COPD Management

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Objectives

- Discuss the burden of COPD on the patient and society
- Review pathophysiologic features of COPD, the GOLD “ABCD” assessment tool, and classification of airflow severity
- Identify the goals of COPD management
- Describe a rational approach to pharmacotherapy for COPD, and selection of agents (Levels of Evidence: A, B, C, D)
- Identify risks/benefits of COPD therapies

Global Initiative for Chronic Obstructive Lung Disease (GOLD)*

Global Strategy for the Diagnosis, Management, and Prevention of COPD

2020 Edition

GOLD Pocket Guide for

Health Care Professionals

*Required reading

GOLD website at www.goldcopd.org

Chronic Obstructive Pulmonary Disease (COPD)

GOLD Definition

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 and influenced by host factors including abnormal lung development

Exacerbations and comorbidities contribute to the overall severity in individual patients, and impact morbidity and mortality.

GOLD website at www.goldcopd.org

COPD Chronic Airflow Limitation

- Caused by a mixture of:
  - Small airways disease (obstructive bronchiolitis)
  - Parenchymal destruction (emphysema)
- Relative contributions vary from person to person
- Chronic inflammation causes structural changes and narrowing of small airways
- Destruction of lung parenchyma leads to loss of alveolar attachments to the small airways and decreases lung elastic recoil → ↓ ability of airways to remain open during expiration
- Best measured by spirometry
- Respiratory symptoms may precede airflow limitation and be associated with acute respiratory events.

GOLD website at www.goldcopd.org

Risk Factors for COPD

Genes (alpha-1 antitrypsin deficiency)

Exposure to particles

- **Tobacco smoke**
- Other types of tobacco e.g., pipe, cigar, water pipe, marijuana
- Occupational dusts & chemicals
- Indoor air pollution e.g., burning of biomass fuels
- Outdoor air pollution

NONSMOKERS MAY DEVELOP COPD

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Lung growth and development

Age & sex - aging and female sex ↑ risk

Respiratory infections

Socioeconomic status

Asthma and airway hyper-reactivity

Chronic bronchitis

COPD and Co-Morbidities

- Cardiovascular Diseases*
  - Ischemic heart disease (IHD)
  - Heart failure (HF)
  - Atrial fibrillation
  - Hypertension
  - Peripheral vascular disease
- Osteoporosis
- Anxiety, depression, and impaired cognitive function
- Lung cancer and other malignancies
- Serious infections, esp. respiratory
- Metabolic syndrome and diabetes
- Gastroesophageal reflux disease
- Bronchiectasis
- Obstructive sleep apnea

***Cardioselective beta-blockers are NOT contraindicated in COPD; improve survival in HF.**

Key Indicators for Considering COPD Diagnosis and Performing Spirometry

- Dyspnea that is:
  - Progressive over time
  - Characteristically worse with exercise
  - Persistent
- Chronic cough
  - May be intermittent and may be unproductive
  - Recurrent wheeze
- Chronic sputum production
  - Any pattern of sputum production may indicate COPD
- Recurrent lower respiratory tract infections
- Hx of risk factors
  - Host factors
  - Tobacco smoke (including popular local preparations)
  - Smoke from home cooking and heating fuels
  - Occupational dusts & chemicals
- Family Hx COPD and/or childhood factors (low birth weight, childhood respiratory infections)

GOLD website at www.goldcopd.org

Medical History

- Exposure to risk factors
- Past medical Hx (asthma, allergy, sinusitis, nasal polyps, childhood respiratory infections)
- Pattern of Sx development
- Hx of exacerbations or previous hospitalization for respiratory disorders
- Comorbidities
- Impact of disease on patient's health status, QOL, and work/economic status
- Social and family support
- Possibilities for reducing risk factors

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COPD Assessment

- Physical exam – rarely diagnostic
- Symptoms
  - COPD Assessment Test (CAT) http://catestonline.org
  - COPD Control Questionnaire (CCQ) http://www.ccq.nl
  - mMRC Dyspnea Scale – only assesses dyspnea
- Degree of airflow limitation (using spirometry)
- Imaging
- Oximetry & arterial blood gases
- Exercise testing
- Biomarkers eg. Blood eosinophil counts

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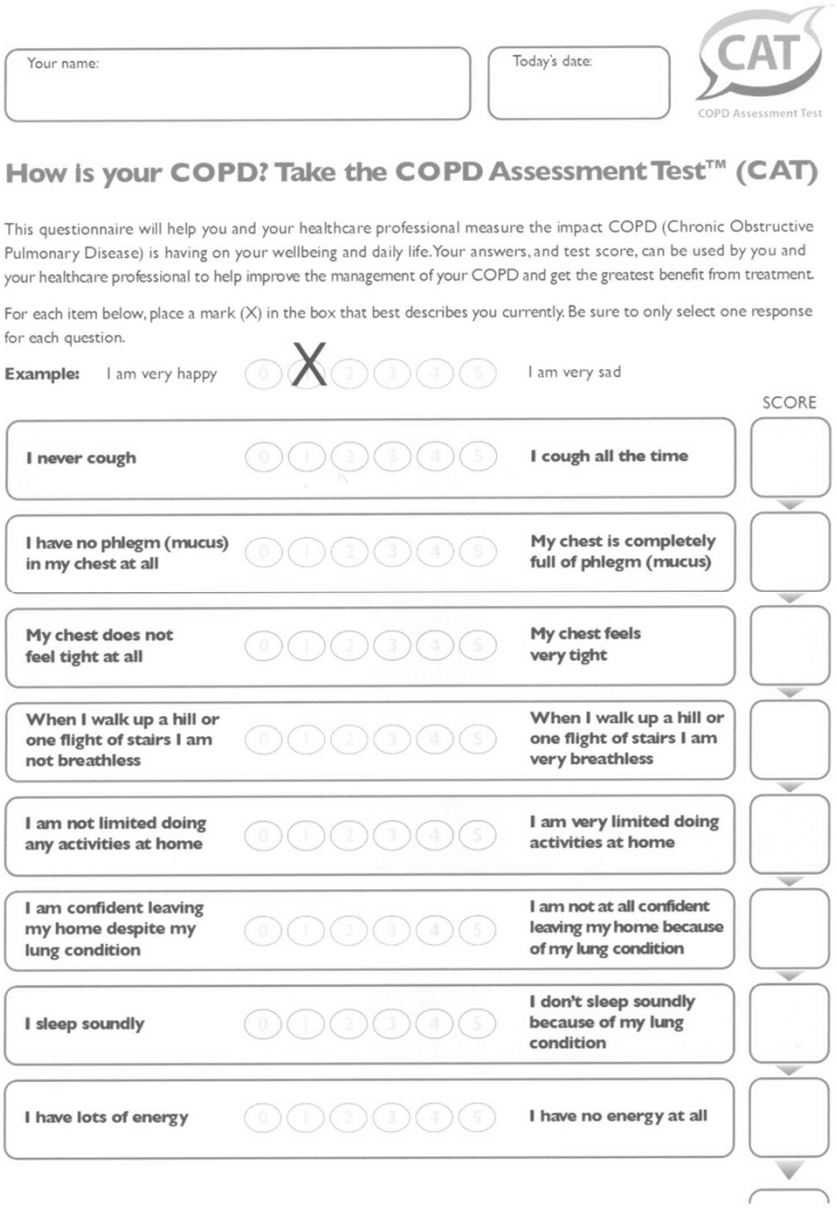

