COPD: A Clinical Review for Outpatient Practice

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Disclosures

I have no financial relationships of any type to disclose.

Definition of COPD

Chronic Obstructive Pulmonary Disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases

Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: Executive Summary—Updated 2003. Bethesda, Md: NHLBI; NIH; 2003.

Objectives

- Definition, background and epidemiology
- Testing
- Severity grading and prognosis
- Prevention
- Treatment – stable and exacerbations

GOLD

- **Global Initiative for Chronic Obstructive Lung Disease**
  - **created in 1998 in collaboration with the NHLBI to increase awareness of COPD among health professionals, public health authorities, and the general public**
  - **aim is to improve prevention and management through a concerted world-wide effort**
  - **prepares scientific reports on COPD, encourages dissemination and adoption of the reports and promotes international collaboration on COPD research**
  - **educational tools that can be adopted for use in a local medical community**

Resources

- GOLD Guidelines: www.goldcopd.org (Evidence-based guidelines updated Jan, 2014)
- American College of Physicians:
  - Clinical Guideline –
    - Diagnosis and Management of Stable COPD: A Clinical Practice Guideline Update from the ACP, ACCP, ATS and ERS
    - Ann Intern Med. 2011; 155:179-191

Resources

- Up To Date References:

- Erbland, M.L. Role of systemic glucocorticoid therapy in COPD In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
- Rennard, S.I. Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
- Ferguson, G.T.Management of stable chronic obstructive pulmonary disease. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
- Stoller, J.K. Management of acute exacerbations of chronic obstructive pulmonary disease. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
- Weiss, S.T.Chronic obstructive pulmonary disease: Prognostic factors and comorbid conditions. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.

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Diagnosis of COPD

- Clinically based on[1,2]:
  - Risk factors (eg, smoking history)
  - Age
  - Symptoms
  - Persistent airflow obstruction (spirometry)
    - Postbronchodilator FEV_1 <80% predicted
    - FEV_1/FVC <70%

1. American Thoracic Society. *Am J Respir Crit Care Med.* 1995;152(5 pt 2):S77-S121.
2. *Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: Executive Summary—Updated 2003.* Bethesda, Md: NHLBI; NIH; 2003.

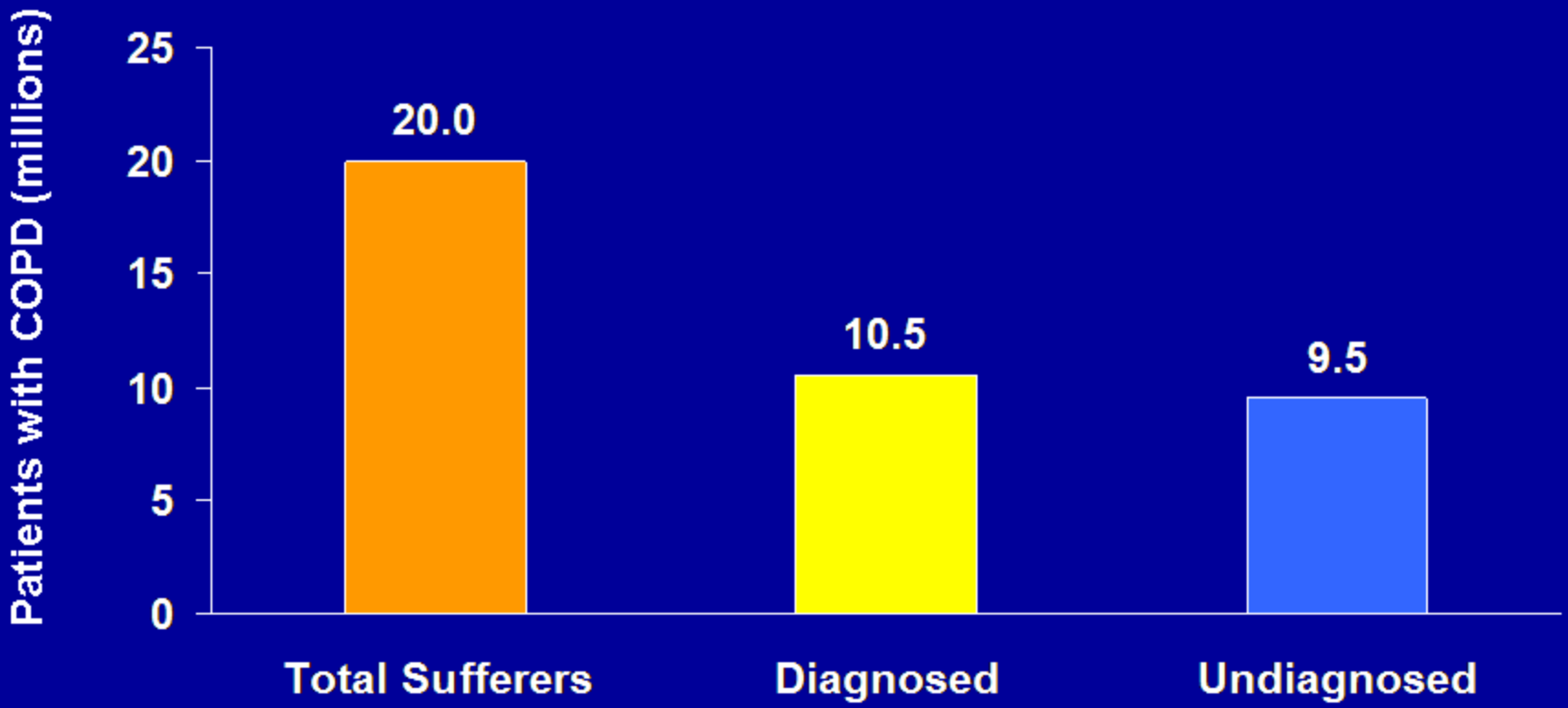
Facts About COPD

- It is the third-ranked cause of death in the United States, killing more than 120,000 individuals each year (after cardiovascular disease and malignancies).
- The burden of COPD is underestimated because it is not usually recognized and diagnosed until it is clinically apparent and moderately advanced.
- Prevalence, morbidity and mortality vary appreciably across countries but in all countries where data are available, COPD is a significant health problem in both men and women.
- The burden of COPD is projected to increase in coming decades due to continued exposure to COPD risk factors and the aging of the world's population.
- It is an important disease in developing countries in which the use of biomass fuels for cooking is common.

Facts About COPD

- Economic Burden:
  - US: direct costs = $29.5 billion/indirect costs = $20.4 billion
  - Exacerbations account for the majority of the burden of the disease
  - Costs increase with disease severity
  - Underestimate the staggering costs of personal caregiving by a family member

