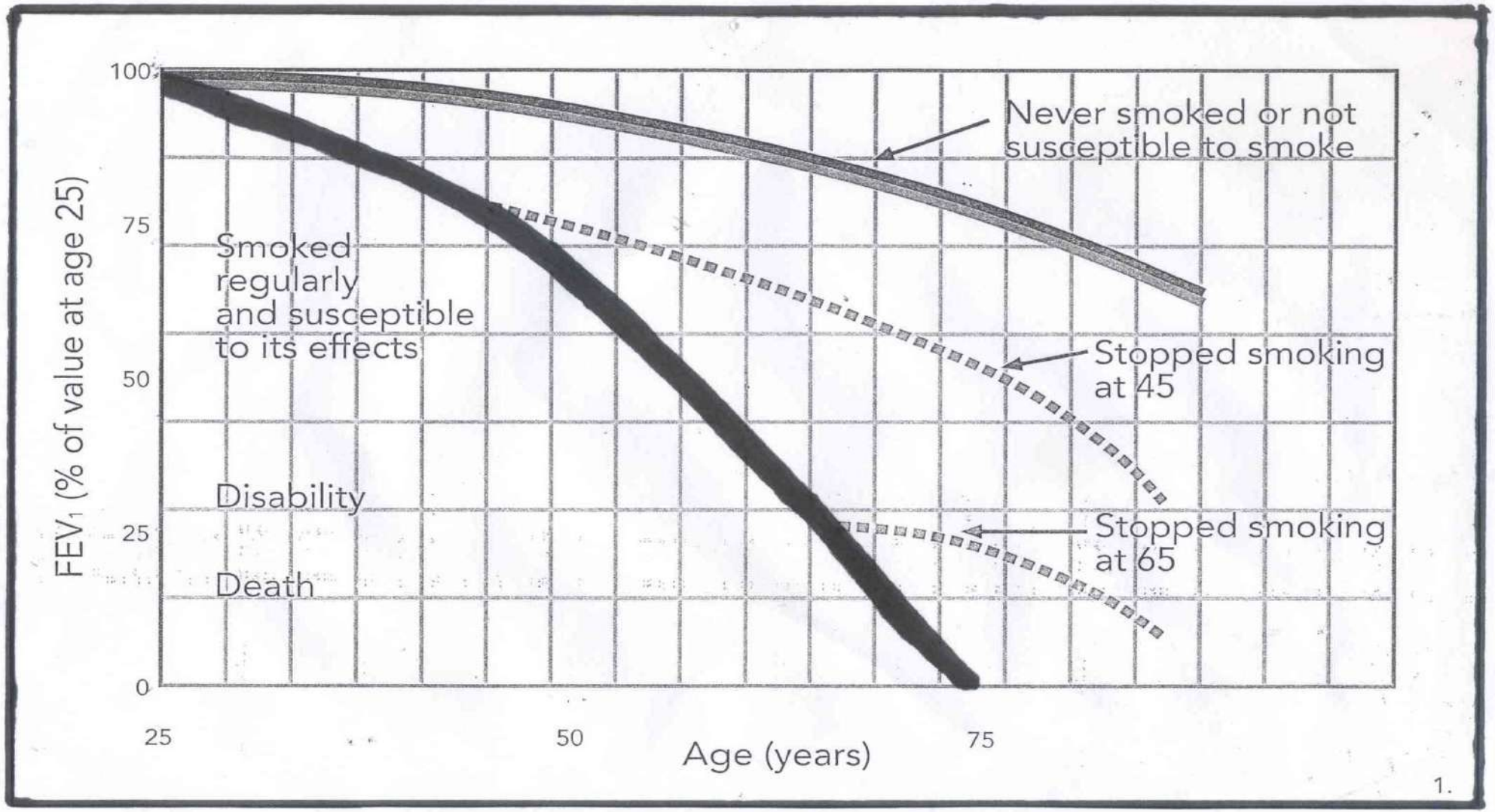


FIGURE 2 - Risks for various men if they smoke: differences between these lines illustrate effects that smoking, and stopping smoking can have on FEV1 of man who is liable to develop Chronic obstructive lung disease if he smokes. (BMJ, 1977)

Vaccination

- Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization)24 and death in COPD patients.

- Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients ≥ 65 years of age

Table 3.2. Vaccination for stable COPD

- Influenza vaccination reduces serious illness and death in COPD patients **(Evidence B)**.
- The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been shown to reduce the incidence of community-acquired pneumonia in COPD patients aged < 65 years with an FEV_1 < 40% predicted and in those with comorbidities **(Evidence B)**.
- In the general population of adults ≥ 65 years the 13-valent conjugated pneumococcal vaccine (PCV13) has demonstrated significant efficacy in reducing bacteremia and serious invasive pneumococcal disease **(Evidence B)**.

Pulmonary Rehabilitation

Exercise training

– 6–12 weeks;

longer programs result in larger effects

– 20–30 min walking per session, to limits of symptoms

Patient education

- Smoking cessation,
- COPD natural history and management,
- self-management,
- exacerbations

Assessment and follow-up

Nutritional support

Rehabilitation, Education & Self-Management

Table 3.8. Pulmonary rehabilitation, self-management and integrative care in COPD
Pulmonary rehabilitation
• Pulmonary rehabilitation improves dyspnea, health status and exercise tolerance in stable patients **(Evidence A)**.
• Pulmonary rehabilitation reduces hospitalizations among patients who have had a recent exacerbation (≤ 4 weeks from prior hospitalization) **(Evidence B)**.
Education and self-management
• Education alone has not been shown to be effective **(Evidence C)**.
• Self-management intervention with communication with a health care professional improves health status and decreases hospitalizations and emergency department visits **(Evidence B)**.
Integrated care programs
• Integrated care and telehealth have no demonstrated benefit at this time **(Evidence B)**.

Pharmacological therapy

Table 3.3. Commonly used maintenance medications in COPD*					
Drug	**Inhaler (mcg)**	**Solution for nebulizer (mg/ml)**	**Oral**	**Vials for injection (mg)**	**Duration of action (hours)**
Beta$_2$-agonists					
Short-acting					
Fenoterol	100-200 (MDI)	1	2.5 mg (pill), 0.05% (syrup)		4-6
Levalbuterol	45-90 (MDI)	0.1, 0.21, 0.25, 0.42			6-8
Salbutamol (albuterol)	90, 100, 200 (MDI & DPI)[+]	1, 2, 2.5, 5 mg/ml	2, 4, 5 mg (pill), 8 mg (extended release tablet) 0.024%/0.4 mg (syrup)	0.1, 0.5 mg	4-6, 12 (extended release)
Terbutaline	500 (DPI)		2.5, 5 mg (pill)	0.2, 0.25, 1 mg	4-6
Long-acting					
Arformoterol		0.0075[+]			12
Formoterol	4.5-9 (DPI)	0.01[^]			12
Indacaterol	75-300 (DPI)				24
Olodaterol	2.5, 5 (SMI)				24
Salmeterol	25-50 (MDI & DPI)				12
Anticholinergics					
Short-acting					
Ipratropium bromide	20, 40 (MDI)	0.2			6-8
Oxitropium bromide	100 (MDI)				7-9
Long-acting					
Aclidinium bromide	400 (DPI), 400 (MDI)				12
Glycopyrronium bromide	15.6 & 50 (DPI)[+]		1 mg (solution)	0.2 mg	12-24
Tiotropium	18 (DPI), 2.5 & 5 (SMI)				24
Umeclidinium	62.5 (DPI)				24
Combination of short-acting beta$_2$-agonist plus anticholinergic in one device					
Fenoterol/ipratropium	50/20 (SMI)	1.25, 0.5 mg in 4ml			6-8
Salbutamol/ipratropium	100/20 (SMI), 75/15 (MDI)	0.5, 2.5 mg in 3ml			6-8