Your name:

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 1 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**	

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

Modified MRC (mMRC) Dyspnea Scale

Please Tick in the Box That Applies to You/One Box Only

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

Fletcher CM. BMJ 1960; 2:1862

Role of Spirometry

- Diagnosis
- Assessment of severity of airflow obstruction (for prognosis)
- Follow-up assessment
  - Therapeutic decisions
    1) Pharmacological in selected circumstances (discrepancy between spirometry & level of Sx)
    2) Alternative diagnoses
    3) Nonpharmacological interventions
  - ID of rapid decline
  - **There is only weak correlation between FEV_1 and symptoms**

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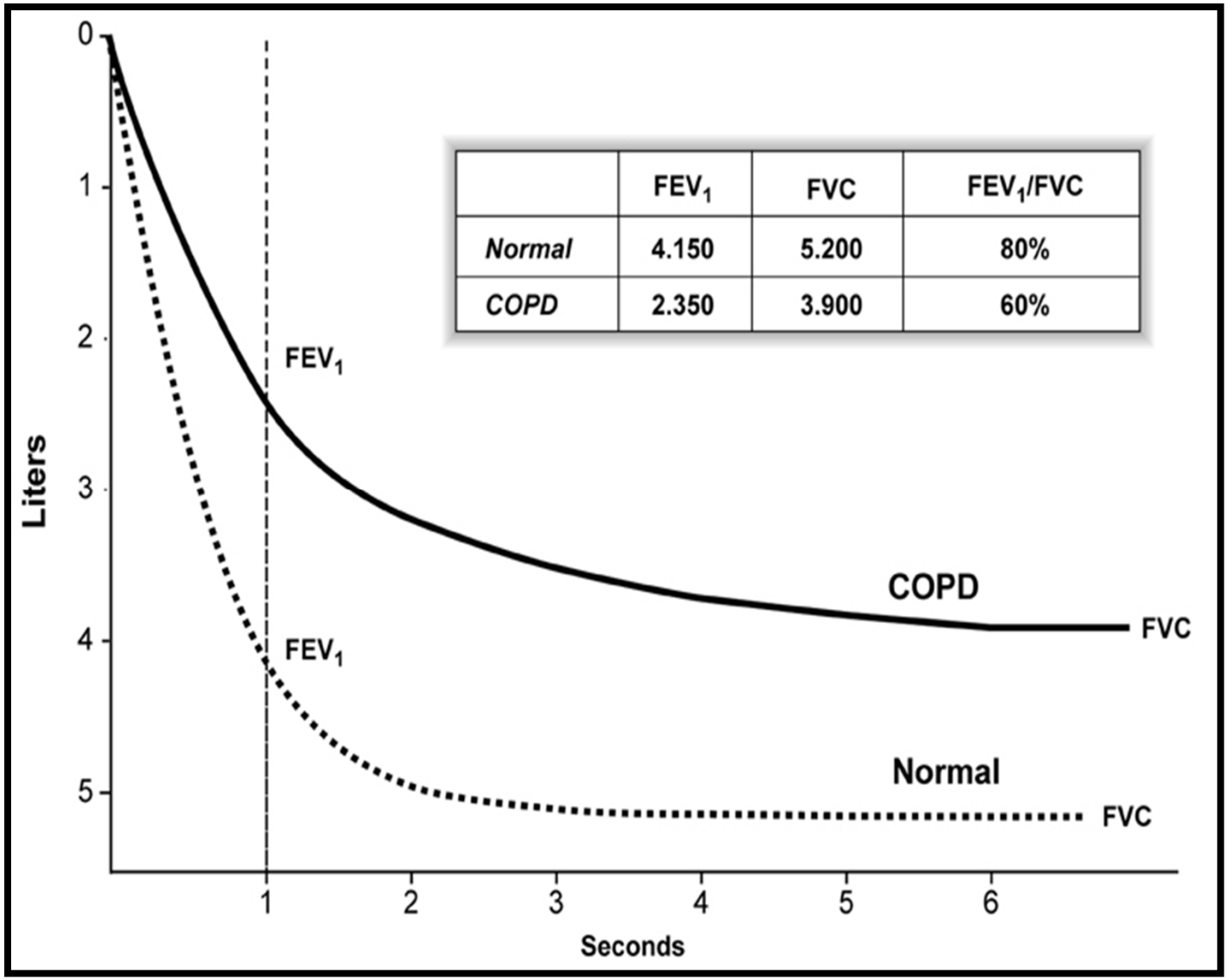
Spirometry: Normal and Patients with COPD