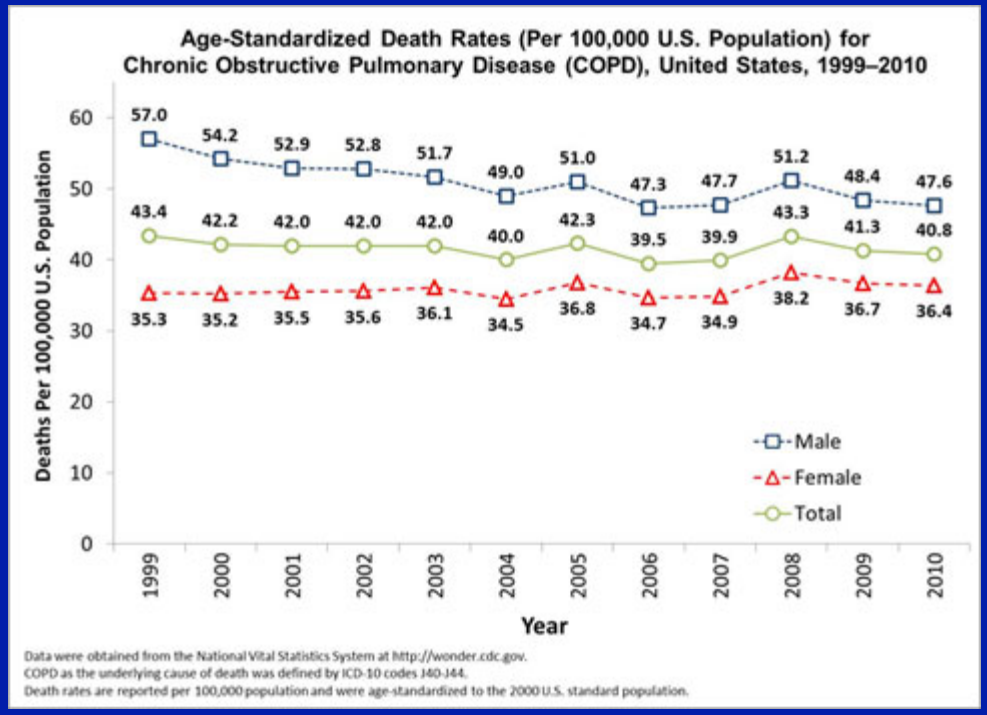
Prevalence of COPD in the US



Among the 10.5 million patients who have been diagnosed, research shows that nearly 40% are not being treated with prescription medications.

Data on file (analysis of data from NHANES III, 1988-1994), GlaxoSmithKline.
Mannino et al. *MMWR*. 2002;51(SS-6):1-16.

Death Rates from COPD



Although death rates for COPD have declined among US men between 1999 (57.0 per 100,000) and 2010 (47.6 per 100,000) in the United States, there has been no significant change among death rates in women (35.3 per 100,000 in 1999 and 36.4 per 100,000 in 2010).

Risk Factors for COPD

Genes

Exposure to particles

- Tobacco smoke
- Occupational dusts, organic and inorganic
- Indoor air pollution from heating and cooking with biomass in poorly ventilated dwellings
- Outdoor air pollution

Lung growth and development

Gender

Age

Respiratory infections

Socioeconomic status

Asthma/Bronchial hyperreactivity

Chronic Bronchitis

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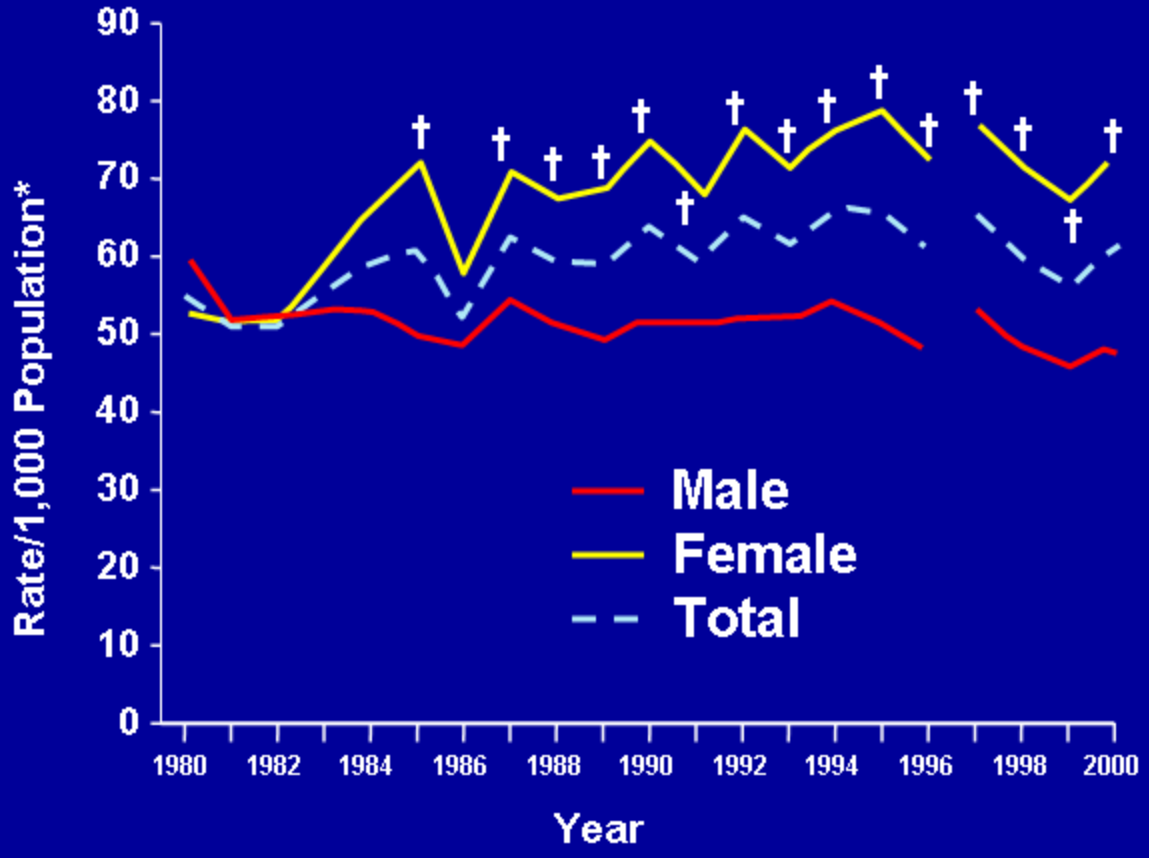
Facts About COPD

- Cigarette smoking is the primary cause of COPD.
- In the US 47.2 million people (28% of men and 23% of women) smoke.
- The WHO estimates 1.1 billion smokers worldwide, increasing to 1.6 billion by 2025. In low- and middle-income countries, rates are increasing at an alarming rate.

Prevalence of COPD in the US



- Since 1987, the prevalence of COPD among women has been significantly higher than that among men

*Age-adjusted to 2000 US population.
†Represents a statistically significant difference from rate among males.

Mannino et al. *MMWR*. 2002;51(SS-6):1-16.

COPD

- **Becoming a women's health issue:**
  - **In North America, the patient with COPD is more commonly a woman.**
  - **Women are more likely to develop COPD at a younger age.**
  - **Women have a higher likelihood of developing COPD with less tobacco smoke exposure (Smaller airway caliber, smaller lung volumes – increased concentration of noxious substances for the same amount of exposure; increased tendency toward airflow obstruction).**