Pharmacologic Therapy

Combination of long-acting beta$_2$-agonist plus anticholinergic in one device				
Formoterol/aclidinium	12/400 (DPI)			12
Formoterol/glycopyrronium	9.6/18 (MDI)			12
Indacaterol/glycopyrronium	27.5/15.6 & 110/50 (DPI)[‡]			12-24
Vilanterol/umeclidinium	25/62.5 (DPI)			24
Olodaterol/tiotropium	5/5 (SMI)			24
Methylxanthines				
Aminophylline		105 mg/ml (solution)	250, 500 mg	Variable, up to 24
Theophylline (SR)		100-600 mg (pill)	250, 400, 500 mg	Variable, up to 24
Combination of long-acting beta$_2$-agonist plus corticosteroids in one device				
Formoterol/beclomethasone	6/100 (MDI)			
Formoterol/budesonide	4.5/160 (MDI), 4.5/80 (MDI), 9/320 (DPI), 9/160 (DPI)			
Formoterol/mometasone	10/200, 10/400 (MDI)			
Salmeterol/fluticasone	5/100, 50/250, 5/500 (DPI), 21/45, 21/115, 21/230 (MDI)			
Vilanterol/fluticasone furoate	25/100 (DPI)			
Phosphodiesterase-4 inhibitors				
Roflumilast		500 mcg (pill)		

MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler

* Not all formulations are available in all countries; in some countries other formulations and dosages may be available

[‡] Dose availability varies by country

^ Formoterol nebulized solution is based on the unit dose vial containing 20 mcg in a volume of 2.0 ml

[†] Dose varies by country

Anti-inflammatory Therapy in Stable COPD

Table 3.5. Anti-inflammatory therapy in stable COPD

Inhaled corticosteroids

- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)**.
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**.
- Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms and health status **(Evidence A)** and reduces exacerbations **(Evidence B)** compared to ICS/LABA or LAMA monotherapy.

Oral glucocorticoids

- Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**.

PDE4 inhibitors

- In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:
  - » A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)**.
  - » A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations **(Evidence B)**.

Antibiotics

- Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)**.
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**.

Mucolytics/antioxidants

- Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations **(Evidence B)**.

Other anti-inflammatory agents

- Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)**.
- Leukotriene modifiers have not been tested adequately in COPD patients.

The Inhaled Route

Right inhaler for the Right patient

Oxygen Therapy & Ventilatory Support in Stable COPD

During exacerbations of COPD. Noninvasive ventilation (NIV) in the form of noninvasive positive pressure ventilation (NPPV) is the standard of care for decreasing morbidity and mortality in patients hospitalized with an exacerbation of COPD and acute respiratory failure