	FEV_1	FVC	FEV_1/FVC
Normal	4.150	5.200	80%
COPD	2.350	3.900	60%

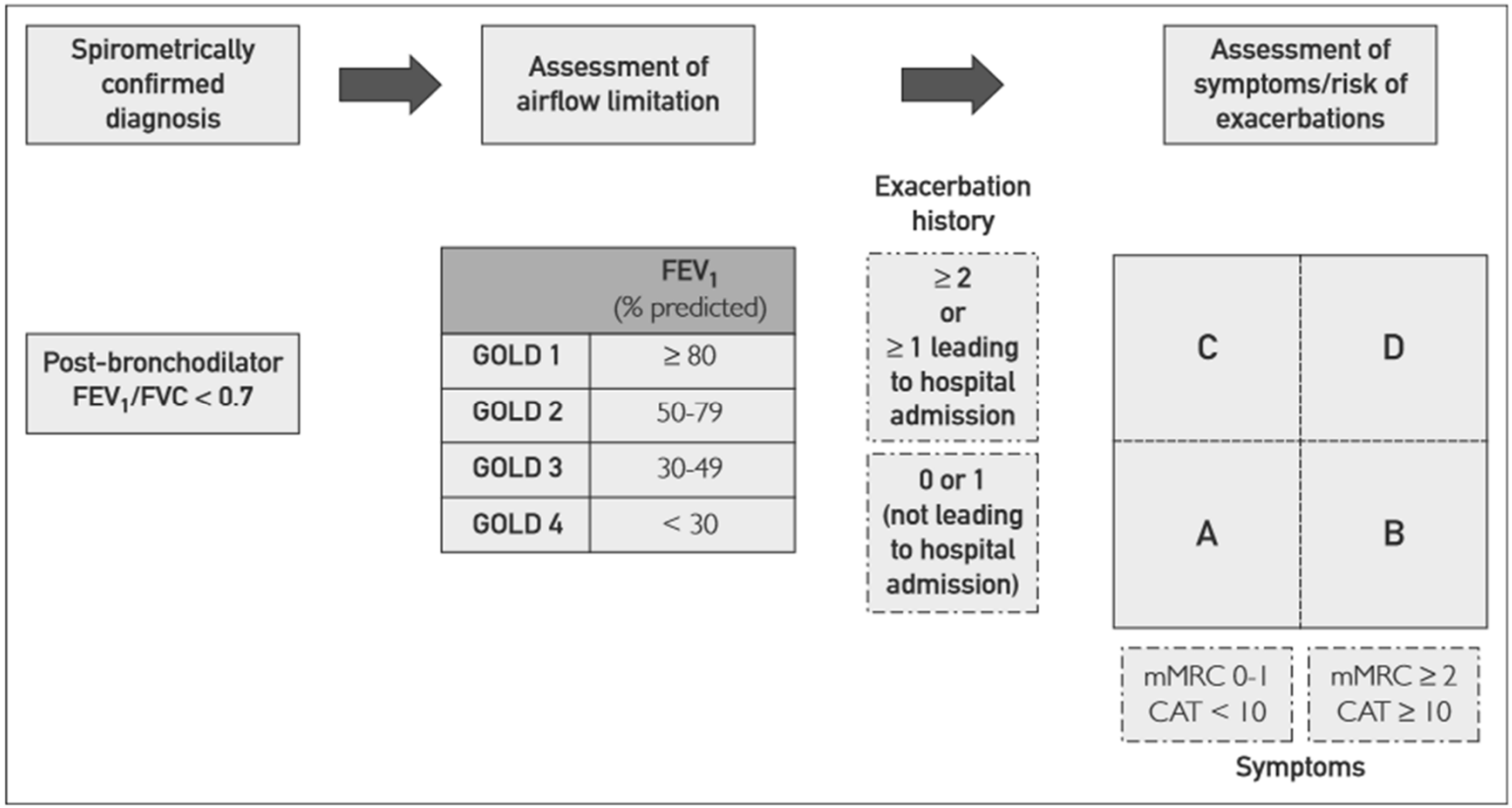
Classification of Severity of Airflow Limitation in COPD
(Based on Post-Bronchodilator FEV_1)

IN PATIENTS WITH $FEV_1/FVC < 0.70$

Gold I: Mild	$FEV_1 \geq 80\%$ predicted
Gold II: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
Gold III: Severe	$30\% \leq FEV_1 < 50\%$ predicted
Gold IV: Very Severe	$FEV_1 < 30\%$ predicted

GOLD website at www.goldcopd.org

Refined COPD Assessment (ABCD Tool)



GOLD website at www.goldcopd.org

Dual Goals for Management of Stable COPD

- Reduce Symptoms
  - Relieve symptoms
  - Improve exercise tolerance
  - Improve health status
- Reduce Risk
  - Prevent and treat exacerbations
  - Prevent disease progression
  - Reduce mortality

GOLD website at www.goldcopd.org

General Treatment Measures for COPD

- Avoid risk factors; emphasize smoking cessation
- Minimize risk of infection
  - Influenza vaccine annually – reduces serious illness & death, ↓ # exacerbations, ↓ risk of ischemic heart disease
  - Pneumococcal vaccine, PCV13 or PPSV23 (refer to CDC recs)
- Minimize psychosocial stress
- Maintain regular physical activity
- Pulmonary rehabilitation
- Maintain adequate nutrition
- Avoid potential drug interactions or ADRs
  - Theophylline

GOLD website at www.goldcopd.org

Pharmacologic Therapies for Stable COPD

- Bronchodilators
  - Beta-agonists
    - Short-acting (SABA)
    - Long-acting (LABA)
  - Antimuscarinic antagonists
    - Short-acting (SAMA)
    - Long-acting (LAMA)
  - Combo of SABA and SAMA in one device
  - Combo of LABA and LAMA in one device
  - Methylxanthines

GOLD website at www.goldcopd.org

Pharmacologic Therapies (cont.)

- Anti-inflammatory therapies
  - Inhaled corticosteroids
  - Combos (ICS & LABA, ICS/LAMA/LABA)
  - Oral glucocorticoids
  - PDE_4 inhibitors
  - Antibiotics
  - Mucoregulators and Antioxidant Agents
  - Others

GOLD website at www.goldcopd.org

Bronchodilators*

- Short acting beta-agonists (SABAs)
  - albuterol, levalbuterol
- Long acting beta-agonists (LABAs)
  - salmeterol, formoterol, arformoterol, indacaterol, vilanterol, olodaterol
- Short acting antimuscarinic agents (SAMAs)
  - Ipratropium bromide
- Long acting antimuscarinic agents (LAMAs)
  - Tiotropium, aclidinium bromide, umeclidinium, glycopyrronium bromide (glycopyrrolate), revefenacin
- Theophylline

*Single agents and combinations in one device

How Do Bronchodilators Improve Lung Function* in COPD?

- Reduce dynamic hyperinflation
- Increase inspiratory capacity
- Decrease work of breathing
- Improve ventilatory capacity
- Decrease exertional dyspnea
- Bronchodilate (increase FEV_1)

OUTCOMES: ↓ symptoms, ↑ exercise tolerance, ↓ frequency and severity of exacerbations

* No conclusive evidence of modification of long-term decline

Key Points for Inhalation of Drugs

- Choice of inhaler device has to be individualized; depends on access, cost, prescriber, **patient's ability and preference**
- Provide instructions, demonstration, and rechecks of technique
- Inhaler technique (and RX adherence) should be assessed before modifying Rx.

GOLD website at www.goldcopd.org

Bronchodilators (BD) in Stable COPD

- Inhaled BD are central to Sx management & given on a regular basis to prevent or ↓ Sx (A)
- Regular & prn SABA or SAMA improve FEV_1&Sx (A)
- Combo. SABA & SAMA superior (A)
- LABAs & LAMAs significantly ↑ lung function, ↓ dyspnea, ↑ health status & ↓ exacerbation rates (A); LAMA>LABA(B)
- Combo. LABA & LAMA superior (A, B)
- Tiotropium ↑ effectiveness of pulm. rehab. (B)
- Theophylline has modest benefits (B)

GOLD website at www.goldcopd.org

Anoro® Ellipta

- Combination of umeclidinium (LAMA) and vilanterol (LABA), indicated for long-term, once-daily, maintenance Tx of airflow obstruction in COPD
- Ellipta delivery of 2 double-foil blister strips
  - 62.5 mcg umeclidinium
  - 25 mcg vilanterol
- Not yet approved for Tx of asthma
- Caution with ketoconazole and other strong CYP3A4 inhibitors; potential for increased cardiovascular adverse effects