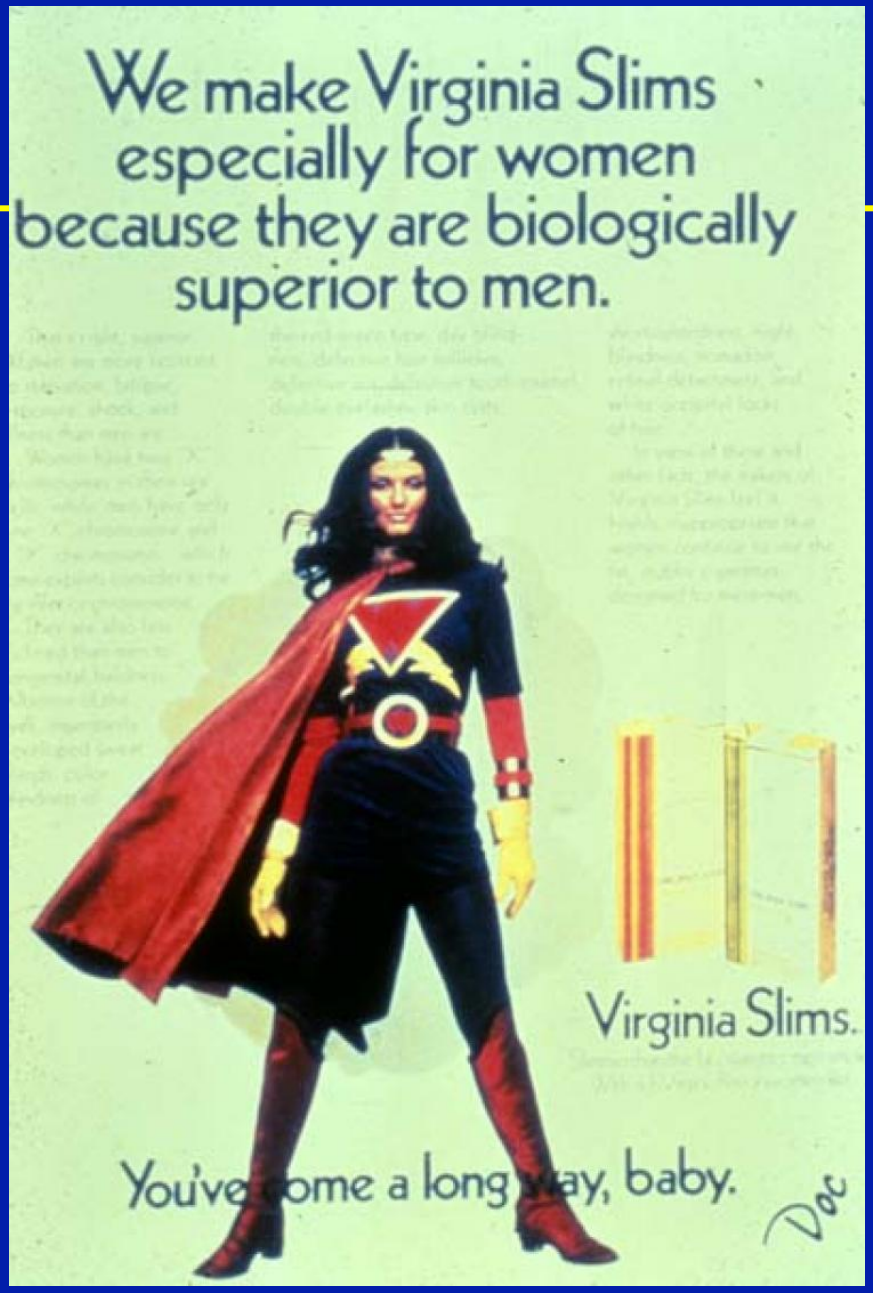
COPD

Severity of COPD	Smoking History In Pack Years	
	Women	Men
Mild	35.1	60.1
Moderate	54.8	65.9
Severe	58.5	67.4

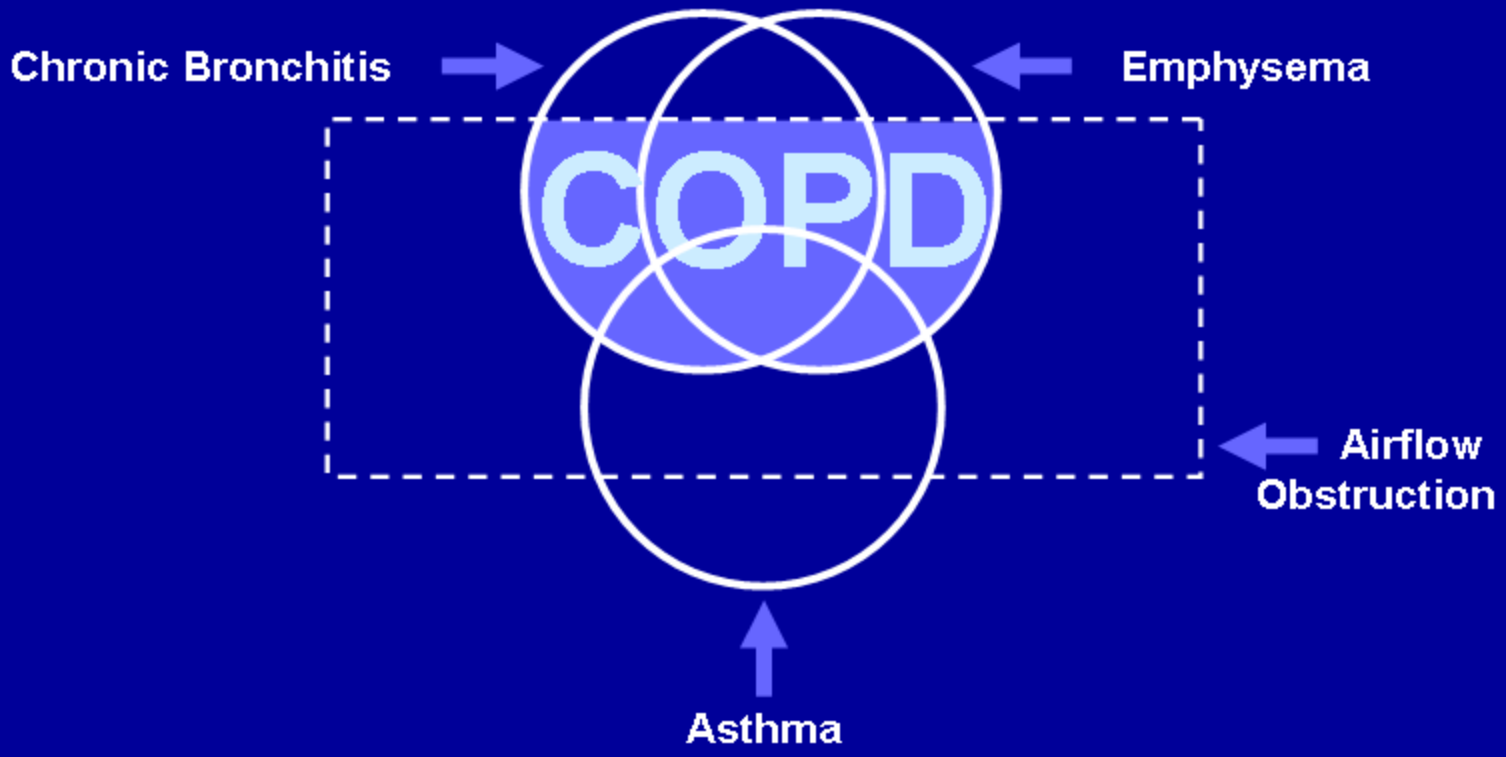
Carter R, Nicotra B, Huber G.Chest 1994;106:1730–9.

Tobacco Use

- **Women have a harder time remaining smoke-free in the long term.**
  - **One theory is that there are gender differences with regard to the physical response to nicotine. Women may have greater withdrawal symptoms.** ***(Pomerleau, et al, 1991; Br J Addict; 86:527-31)***
  - **Women might be more sensitive to lack of support from their partners.**
  - **Women may be more sensitive to social cues to smoke.** ***(Cook, et al, 1999, Thorax, 54: 357-66)***


We make Virginia Slims especially for women because they are biologically superior to men.
Virginia Slims.
You've come a long way, baby.
Doc

Spectrum of COPD[1]



Approximately 80% of patients with COPD have associated chronic bronchitis[2]

1. Adapted from American Thoracic Society. *Am J Respir Crit Care Med*. 1995;152(5 pt 2):S77-S121.
2. National Center for Health Statistics. National Health Interview Survey, 1997-2001.

