Chronic Obstructive Lung Disease (COPD)

Trials

- Global initiative for chronic Obstructive Lung Disease (GOLD)
- American Thoracic Society / European Respiratory Society (ATS/ERS)

Epidemiology

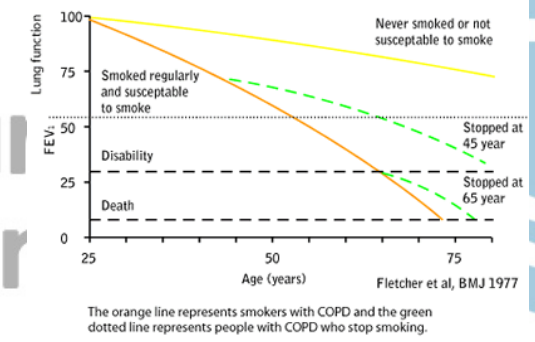
- Fourth leading of cause of death
- Stage I is markedly underdiagnosed

Definition

- Abnormal inflammatory response to a noxious agent resulting in airflow obstruction that is preventable but once initiated not fully but partially reversible and exponentially progressive (at year 1 FEV_1 decline is 30mL/yr vs at year 15 FEV_1 decline is 66mL/yr) though variable in its course from pt to pt
- NB the terms emphysema (pathologic term that is used clinically) and bronchitis (clinical term that fails to incorporate airway obstruction as some pts have significant airflow limitation w/o chronic cough and sputum production for ≥3mo/yr for ≥2yrs) are not great terms to use as most pts have components of both

Course

- It is important to note that COPD is exponentially progressive though variable in its course from pt to pt ultimately depending on degree of exposure to noxious agent… even in actively smoking pts with severe COPD the cessation of smoking can result in improvement… a classic graph by Fletcher and Peto in 1977 demonstrates this change where change in FEV1 approaches that of a pt who has never smoked in a COPD pt who stops smoking regardless of age



The orange line represents smokers with COPD and the green dotted line represents people with COPD who stop smoking.

Pathogenesis

- Combination of…
  - Genetic Predisposition
    - Defined Genetic Mutations like alpha-1-antitrypsin syndrome (this genetic component is so strong than many pts do not have an environmental exposure at all but still develop COPD)
    - Polygenic Milieu and to get a clear sense of whether the pt has a genetic predisposition ask about FHx of smokers with COPD
    - Poor Lung growth and development b/c of low birth weight, prematurity, childhood viral infections, etc
  - Environment Exposure
    - Tobacco Smoke
      - NB women appear to be more susceptible to tobacco smoke then men
      - NB only 25% of smokers develop COPD hence genetic predisposition (but likely an underestimate given the under-diagnosis of Stage I)
    - Occupational Exposure to Organic Dusts, Chemical Agents, Fumes, etc
    - Indoor Air Pollution from Biomass Smoke (eg. the burning of wood, crop residues, animal feces inside homes for energy)
    - Outdoor Air Pollution from Biomass Smoke (eg. fossil fuel combustion from cars)
    - Recurrent Severe Childhood Infections
    - Asthma
- If the combination of both environmental exposure and genetic predisposition is significant then a unique type of inflammation occurs (refer below) that then results in…

(1) Peripheral Airway (~bronchitis)
    a. goblet cell hyperplasia, enlarged submucosal glands leading to mucus hypersecretion causing chronic productive cough
    b. airwall thickening, peribronchial fibrosis, luminal inflammatory exudates leading to airway narrowing aka obstructive bronchiolitis and subsequent air trapping leading to reduced inspiratory capacity and thus DOE
    c. squamous metaplasia and thus cancer
    d. loss of cilia and thus infection
(2) Parenchyma (~emphysema)
    a. alveolar wall destruction w/ apoptosis of epithelial/endothelial cells leading to gas exchange abnormalities
    b. loss of alveolar radial traction attachments to small airways leading to bullae and air trapping
        i. Centro-lobular aka only respiratory bronchioles (environmental: smoke, air pollution, etc)
        ii. Pan-lobular aka entire acinus (genetics: alpha-1 antitrypsin syndrome, etc)
(3) Pulmonary Vasculature
    a. initial hypoxic vasoconstriction followed by thickened intima, endothelial dysfxn, smooth muscle hyperplasia leading to pulm HTN and subsequent cor pulmonale

- NB eventually remodeling fibrosis occurs
- NB systemic symptoms (refer)

S/S

- Fat Blue Bloater w/ Chronic Productive (sometimes not productive) Cough (NB pts can have cough w/ production for many years before airflow limitation is observed, the converse is also observed)
- Thin Pink Puffer w/ Chronic Dyspnea
- central (mucosal) cyanosis, hyperressonance w/ barrel shaped chest, hunched over, shallow rapid breaths, pursed lip breathing, accessory muscle use, prolonged expiratory phase, asterixis from hypercapnea
- Extrapulmonary Effects 2/2 chronic hypoxia and imbalanced oxidative stress and proteinases
    - R-CHF (Cor Pulmonale)
    - Weight Loss, Anorexia, Cachexia, Nutritional Abnormalities
    - Anxiety/Depression and Sleep Disorders
    - Skeletal Muscle Wasting/Dysfunction
    - Cough Syncope and Rib Fractures
    - CAD
    - OP
    - DM
    - Anemia
    - Glaucoma