Breo® Ellipta 100/25 + 200/25

- Combination of fluticasone furoate (ICS) and vilanterol (LABA), indicated for long-term, once-daily, maintenance Tx of airflow obstruction in COPD & asthma (≥ age 18)
- Ellipta delivery of 2 double-foil blister strips
  - 100 or 200 mcg fluticasone furoate
  - 25 mcg vilanterol
- Caution with known strong CYP3A4 inhibitors; potential for increased systemic corticosteroid & cardiovascular adverse effects

Trelegy® Ellipta

- Combination of fluticasone furoate (ICS), umeclidinium (LAMA) and vilanterol (LABA)
- First FDA-approved once-daily **triple** therapy for COPD
- Maintenance Rx to control Sx in adult patients with moderate-severe COPD not controlled by ICS/LABA
- Reduces COPD flares in patients with Hx of exacerbations

Tiotropium (Spiriva®)

- Potent, long-acting muscarinic antagonist (LAMA)
- Quaternary ammonium structure, so poorly absorbed
- Selectively blocks M-1 and M-3 receptors over M-2 receptor
- Once daily dosing results in a dose-related bronchodilation that persists for > 24 hours
- Monitor more closely in moderate-severe renal failure
- Favorable side effect profile
  - Dry mouth ~ 16% (women > men)
  - Avoid powder in the eyes
  - 3/08 FDA posting of Early Communication regarding stroke and CV events/deaths
  - No ↑ risk overall for CV events (including stroke) based on 10/08 UPLIFT and pooled trial data base of > 17,000 patients

Tiotropium Respimat and Risk of Death in COPD: TIOSPIR trial

- Safety concerns with Tio Respimat in post-hoc pooled analyses of prior trials (5 mcg a/w excess mortality, rate ratio 1.33) and meta-analyses
- R, DB, PG trial (n = 17,135 COPD pts) of safety and efficacy; mean F/U 2.3 yrs
  - Tio Respimat 2.5 mcg qd
  - Tio Respimat 5 mcg qd
  - Tio Handihaler 18 mcg qd
- Outcomes: risk of death (noninferiority); COPD exacerbation (superiority); CV safety
- Conclusions: Tio Respimat 5 mcg or 2.5 mcg had safety profile and exac. efficacy similar to Tio Handihaler 18 mcg.

Wise RA et al. N Engl J Med 2013; 369(16): 1491-1501

Tiotropium bromide 2.5mcg/Olodaterol 2.5mcg (LAMA & LABA) (Stiolto Respimat®)

- FDA approval as long term maintenance for COPD to control Sx; updated to include efficacy data against COPD flare-ups
- Administered 2 puffs once daily
- Not indicated for COPD Sx relief or for asthma

Aclidinium Bromide

- Delivered as DPI Tudorza Pressair® 400 mcg bid
- Long-acting antimuscarinic agent (LAMA), comparable to tiotropium
- Not for acute use (maintenance Tx COPD)
- Most common ADRs: H/A, cough, nasopharyngitis
- Warnings: worsening open-angle glaucoma, urinary retention
- Potential for CYP450-related metabolic drug interactions (no studies)
- Reports of ↑ risk for major adverse CV events (Chest 2018 meeting); 4/1/19 updated FDA labeling with ASCENT trial data: no associated major adverse CV events (MACE)

Aclidinium 400 mcg & Formoterol 12 mcg

- Fixed dose LAMA/LABA combo., delivered as Duaklir® Pressair
- Twice daily dosing
- 3 Phase 3 trials demonstrating significant lung function improvements in moderate-severe COPD
- 1 Phase 4 trial showing reduction in COPD exacerbations
- Cautions as per individual components

https://www.duaklir.com

Glycopyrrolate 15.6 mcg (Seebri Neohaler®) Indacaterol 27.5 mcg/Glycopyrrolate 15.6 mcg (Ultibron Neohaler®)

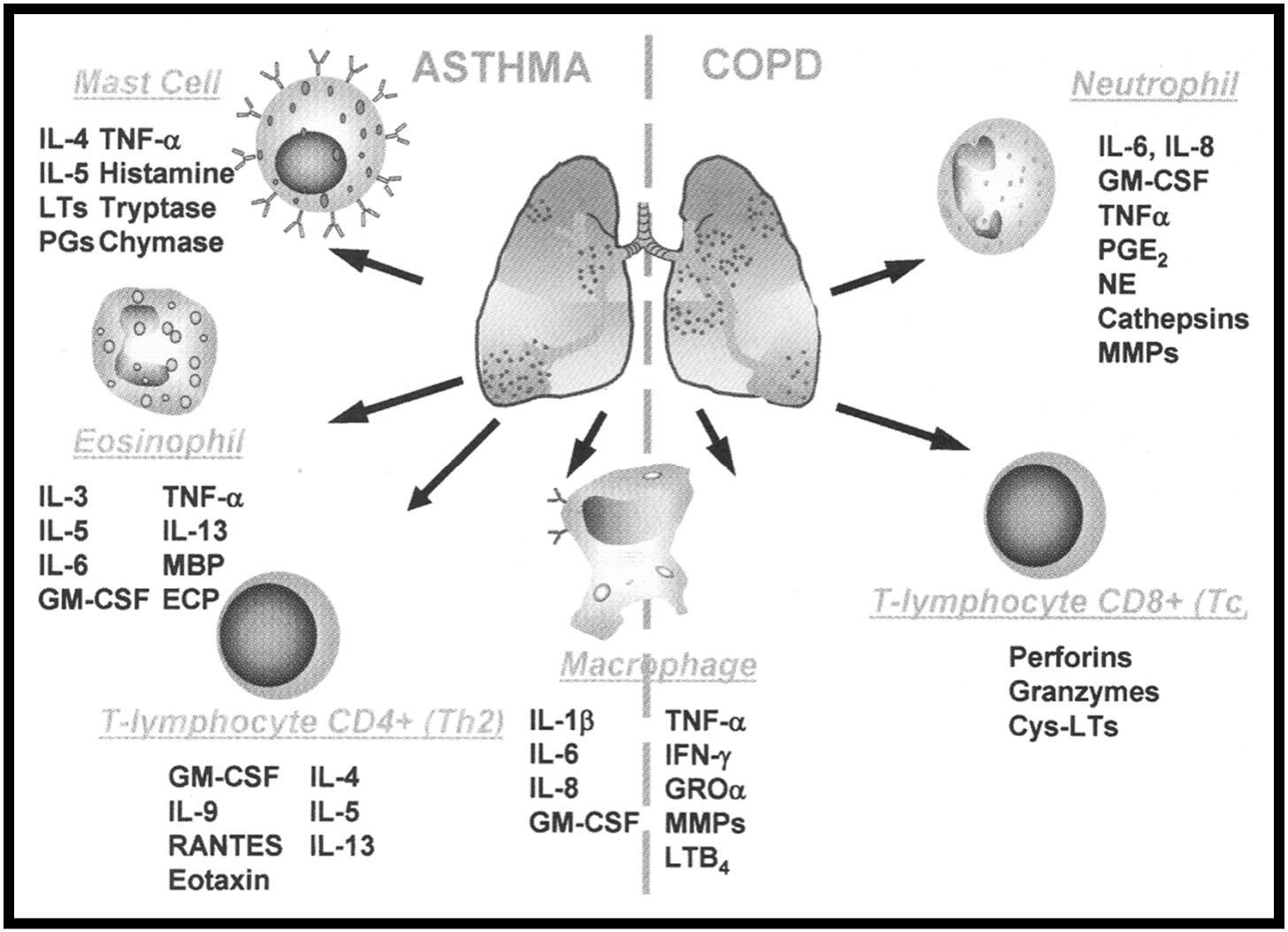
- FDA approved as long-term maintenance for COPD
- Administered twice-daily
  - Lung function improvements
  - Reduced use of rescue medication
  - Improved health-related QOL
- Adverse events
  - Sore throat, runny nose, ↑ BP, back pain
- NOT INDICATED IN ACUTELY DETERIORATING COPD OR RELIEF OF SYMPTOMS