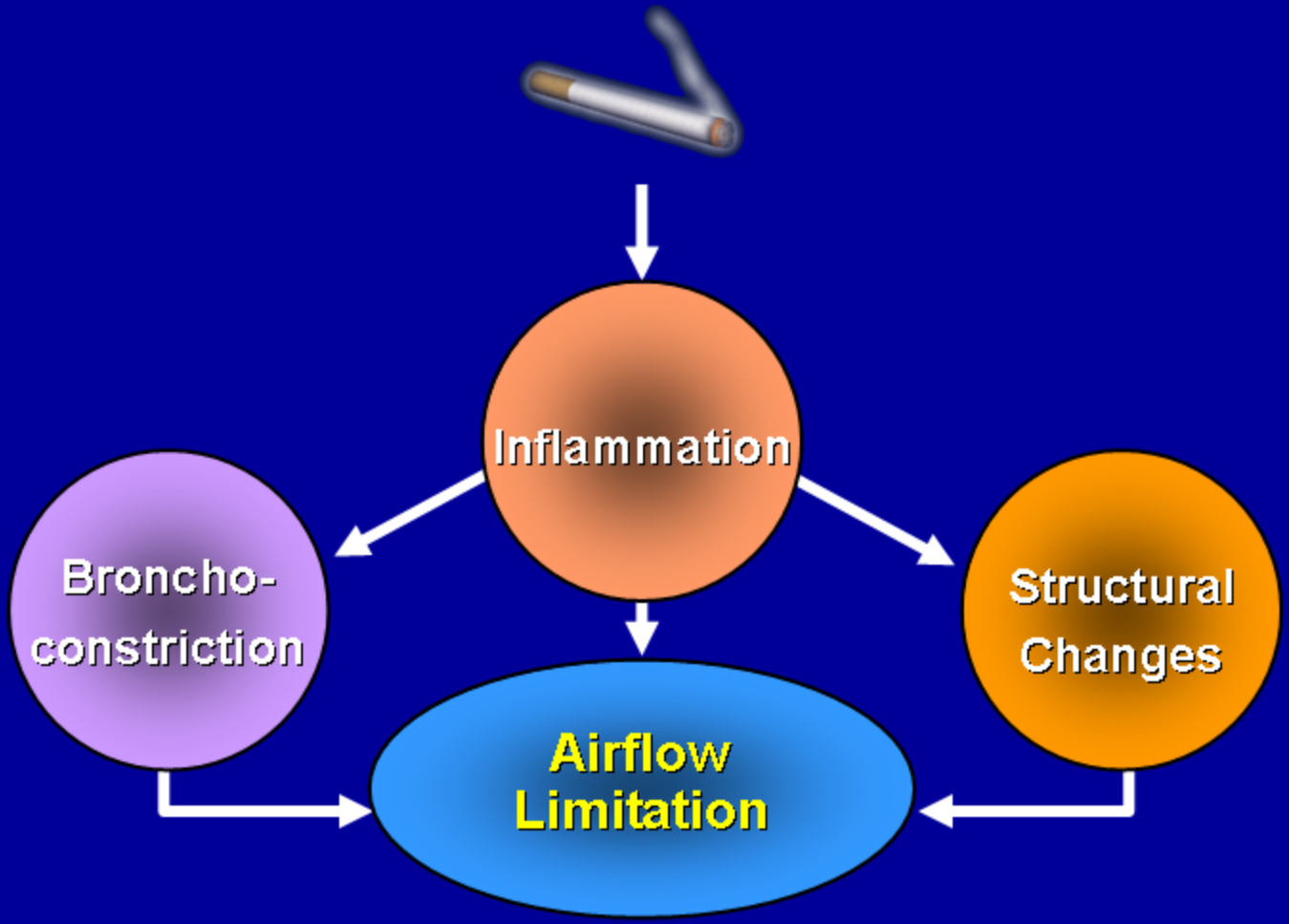
Airflow Obstruction

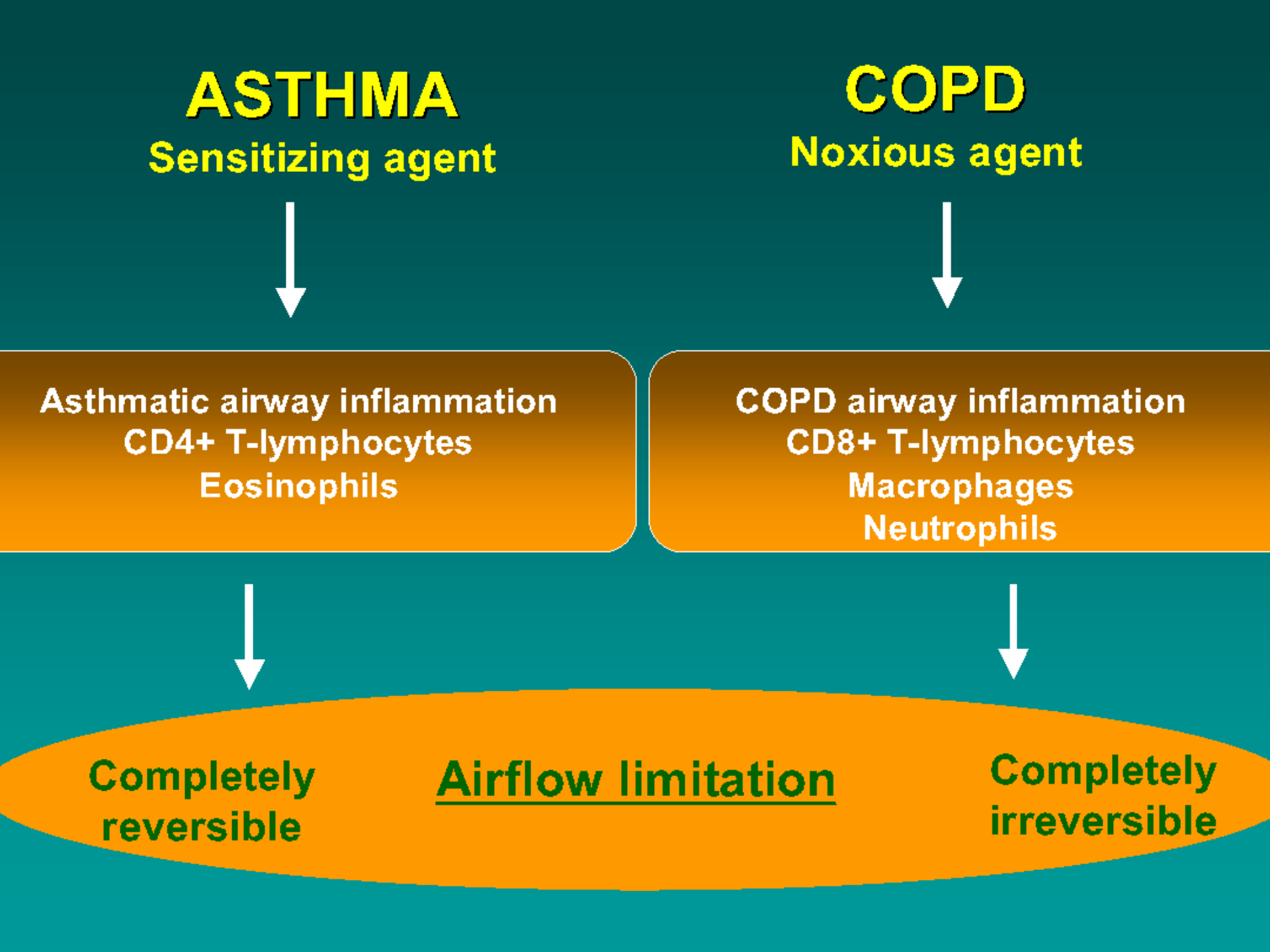
- Irreversible
  - Fibrosis and narrowing of the airways
  - Loss of elastic recoil due to alveolar destruction
  - Destruction of alveolar support that maintains patency of small airways
- Reversible*
  - Inflammatory cells, mucus, and plasma exudate in bronchi
  - Smooth muscle contraction in peripheral and central airways
- Differentiating COPD from other obstructive lung diseases can be difficult because many patients with COPD have a reversible component to their disease

*Reversible defined as ≥ 12% and 200-mL increase in FEV_1 following inhalation of albuterol.

Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: Executive Summary—Updated 2003. Bethesda, Md: NHLBI; NIH; 2003.

COPD Is a Complex Disease




ASTHMA
Sensitizing agent
COPD
Noxious agent
Asthmatic airway inflammation
CD4+ T-lymphocytes
Eosinophils
COPD airway inflammation
CD8+ T-lymphocytes
Macrophages
Neutrophils
Completely reversible
Airflow limitation
Completely irreversible

Bronchoconstriction in COPD

- May be partially reversible in many patients with COPD
- Airway hyperresponsiveness may develop after exposure to tobacco smoke or other environmental insults
- Chronic inflammation is associated with increase in amount of smooth muscle in airway wall

Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop Report. Bethesda, Md: NHLBI; NIH; March 2001. NIH publication 2701A.

Structural Changes* in COPD

- Epithelial changes
  - Ciliary dysfunction
  - Increase in mucus-secreting cells
- Fibrosis of the small airways
- Destruction of alveolar walls
  - Reduction in area for gas exchange
  - Loss of elastic recoil (emphysema)
- Vascular changes may lead to pulmonary hypertension

*** No medication has been shown to reverse the structural changes associated with COPD.**

Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop Report. Bethesda, Md: NHLBI; NIH; March 2001. NIH publication 2701A.

Spirometry

- Why do it? -
  - **Spirometry is needed to make a firm diagnosis of COPD.**
  - **Together with the presence of symptoms, spirometry helps stage COPD severity and can be a guide to specific treatment steps.**
  - **The lower the %predicted FEV1, the worse the prognosis.**
  - **FEV1 declines over time and faster in COPD than in healthy subjects. Spirometry can be used to monitor disease progression (every 12 months).**
  - **FEV1 < 1 liter may indicate need for supplemental O2**

ABG

- Measurement of arterial blood gas tension should be considered in all patients with FEV_1 < 40% predicted or clinical signs suggestive of respiratory failure or right heart failure.

Peak Flow Measurement

- Conflicting data on the use of PEF for monitoring COPD
  - Many patient with COPD have associated parenchymal change, which produces a “tethering” effect on the bronchial tubes
  - This tethering will limit the variability in the PEF measurement, rendering it insensitive
  - Patients with COPD should not be reassured by a stable PEF if their clinical symptoms are worsening

Factors Determining Severity Of COPD

- Severity of symptoms
- Severity of airflow limitation
- Frequency and severity of exacerbations
- Presence of complications of COPD
- Presence of respiratory insufficiency
- Comorbidity
- General health status
- Number of medications needed to manage the disease

Classification by Severity

GOLD classification in patients with FEV1/ FVC <70%:

I: Mild	FEV1 80%
II: Moderate	FEV1 50-80%
III: Severe	FEV1 30-50%
IV: Very Severe	FEV1 <30%

BODE Staging

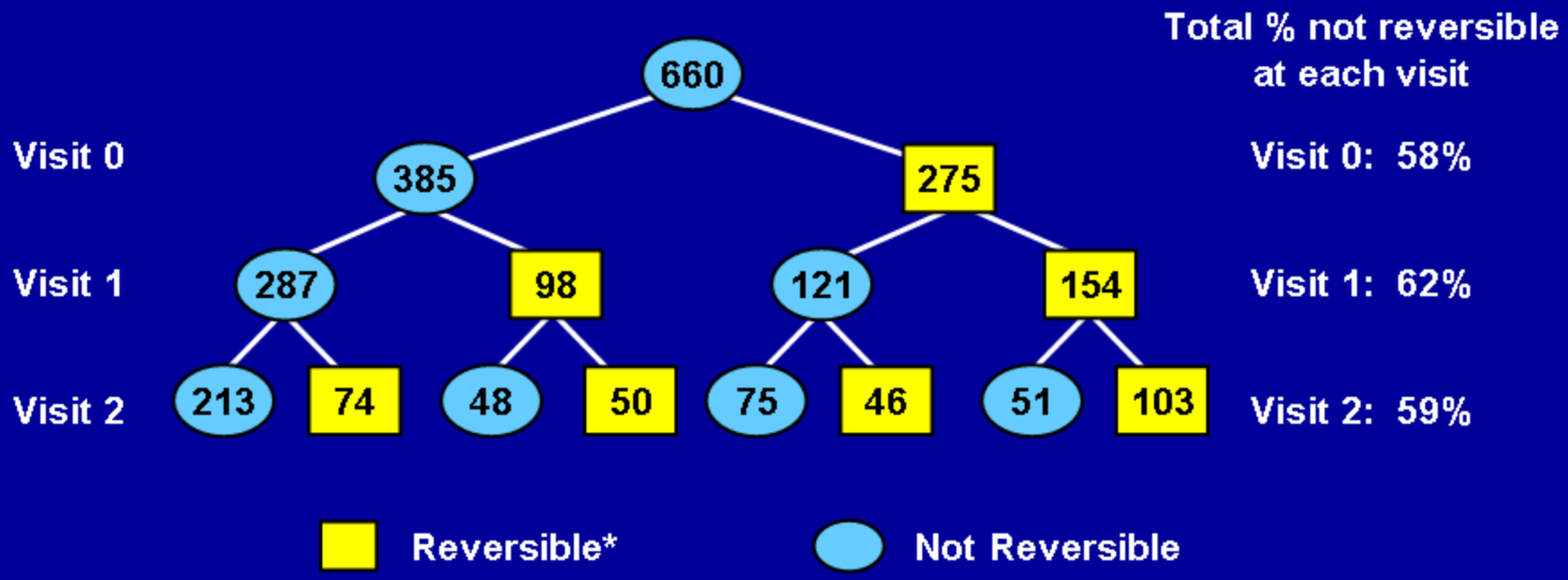
Celli BR, Cote CG, Marin JM, et. al.. *N Engl J Med*. 2004 Mar 4;350(10):1005-12.

- **BODE** stands for **B**ody mass index, airflow **O**bstruction, **D**yspnea and **E**xercise capacity
- **More Global assessment tool for establishing prognosis with COPD**
  - **6 minute walk distance, MMRC Dyspnea score and BMI in addition to spirometry**
- **Higher score = increased mortality at 4 years**

BODE Staging

- BODE calculator may be found on Up to Date
- Four year survival:
- 0-2 Points: 80%
- 3-4 Points: 67%
- 5-6 Points: 57%
- 7-10 Points: 18%
-

Changes in Responder Classification After Albuterol and Ipratropium Bromide



Numbers in circles refer to the total classified as positive responders at that visit and those in squares are the nonresponders on the same occasion.