Dx

- Clinical (Sx + Exposure)
- PFTs (any current smoker or former smoker >40yo OR any person with S/S of COPD should undergo PFTs)
    - Non-Reversible Obstructive Spirometery
    - Hyperinflation Plethysmogragraphy
    - Abnormal Gas Exchange D_LCO (very low in emphysema vs mildly low in bronchitis)
- CXR (hyperinflation signified by flattened diaphragm and increased (>4.5cm) retrosternal airspace, increased (>90°) diaphragm/sternal angle, hyperlucency, rapid tapering of vascular markings w/ little peripheral markings, bullae)
- ECG (Right Heart Strain)
- ABG (hypoxic and hypercarbic chronic respiratory failure)
- Polycythemia (Hct >55%) 2/2 chronic hypoxia
- TTE (Pulm HTN w/ MPAP >30mmHg)
- Check Alpha-1-antitrypsin in young Caucasians w/ COPD esp if +FHx of lung/liver disease

Prognosis

- BODE Index (? = ?% 5yr mortality)
    - Body mass index ($\leq$21 = +1)
    - Obstruction (FEV_1) (50-60% = +1, 35-50% = +2, <35% = +3)
    - Dyspnea (MMRC scale) (walking level = +1, after 100yards = +2, with ADL = +3)
    - Exercise capacity (Distance Walked in 6min) (250-350m = +1, 150-250m = +2, <150 = +3)
    - NB much better that FEV1 alone at predicting risk of death

Staging & Tx (Based on objective and subjective findings but they usually correlate)

Stage	Objective Airflow Limitation (after you confirm obstruction w/ FEV1/FVC <0.7 then perform BD and the post BD PEV1 is used to classify pts)	Subjective Symptoms, Complications, Exacerbations, etc	Tx
I (Mild) BODE 0-2	>80% of Predicted	Cough that is often ignored or attributed to aging, lack of conditioning, etc therefore pts often do not seek medical attention as pts often tend to modify their lifestyle to perform activities	PRN Short Acting BD Prevention Exercise
II (Moderate) BODE 3-4	80-50% of Predicted	+ Dyspnea (pt often senses something is wrong and this is the stage where pts seek medical attention b/c dyspnea is concerning to most pts) NB sometimes pts are asymptomatic even at this stage	+ Scheduled Long Acting BD Pulm Rehab
III (Severe) BODE 5-6	50-30% of Predicted	+ Sx now impact quality of life w/ decreased exercise capacity, fatigue, slow walking, and presence of exacerbations	+ ICS Follow ABGs and Hct
IV (Very Severe) BODE 7-10	<30% of Predicted or Chronic Respiratory Failure (PaO2 <60mmHg ± PaCO2 >50mmHg)	+ Pulmonary HTN and Cor Pulmonale	+ Oxygen Experimental Surgical Tx

	COPD	Asthma
Cells	Macrophages, CD8+ Lymphocytes, Neutrophils	Eosinophils, CD4+ Lymphocytes, Neutrophils
Reversibility	Less	More
Hyperresonsiveness to Methacholine Challenge	• primarily narrowing (hence bronchodilators better and thus use b/f corticosteroids) • asthma (respond better to BA than AC) vs COPD (respond better to AC than BA)	• primarily inflammation (hence corticosteroids better and thus use b/f bronchodilators) • The effect of CS is much less in COPD than in asthma even though COPD is also an inflammatory process, also the results of ICS are inconsistent (some studies show decreased neutrophils while others actually show increased neutrophils)
Cytokines	IL-1, IL-6, IL-8, TNF-alpha	IL-4, IL-5, IL-13, Eotaxin
Oxidative/Protease Stress	Significant Normal Lung Inflammation to a noxious stimulus that becomes amplified b/c of oxidative/protease stress that is created from smoke and released from inflammatory cells	Mild
Site	Peripheral Airways Parenchyma Pulmonary Vasculature	Peripheral Airways
S/S	Sx all day long Chronic Hx Clear h/o smoking	Sx are episodic Shorter Hx No Clear h/o noxious stimulant
Tx	• Reduction of therapy once Sx control is achieved (aka "Step Down" approach) is NOT possible unlike in asthma as even with the best possible care COPD will always worsen • There is no specific treatment algorithm unlike in asthma • Unlike in asthma in COPD LABA can be used alone (aka not with ICS) • CS increase the likelihood of PNA but there is no change in overall mortality (better OR worse), may slow FEV1 loss, decreases exacerbations	