Revefenacin (Yupelri®)

- First FDA–approved nebulized LAMA for COPD maintenance
- Once daily dose of 175 mcg (3ml) via a standard jet nebulizer (unit-dose vial) eg. PARI LC Sprint nebulizer over 8 minutes
- Common AEs: cough, nasopharyngitis, URI, headache, back pain (≥ 2% + more common than placebo)
- Sx of acute narrow-angle glaucoma (eg. eye pain or discomfort, blurred vision, visual changes) should be reported
- Sx of worsening urinary retention should be reported
- Acceptable 1 year cardiovascular safety profile
- Do not administer with other anticholinergics
- Do not administer with OATP1B1 and OATP1B3 inhibitors (eg rifampin, cyclosporine), due to ↑ exposure of active metabolite

http://www.theravance.com

Inflammation in Asthma vs COPD



Antiinflammatory Therapy in Stable COPD and Evidence Level

- Inhaled corticosteroids
  - Long-term ICS monotherapy not recommended (A)
  - ICS/LABA combo is more effective than individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD (A)
  - ICS increases risk of pneumonia especially in patients with severe disease (A)
- Oral glucocorticoids
  - Long-term use has numerous side effects (A) with no evidence of benefits (C)
- Leukotriene modifiers
  - Have not been tested adequately in COPD

Hirsutism

⇑ Facial hair

Acne

Supraclavicular fat pads

Poor wound healing

Reddish-purple abdominal striae

Thin skin and subcutaneous tissue

‘Moon face’

Red cheeks

‘Buffalo hump’

Weight gain

Bruises

Pendulous abdomen

Thin extremities with muscle atrophy

Factors to Consider When Initiating ICS with 1 or 2 Long-Acting Bronchodilators (BD) in COPD

- Strong Support
  - Hx hospitalization(s) for COPD exacerbations, despite long-acting BD maintenance
  - ≥ 2 moderate COPD exacerbations per year, despite long-acting BD maintenance
  - Blood eosinophils > 300 cells/mcL
  - Hx of, or concomitant, asthma

- Consider use
  - 1 moderate COPD exacerbation per year, despite long-acting BD maintenance
  - Blood eosinophils 100-300 cells/mcL

- Against use
  - Repeated pneumonia events*
  - Blood eosinophils < 100 cells/mcL
  - Hx mycobacterial infection

***Risks include: smokers, ≥ 55 years, BMI < 25 Kg/M^2, poor MRC dyspnea grade +/or severe airflow limitation, eos count < 2%**

Antiinflammatory Therapy in Stable COPD and Evidence Level (cont)

- PDE4 inhibitors
  - In patients with chronic bronchitis, severe to very severe COPD and Hx of exacerbations:
    1) Improve lung function and ↓ mod-severe exacerbations (A)
    2) Improve lung function and ↓ exacerbations in patients on fixed dose LABA/ICS combos (A)
  - Antibiotics
    - Long-term azithromycin and erythromycin ↓ exacerbations over one year (A)
    - Azithromycin is associated with ↑ incidence of bacterial resistance (A) and hearing test impairments (B)
  - Mucolytics
    - Regular use of N-acetylcysteine and carbocysteine ↓ risk of exacerbation in select populations (B)
  - Others
    - Simvistatin does not prevent COPD exacerbations in those without indications for statins (A)

Roflumilast (Daliresp®)

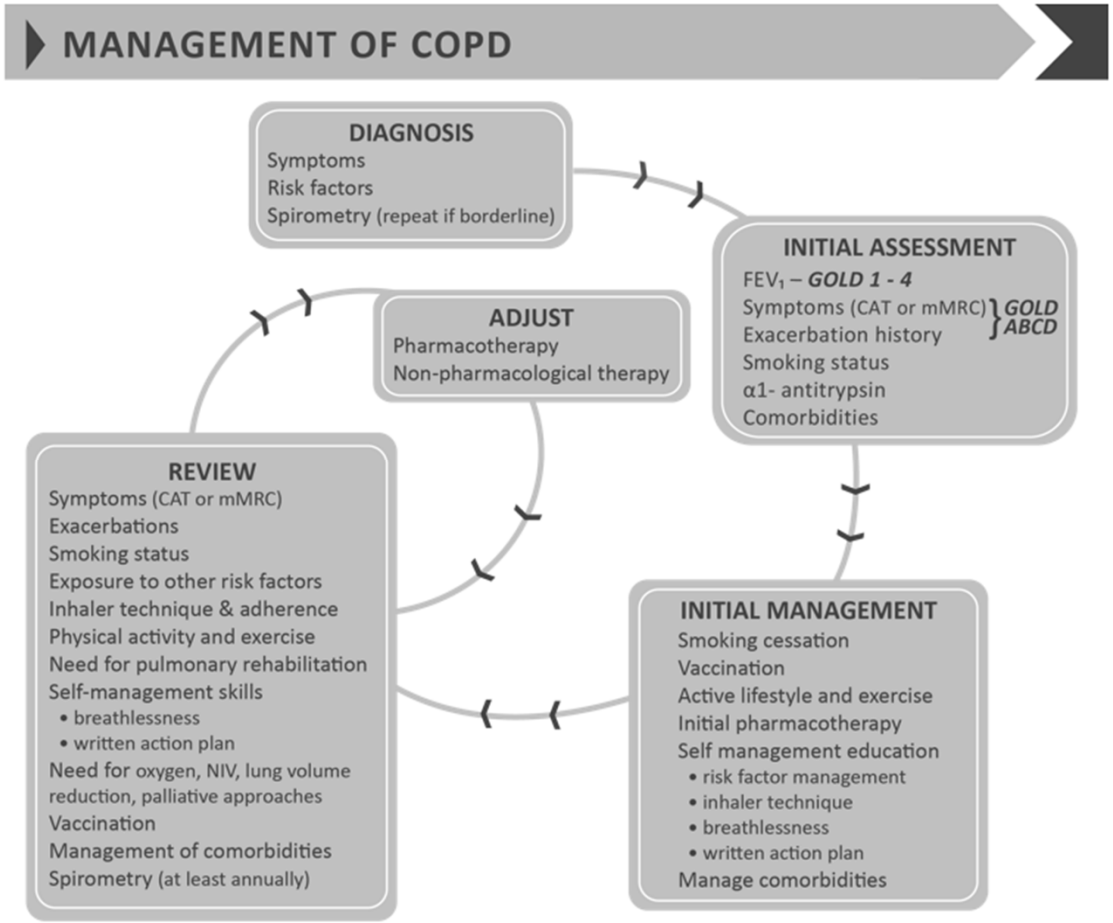
- (PDE)4 inhibitor
- 500 mcg tablet once daily, with or w/o food
- FDA approved to ↓ risk of COPD exacerbations in severe and very severe COPD associated with chronic bronchitis and Hx exacerbations (GOLD 3 & 4)
- Medication guide
  - Mental health problems including suicidal thoughts and behavior
  - GI Symptoms and Weight loss (ave. 2Kg)
- Use with CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP1A2 will ↑ systemic exposure and may ↑ ADRs (erythromycin, ketoconazole, fluvoxamine, cimetidine)
- Determinants of response: Prior hospitalization for exacerbation, greater exacerbation frequency, ↑ blood eosinophils.