* Reversible defined as ≥ 12% and 200-mL increase in FEV_1 following 4 puffs (360 mcg) of albuterol.

Calverley et al. *Thorax*. 2003;58:659-664.

Objectives of COPD Management

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat exacerbations
- Prevent and treat complications
- Reduce mortality
- Minimize side effects from treatment

Reduce Risk Factors

- Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals and air pollutants are important goals to prevent the onset and progression of COPD.
- Smoking cessation is the single most effective (and cost-effective) intervention to reduce the risk of developing COPD and preventing its progression.

Reduce Risk Factors

- Brief tobacco dependence treatment is effective and every tobacco user should be offered at least this treatment at every visit to a health care provider.
- Counseling by a physician results in significant increases in quit rates compared with self-initiated strategies.
- “Dose/response relationship” = increased time/ intensity of counseling leads to greater quit rates
- Practical counseling
- Social support as part of treatment
- Social support outside of treatment

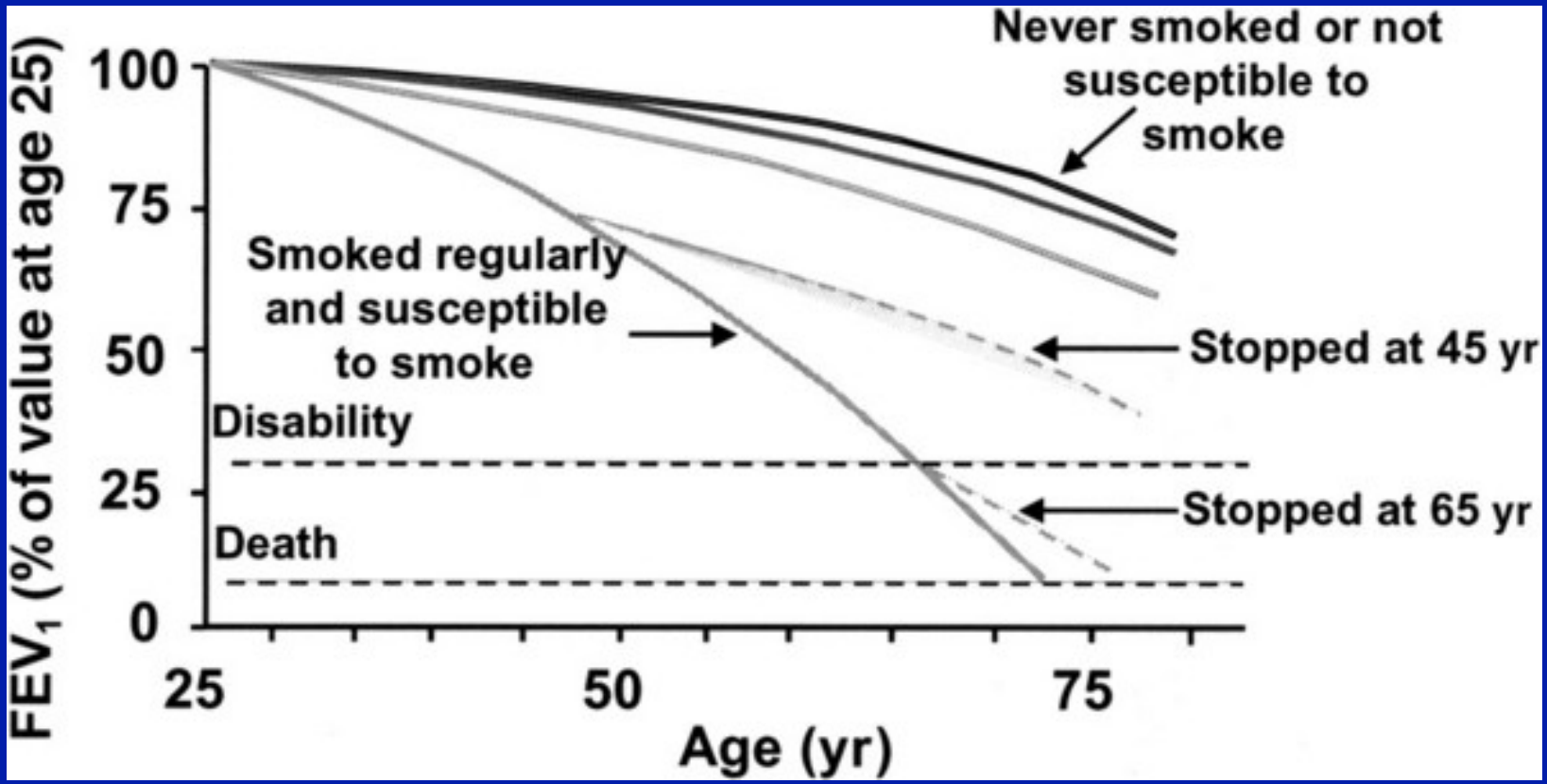
Reduce Risk Factors

- At least one smoking cessation pharmacotherapy should be added to counseling if necessary and in the absence of contraindications.
  - Varenicline
  - Bupropion
  - Nicotine gum, inhaler, nasal spray and patch

Smoking Cessation

- ASK — systematically identify tobacco users at each visit
- ADVISE — strongly urge all tobacco users to quit
- ASSESS — determine willingness to make a quit attempt
- ASSIST — aid the patient in quitting
- ARRANGE — schedule followup contact

Smoking Cessation



Fletcher C., Peto R.: *British Medical Journal;* 1. 1645-1648.1977

Manage Stable COPD

- None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease. Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications.
- The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease.

Bronchodilators

- Short acting beta-2 agonists (SABA)
  - *Albuterol, terbutaline (Brethine), levalbuterol (Xopenex), fenoterol (Berotec)*
- Long-acting beta-2 agonists (LABA)
  - *Formoterol (Foradil), salmeterol (Serevent)*
- Short-acting anticholinergics (SAMA)
  - *Ipratropium (Atrovent)*
- Long-acting anticholinergics (LAMA)
  - *Aclidinium (Tudorza), tiotropium (Spiriva)*
- Combo short-acting
  - *Fenoterol/ipratropium (Berodual), albuterol/ipratropium (Combivent)*
- Combo long-acting (investigational)
  - *Vilanterol/umeclidinium (Anoro), indacterol/glycopurronium (Ultibro Breezhaler)*
- Methylxanthines
  - *Aminophylline, theophylline*

Bronchodilators

- Inhaled therapy is preferred.
- The choice between beta$_2$-agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects.

Bronchodilators

- Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
- Regular treatment with long-acting inhaled bronchodilators is more effective and convenient than treatment with short-acting bronchodilators, but more expensive.
- Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Bronchodilators - Benefits

- Regular and prn SABA improve FEV1 and symptoms
- Use of SABA in high doses prn in patients already treated with LABA is not supported by evidence and may be troubled by side effects.
- LABA significantly improve FEV1, dsypnea, QOL and exacerbation rate, but have no effect on mortality or rate of decline of lung function.
- Tiotropium reduces exacerbations and hospitalizations, improves symptoms and health status and improves the effectivness of pulmonary rehab. No benefit on the rate of decline of lung function.
- Tiotropium found superior to salmeterol in reducing exacerbations (small but significant difference).