ABCD of COPD

Figure 2.4. The refined ABCD assessment tool

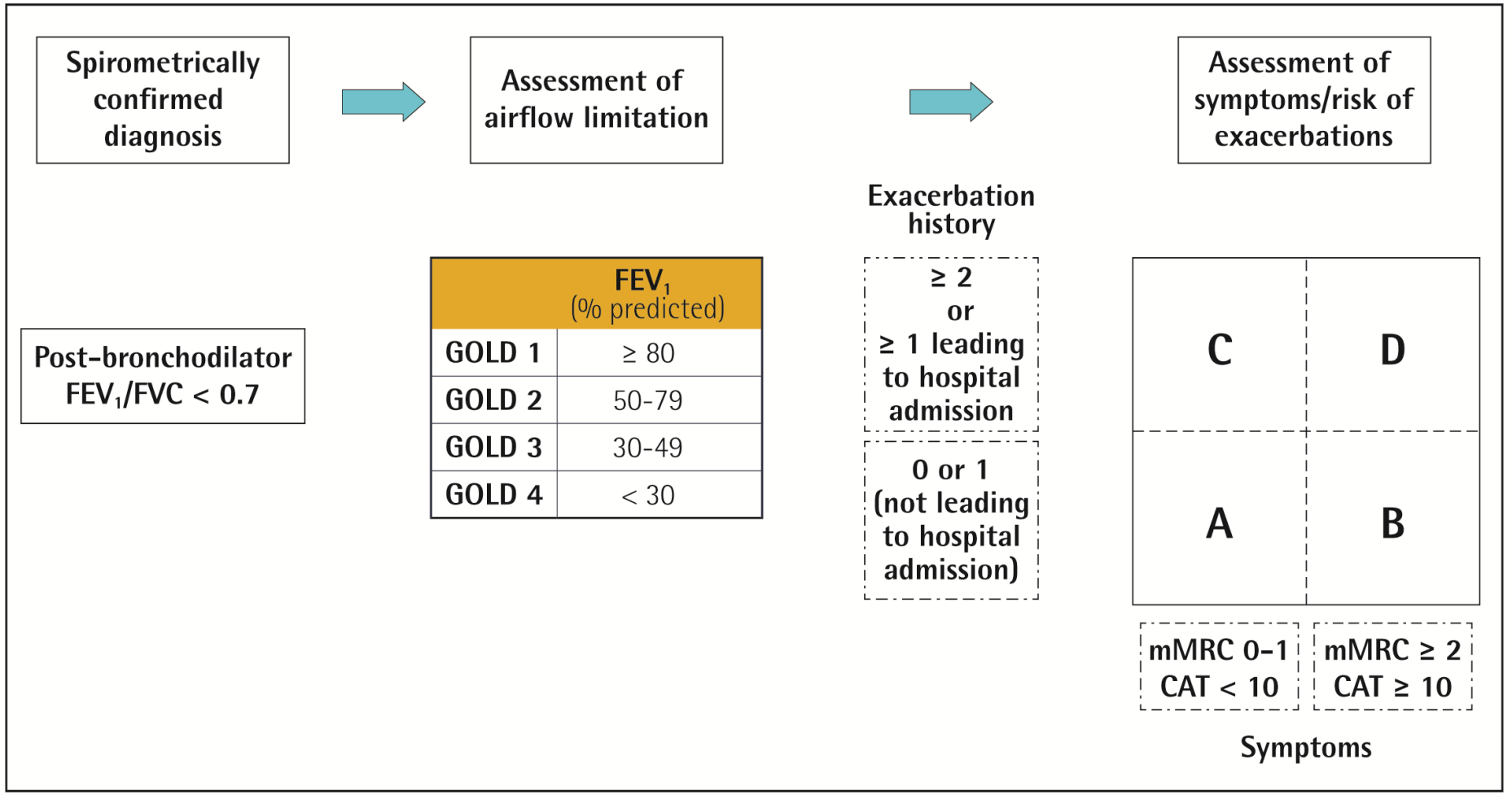
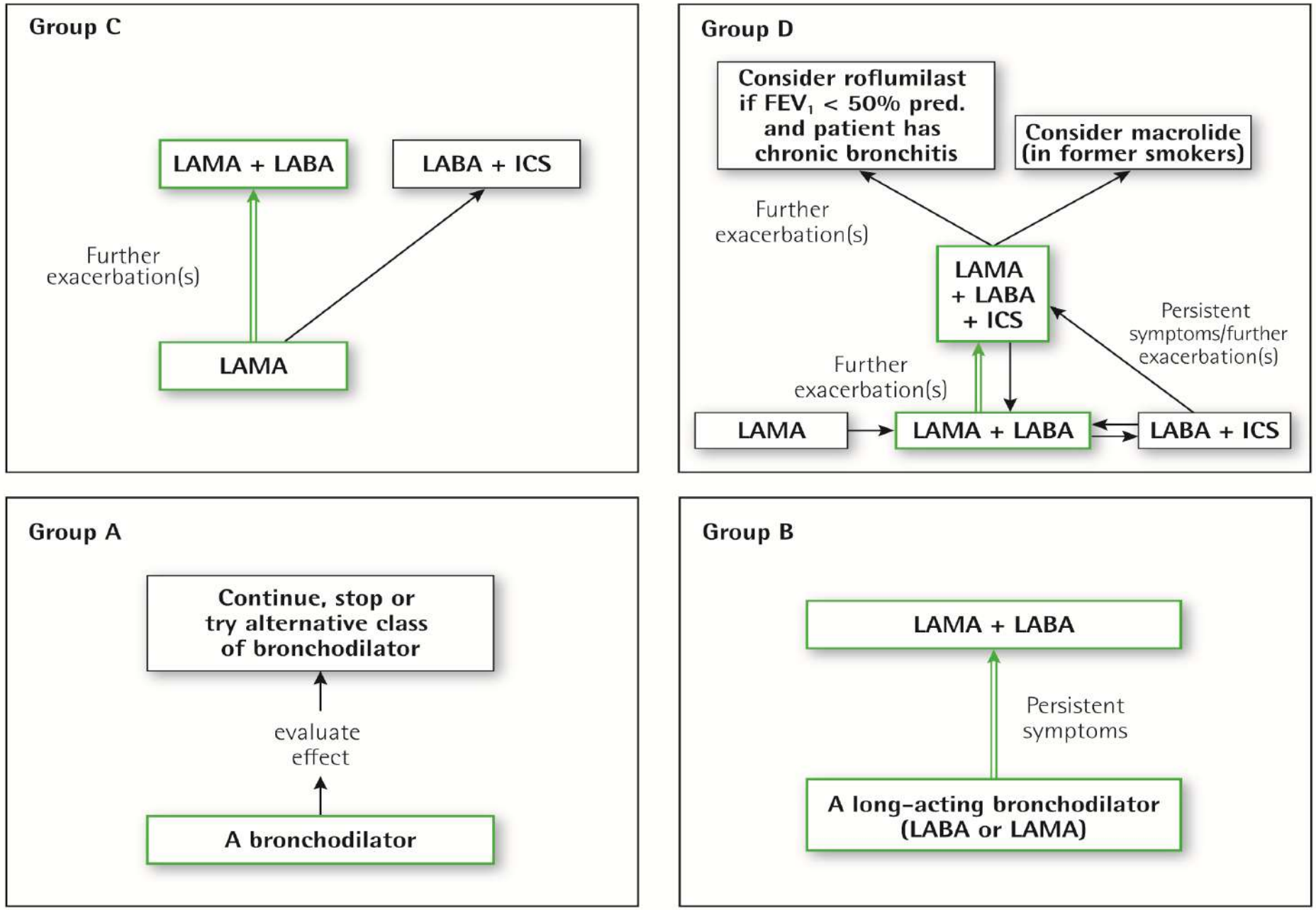


Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



Oxygen therapy

Long-term oxygen therapy is indicated for stable patients who have:

- PaO2 at or below 7.3 kPa (55 mmHg) or SaO2 at or below 88%, with or without hypercapnia confirmed twice over a three week period; or

- PaO2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).

Interventional bronchoscopy and surgery

Surgical or endoscopic LVRS

Bullectomy

Transplant

Management of Exacerbations

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.

- They are classified as:
    - Mild (treated with short acting bronchodilators only, SABDs)
    - Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
    - Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

Classification of hospitalized patients

No respiratory failure:

- Respiratory rate: 20-30 breaths per minute; no use of accessory respiratory muscles; no changes in mental status; hypoxemia improved with supplemental oxygen given via Venturi mask 28-35% inspired oxygen (FiO_2); no increase in $PaCO_2$.

Acute respiratory failure — non-life-threatening:

- Respiratory rate: > 30 breaths per minute; using accessory respiratory muscles; no change in mental status; hypoxemia improved with supplemental oxygen via Venturi mask 25-30% FiO_2; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated 50-60 mmHg

Acute respiratory failure — life-threatening:

- Respiratory rate: > 30 breaths per minute; using accessory respiratory muscles; acute changes in mental status; hypoxemia not improved with supplemental oxygen via Venturi mask or requiring FiO_2 > 40%; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated > 60 mmHg or the presence of acidosis ($pH \leq 7.25$).

Management of Exacerbations

- Bronchodilators

  .

- Corticosteroids

- Antibiotics

Management of Exacerbations

Respiratory support

Table 5.4. Indications for respiratory or medical intensive care unit admission*

- Severe dyspnea that responds inadequately to initial emergency therapy.
- Changes in mental status (confusion, lethargy, coma).
- Persistent or worsening hypoxemia (PaO_2 < 5.3 kPa or 40 mmHg) and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation.
- Need for invasive mechanical ventilation.
- Hemodynamic instability–need for vasopressors.

*Local resources need to be considered.

Management of Exacerbations

NIV

Table 5.5. Indications for noninvasive mechanical ventilation (NIV)

At least one of the following:

- Respiratory acidosis ($PaCO_2 \geq 6.0$ kPa or 45 mmHg and arterial pH ≤ 7.35).
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces.
- Persistent hypoxemia despite supplemental oxygen therapy.