Macrolides and Prevention of COPD Exacerbations

- Albert RK. NEJM 2011; 365(8): 689-98
  - azithromycin 250 mg qd vs placebo > 1 year
  - ↓freq. of exacerbations (1.48 vs. 1.83 per pt yr, p = 0.01)
  - ↑ QOL
  - ↑ hearing decrements (25% vs 20%, p = 0.04)
- ?? Risk of ↑ macrolide-resistance bacteria

Yamaya M et al: Eur Respir J 2012; 40: 485-494

Management of COPD



Initial Pharmacological Treatment

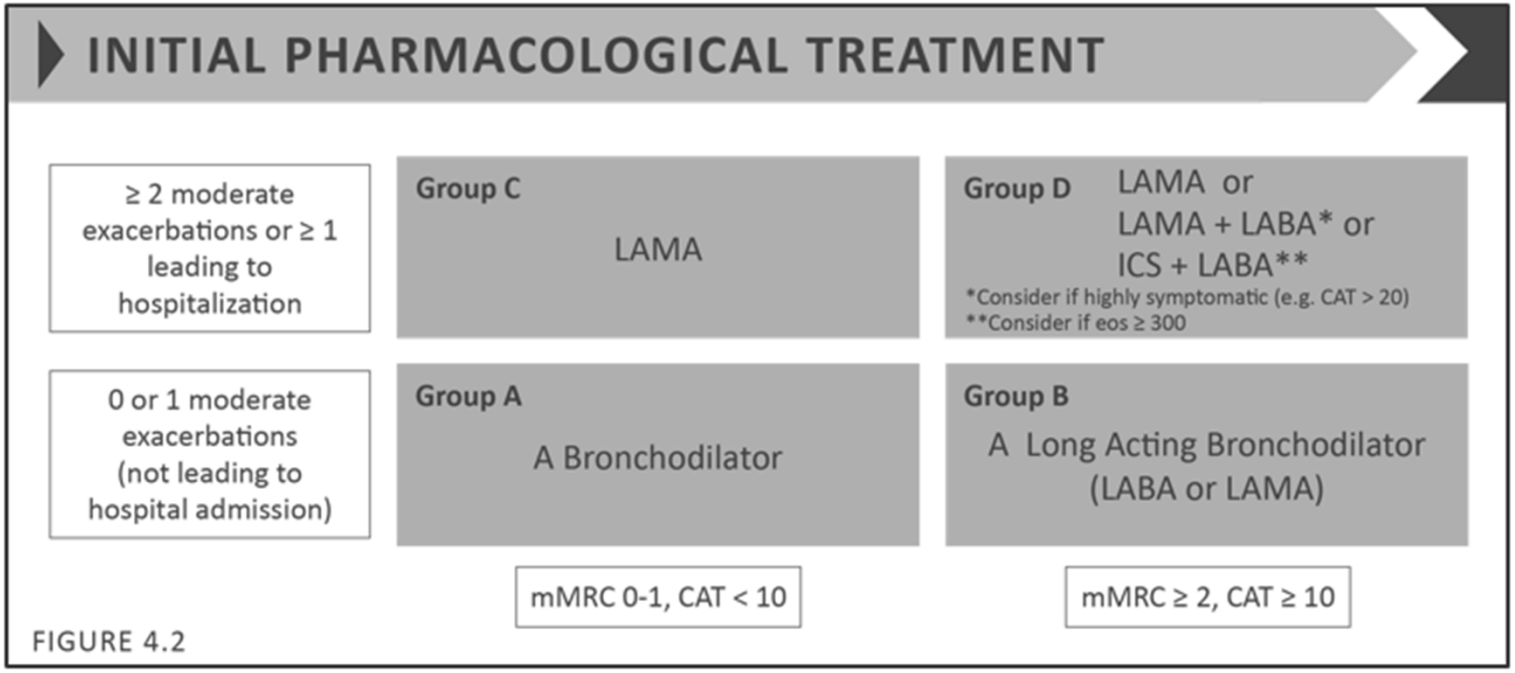


FIGURE 4.2