Bronchodilators – Side Effects

- SABA/LABA – arrythmias, sleep disturbance, worsened GERD, anxiety, tremor

- SAMA/LAMA – dry mouth/mucous membranes, urinary retention, constipation

Inhaled Steroids

- Beclomethasone
- Budesonide
- Fluticasone

- Combination:
  - LABA/Inhaled Steroid:formoterol/budesonide (Symbicort), formoterol/mometasone (Dulera),salmeterol/fluticasone (Advair), vilanterol/fluticasone (Breo Ellipta)

Inhaled Steroids - Benefits

- Regular treatment with ICS improves symptoms, lung function and QOL and reduces the frequency of exacerbation in patients with FEV1 < 60% pred. ICS do not modify the long term decline of FEV1 or mortality.
- ICS/LABA combo more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD.
- Combination therapy may reduce mortality.
- Studies of triple therapy (ICS/LABA/LAMA) are limited and more data are needed.

Inhaled Steroids – Side Effects

- Oral candidiasis, hoarse voice, oral/throat irritation, skin bruising.

- Association with an increased risk of pneumonia. Singh, S et al Archives of Internal Medicine 2009; 169(3): 219-229. Meta-analysis that found that among patients with COPD, inhaled corticosteroid use for at least 24 weeks is associated with a significantly increased risk of serious pneumonia, without a significantly increased risk of death.

- Long term treatment with triamcinolone is associated with an increased risk of reduced bone density (Scanlon, PD et al AJRCCM 2004 Dec 15;170(12):1302-9).but evidence with other ICS is controversial. No clear effect on bone density and fracture rate with budesonide. Treatment over three year period with high dose fluticasone was not associated with decreased bone density.

Systemic Steroids

- Chronic treatment with systemic glucocorticoids should be avoided because of an unfavorable benefit-to-risk ratio.

Phosphodiesterase-4 Inhibitors

- Roflumilast (*Daliresp*)
  - Goal is reduction of inflammation by inhibition of the breakdown of intracellular cAMP.
  - Used as an add-on to regular therapy
  - No direct bronchodilation, though it has been shown to improve FEV1 in patients treated with salmeterol or tiotropium
  - Reduces moderate and severe exacerbations by 15-20% in patients with chronic bronchitis, severe to very severe COPD and history of exacerbations
  - Side effects: nausea, reduced appetite, abdominal pain, diarrhea, sleep disturbance, headache

Special Considerations in Patients with Severe Suppurative Disease

- Aspergillus bronchitis or airway colonization *Chest.* 2006;130(1):222-226 –
  - an uncommon, difficult-to-diagnose chronic exacerbant (bronchoscopy often needed)
  - Patients affected will respond to therapy rapidly
- Chronic macrolide therapy Int J Chron Obstruct Pulmon Dis. 2008 September; 3(3): 331–350.
  - Select population, failing maximal medical therapy;

Supplemental Oxygen

- The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival.
- Indications:
  - PaO2 at or below 55 mmHg or saturation at or below 88% or
  - PaO2 55-60 or saturation less than 90% if pulmonary hypertension, cor pulmonale, polycythemia

Education, Exercise and Pulmonary Rehabilitation

- All COPD patients benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue.

Education, Exercise and Pulmonary Rehabilitation

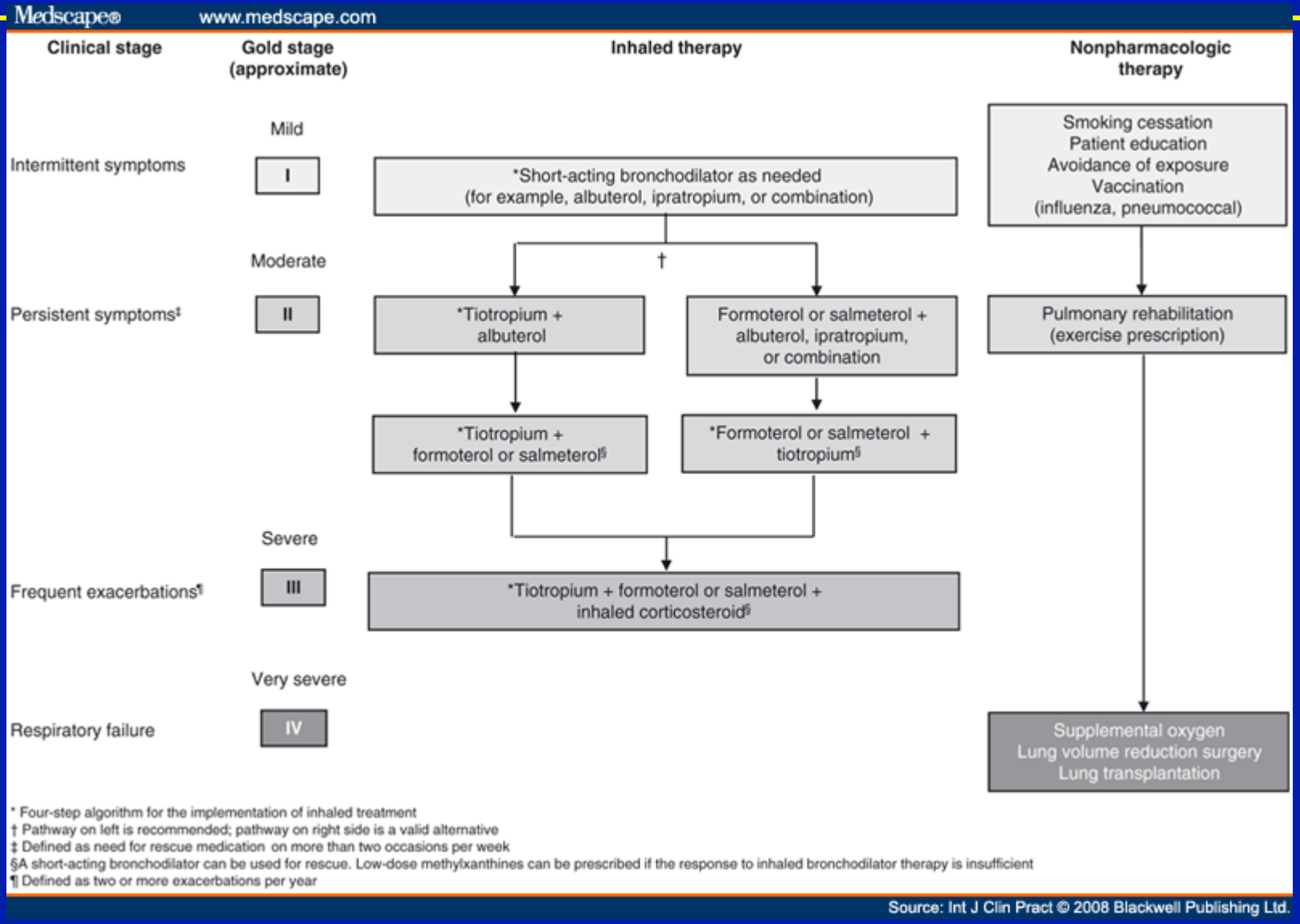
- Emphasizing proper technique with MDI use
- Education regarding medications
- Breathing techniques aimed at decreasing dyspnea, increasing exercise tolerance
- Nutritional advice
- Training - learning how to exercise in a monitored environment
- Smoking cessation
- Support network

A 15 minute office visit is not enough

Education, Exercise and Pulmonary Rehabilitation

- **Griffiths, et al. Lancet 2000; 3555:362-368**
  - **RCT, 81 patients with COPD (FEV1 < 60% predicted)**
  - **multidisciplinary rehab program (6 weeks occupational, physical, nutritional therapy) or usual outpatient therapy**
  - **no difference in hospitalization rates over the 1 year follow-up period**
  - **patients in the rehab group had a shorter length of stay if hospitalized**
  - **rehab group had an improved 10 minute walk and St. George's questionnaire, reduced need for rescue medications**