- VERY IMPORTANT: Only two treatments have been shown to improve the natural history of COPD (aka reduce the decline in lung fxn) and thus mortality: (1) smoking cessation (2) oxygen (NB some say that MV during exacerbations and surgery can change natural history) all other Tx aka pharmacotherapy simply improve Sx and decrease severity and Hz of exacerbations they do not alter the long-term decline in lung function it only addresses Sx/complications/Hz of exacerbations
- Pharmacotherapy (NB inflammation in Asthma vs COPD varies (refer above) as such response to classes of medicines are different)
    - Bronchodilators (BD): Beta Agonists (BA), Anti-Cholinergics (AC), Methylxanthines (considered 2nd line)
    - Corticosteroids (CS)
    - Prophylactic Abx (eg. FQ) have been shown to have NO benefit

    - Antioxidants (eg. NAC) have been shown to have NO benefit
    - Mucolytics (eg. NAC) have been shown to have NO benefit
    - Pulmonary Vasodilators (eg. NO) have been shown to have NO benefit
    - Cough, although a troublesome Sx, has a significant protective role and thus antitussives are NOT recommended
    - LTRAs and MCSs have NO role in COPD (obviously)
- Prevention
    - Smoking Cessation
    - Influenza/Pneumococcal Vaccine
- Pulmonary Rehab
    - educate pt on disease process
    - improve exercise capacity
    - teach smoking cessation strategies
    - address related social conditions (nutrition, weight management, etc)
    - address related psychological conditions (depression, perceived intensity of breathlessness, social isolation, etc)
- Oxygen
    - Landmark Trial: Nocturnal Oxygen Therapy Trial (NOTT)
    - Indications:
        - SaO2 <88% or
        - PaO2 <55mmHg or or
        - PaO2 55-60mmHg AND pulm HTN or cor pulmonale or Hct >55%
        - NB values are determined when pt is walking/resting/sleeping and with optimal medical treatment
    - Rx: source (gas or liquid), method of delivery (FM or NC), duration of use (>15hrs), flow rate at rest (24%) and during exercise (%) and during sleep (%)
        - NB only continuous (>15hrs/d) has been shown to increase survival by preventing the progression of pulmonary HTN
    - Goal: increase PaO2 to >60mmHg at rest and SaO2 to >90% so as to prevent cor pulmonale
    - NB even in Stage IV COPD NPPV has NOT been demonstrated to have an effect on Sx and exacerbations despite its use
- Experimental
    - Roflumilast (PDE III Inhibitor) shown to increase FEV_1
- Surgical
    - Bullectomy: VATS that removes bullae that do not contribute in gas exchange but significantly compress adjacent lung
        - Indications: bullae must occupy >50% of hemithorax and produce definitive displacement of adjacent lung
        - Relieves Sx and Improve PFTs
    - Lung Volume Reduction Surgery (LVRS): part of the lung is removed to reduce hyperinflation
        - Indications: upper lobe emphysema and low exercise capacity
        - Improves PFTs and Increases Survival
        - No comorbid dz and no smoking
    - Lung Transplant
        - Indications: diffuse dz, FEV1 <35% predicted, PaO2 <60mmHg, $PaCO_2$ >50mmHg, and secondary pulmonary HTN
        - improves quality of life but has not been shown to confer a survival benefit after 2yrs
- Exacerbations
    - Causes: Tracheobronchial Infection (Mild Exac: Typicals or Atypicals vs Mod Exac: MDRB, Enterobacteriaceae vs Severe Exac: *P. aeruginosa*) or Environmental Triggers (noted above) NB the cause of 1/3 of exacerbations cannot be identified
    - Sx: subjective worsening of Sx accompanied by wheezing, change in color/viscosity/volume of sputum, addition of constitutional Sx (fever, insomnia vs sleepiness, fatigue, confusion) over a 2d period
    - Px: tachycardia/tachypnea, accessory muscle use, central cyanosis, CHF, AMS
    - Dx: spirometry, ABG, CXR, CBC, EKG/Tele (b/c they get arrhythmias)
    - Tx
        - SABA/SACA Neb + SCS + Abx (if need MV or have SOB + increase sputum volume + increased purulence)
        - Oxygen (WATCH for CO_2 retention b/c of loss of hypoxic respiratory drive) vs Noninvasive Positive Pressure Ventilation (NPPV) (if accessory muscle use or pH $\leq$7.35 and $PaCO_2$ >45mmHg and tachypnea >25bpm = results in 60% decrease intubation rate, shorter hospital stay, and decreased in-hospital mortality) vs Invasive MV (if AMS, HD instability, high r/o aspiration, etc or above indications worsen despite NPPV)
    - Prognosis: 10% hospital mortality and if pt survives then 50% 3yr mortality (all directly related to degree of respiratory acidosis, comorbidities, and need for MV)

- Before Discharge: assess need for home oxygen, smoking cessation, vaccination, f/u, inform pts of mortality statistics, ensure proper use of meds