Management Cycle

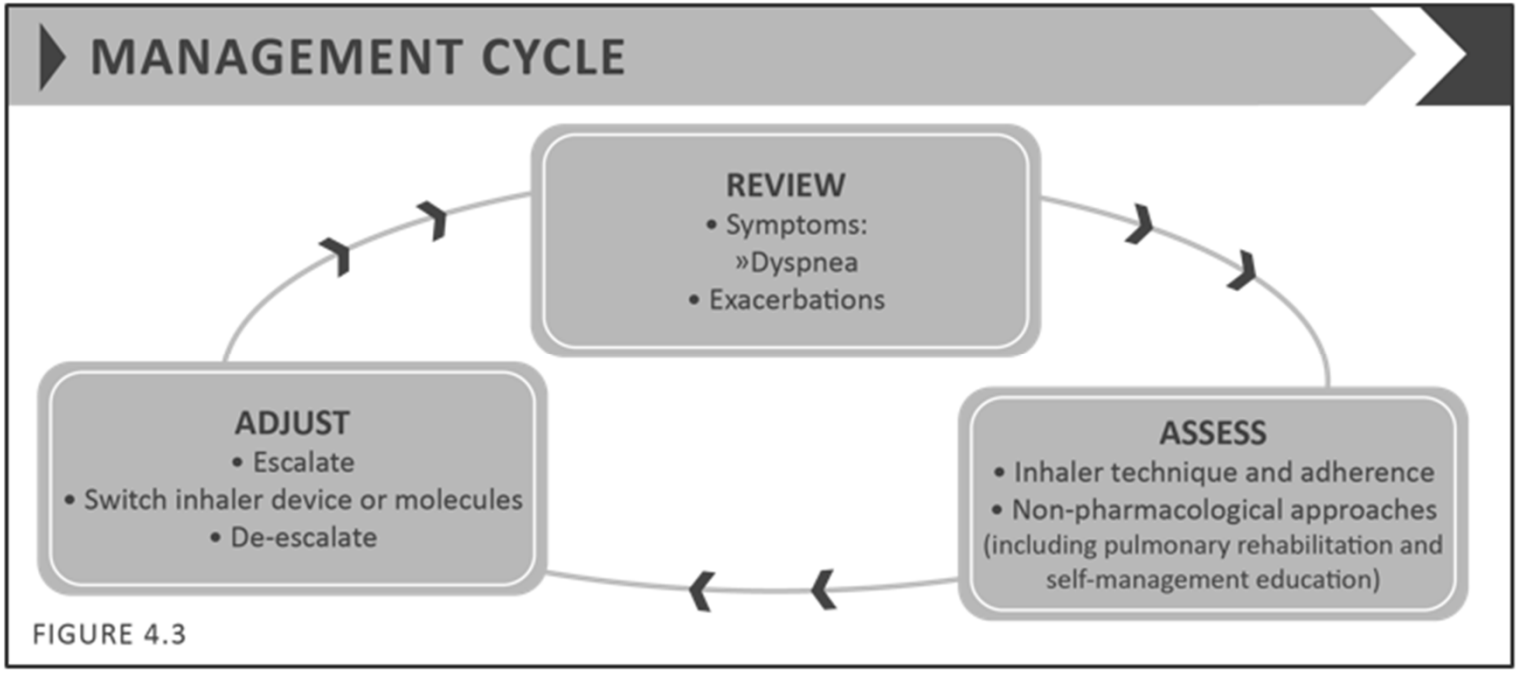


FIGURE 4.3

Follow-Up Pharmacological Treatment

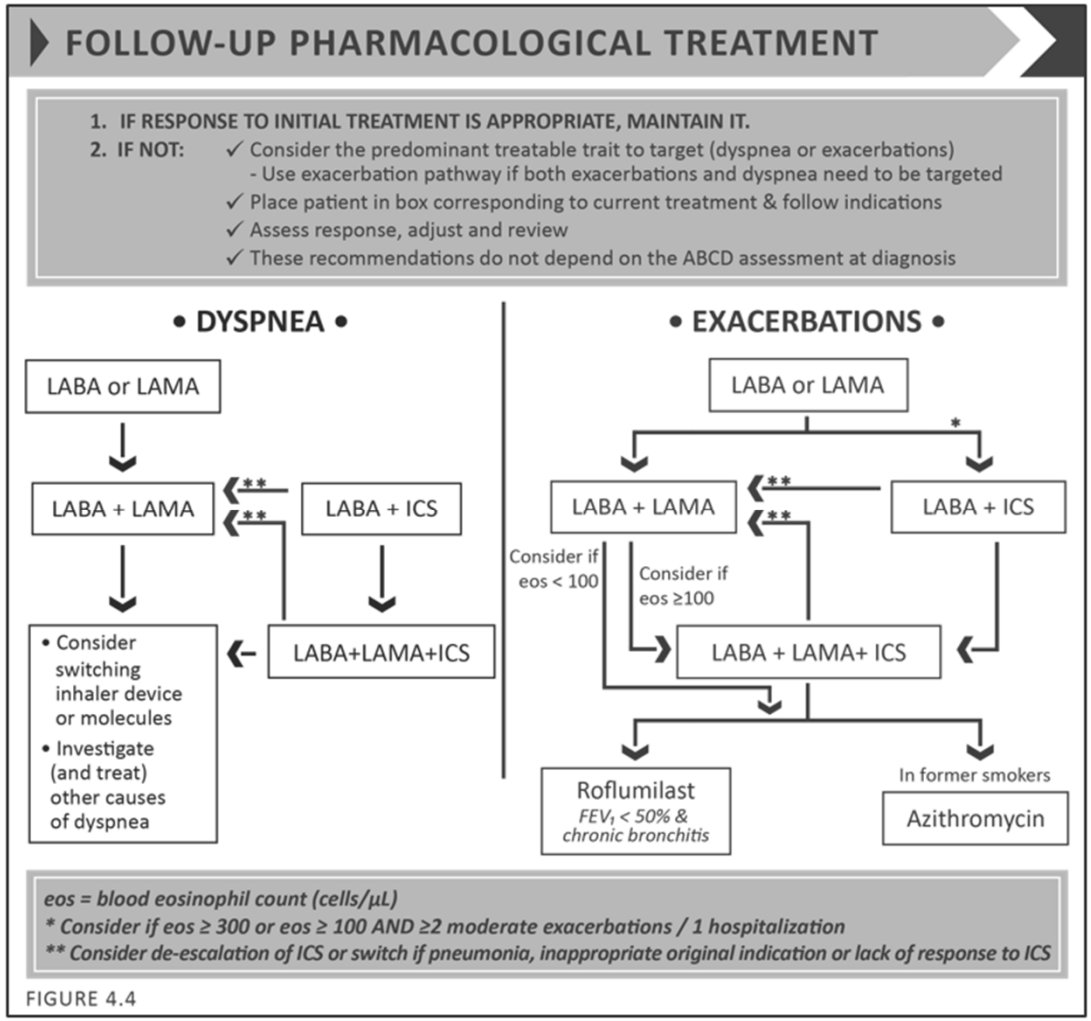


FIGURE 4.4

Prescription of Supplemental Oxygen to COPD Patients

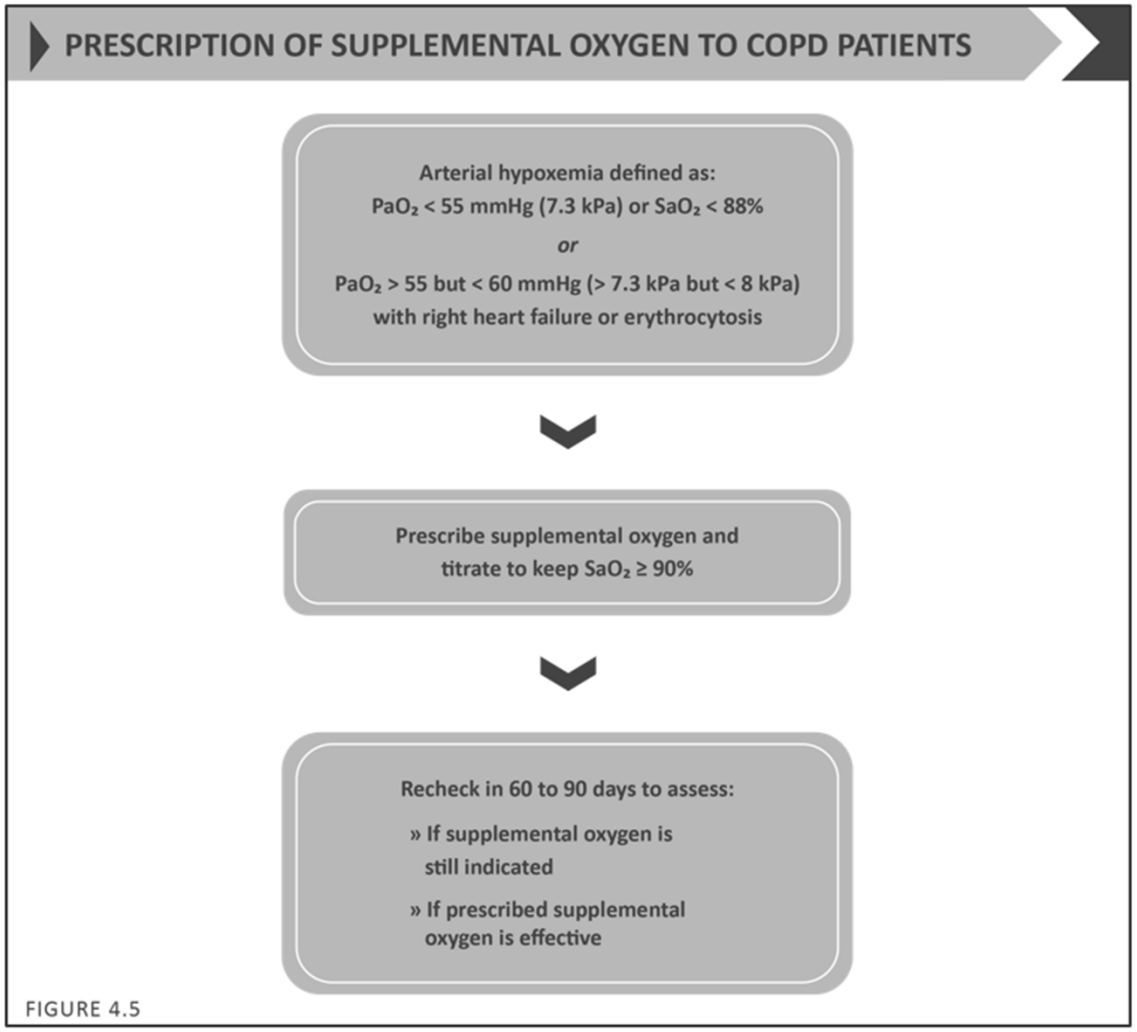
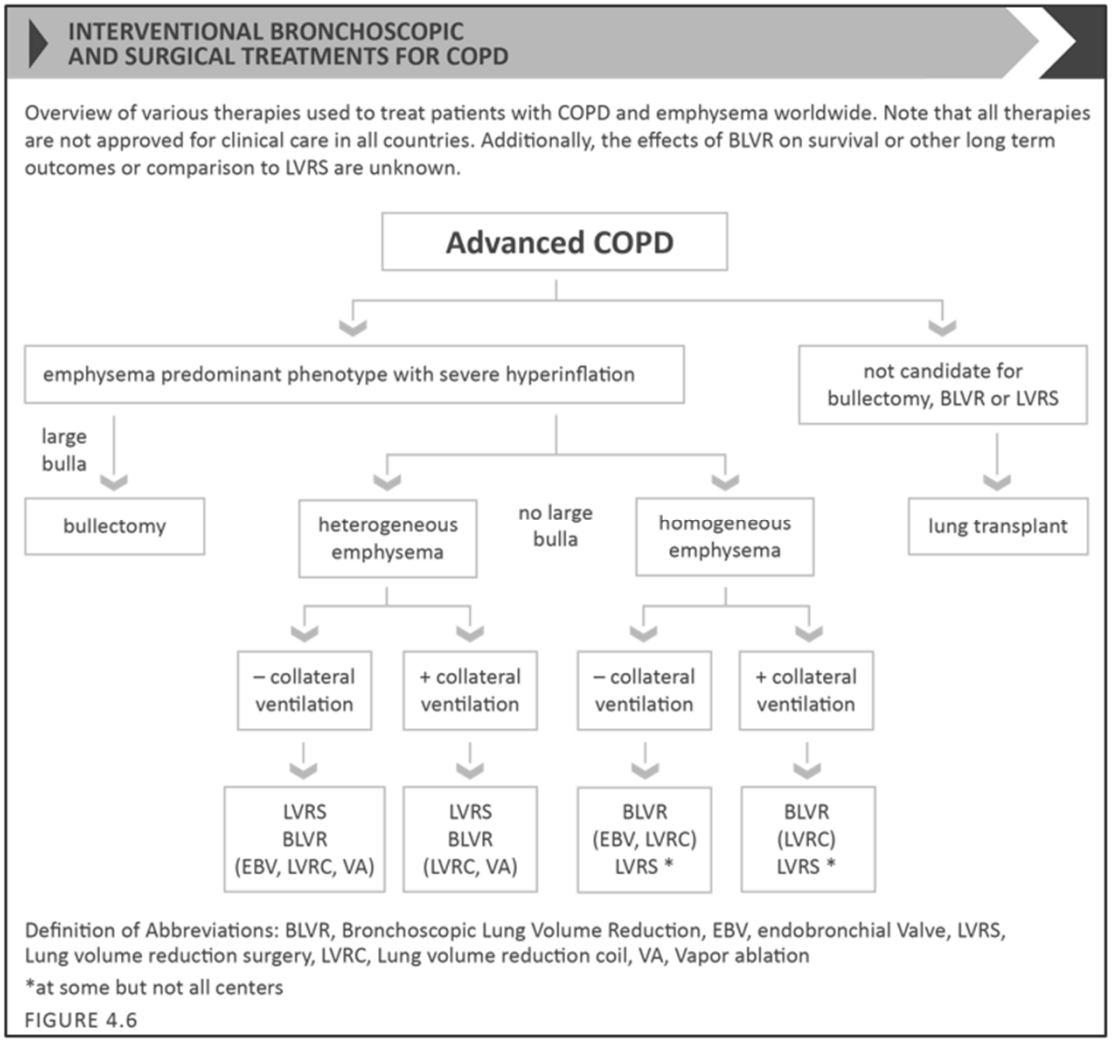


FIGURE 4.5

Interventional Bronchoscopic and Surgical Treatments for COPD



Opportunities in the Care of the Patient with COPD

- Self-management strategies (education & coaching)
- Smoking cessation strategies
- Up-to-date immunizations
- Optimal medication regimens
- Reinforcement of adherence
- Use of inhalation devices
- Provision of homecare equipment (oxygen, nebulizers, hospital beds, etc.)
- Implementation of spirometry in primary care and pharmacy settings
- Management of comorbidities
- Palliative strategies & advance care directives (Group D)
- “Event-driven” and phenotype-specific algorithms