COPD Treatment Algorithm



Treatment of Acute Exacerbations of COPD

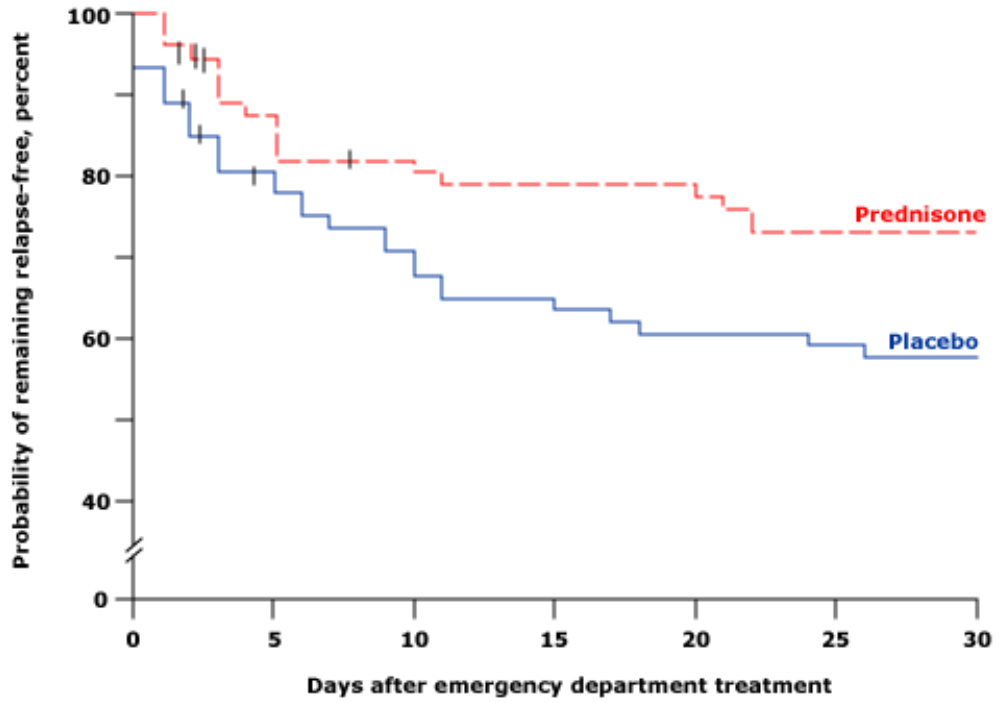
- Bronchodilators
  - increase the dose and/or frequency of existing bronchodilator therapy
  - add anticholinergics if not already used

Treatment of Acute Exacerbations of COPD

- Glucocorticoids
  - if baseline FEV1 < 50% predicted, consideration should be given to steroid taper
  - steroids up-regulate beta agonist receptors in the lungs, hence improving their efficacy
  - hasten recovery, improve lung function and hypoxemia; reduce risk of treatment failure and hospital stay
  - Recent data indicate that 40 mg of prednisone daily for 5 days is sufficient; however, the optimal dosing strategy remains controversial. JAMA 2013; 309(21) 2223-31

Treatment of Acute Exacerbations of COPD

Kaplan-Meier estimates of the probability of remaining relapse-free at 30 days for outpatients with acute exacerbations of COPD treated with prednisone or placebo



Tick marks represent censored data. p=0.04 by the log-rank test.

Data from: N Engl J Med 2003; 348:2623.

UpToDate®

Treatment of Acute Exacerbations

- Antibiotics
  - Moderate or worse COPD patients are chronically colonized with respiratory pathogens. Acute exacerbations of chronic bronchitis have been linked closely to these pathogens, most likely because of the decreased epithelial and subepithelial integrity of the airways.

  Evidence supports use of antibiotics during exacerbation if patient exhibits:
    - Increase in dyspnea, sputum volume and sputum purulence (all three, or two if sputum purulence is included)
    - Requirement for mechanical ventilation
    - 5-10 days

Treatment of Acute Exacerbations of COPD

- Antibiotics
  - Macrolide antibiotics have a demonstrated anti-inflammatory benefit exclusive of their anti-microbial effect that may help to hasten recovery from exacerbations.
  - Consider gram negative coverage for patients with severe airflow obstruction, frequent exacerbations and/or exacerbations requiring mechanical ventilation.

Treatment of Acute Exacerbations of COPD

- **Decision to admit**
  - **marked increase in intensity of symptoms**
  - **severe background COPD**
  - **onset of new physical signs**
  - **failure of exacerbation to respond to initial medical management**
  - **significant comorbidities**
  - **new arrythmias**
  - **diagnostic uncertainty**
  - **older age**
  - **insufficient home support**

Treatment of Acute Exacerbation of COPD

- Items to assess at follow-up visit 4-6 weeks after hospitalization:
  - Ability to cope in usual environment
  - Reassessment of inhaler technique
  - Understanding of recommended treatment regimen
  - Reassess need for supplemental oxygen and/or nebulizer
  - Capacity for performing ADLs
  - Status of comorbidities

Prevention of Exacerbations

- Smoking cessation
- Influenza/pneumococcal vaccine
- Knowledge of current therapy, including inhaler technique
- Treatment with long-acting bronchodilators, with or without inhaled steroids and possibly phosphodiesterase-4 inhibitors
- Pulmonary rehab
- Discuss anxiety, depression, social problems
- Identify principal caregivers

Associated Conditions

- GERD
- Osteoporosis
- Anxiety/Depression
- OSA
- CV Disease
- Cachexia
- Pulmonary hypertension
- Bronchiectasis

Advanced Therapy

- Lung transplant
  - Generally, age < 65 (though some centers will transplant patients in their 70's if otherwise very healthy); non-smoker x > 6 months
  - BODE index exceeding 5; at least one of the following: h/o exacerbation with hypercapnia; pulmonary hypertension, cor pulmonale or both despite supplemental O2; FEV1 <20% of predicted or homogeneous emphysema
  - Improves QOL and functional capacity, short-term survival

Advanced Therapy

- Lung Volume Reduction Surgery
  - Parts of the lung are resected to reduce hyperinflation
  - Improves mechanical efficiency of respiratory muscles, curvature of the diaphragm
  - Increases elastic recoil, improves expiratory flow rates and reduces exacerbations
  - Best outcomes observed in patients with predominantly upper lobe emphysema with low exercise capacity
  - Bullectomy – removal of a single bulla that compresses normal lung

Advanced Therapy

- Bronchoscopic lung volume reduction
  - Still investigational
  - Modest improvements in lung function, exercise tolerance and symptoms but more exacerbations, hemoptysis, pneumonia

Summary

- COPD continues to be a significant cause of death and its burden is underestimated and increasing. It is of particular concern with our aging population, with women and in developing countries.
- Spirometry should be used to establish a diagnosis.
- Prognosis is dependent on more global factors than spirometry measurements alone.
- Smoking cessation and avoidance of other environmental exposures are paramount to preventing progression of disease.

Summary

- Pharmocologic management of stable COPD should utilize a step-wise approach based on severity of disease. Benefits must be weighed against side effects of medications.
- All patients with COPD can benefit from pulmonary rehabilitation.
- Supplemental oxgen, when required is the only therapy for COPD that increases survival.
- Steroids and antibiotics are intrinsic to the acute management of an exacerbation, but the approach to their use is changing.

Summary

- Long-term care of patients with COPD implies constant vigilence with regard to prevention of exacerbations and understanding of multiple comorbidities and psychosocial challenges.

- Lung transplant should be considered in younger patients with severe COPD who have quit smoking.