COPD

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CASE

53 yo man with h/o HTN and HLD presents with 3 Month h/o progressive dyspnea and exercise limitation.

PE:
HR: 109; RR: 22;
BP: 110/55; SpO2: 92% on RA
Thin man with rapid shallow breathing
Lungs: Minimal air movement, decrease intensity of breath sounds
Heart: Mild tachycardia
Ext: Trace B/L pedal edema
COPD definition according to GOLD 2011

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.
Epidemiology and Prevalence

• Over the past 2 decades, the number of deaths associated with COPD has almost doubled.

• COPD is now the fourth leading cause of death globally.

• The world Health Organization (WHO) has predicted that COPD will become the third most common cause of death in the world by 2030.
Burden of COPD

- COPD is a major public health problem in US
- 13.7 million, or 6.5% of all adults are diagnosed with COPD
- The condition accounts for 1 out of every 20 deaths
- The third leading cause of death in US
- 2nd leading cause of disability
Prevalence of COPD in the United States was stable from 1998-2009 and has remained higher in women than in men.

Third National Health and Nutrition Examination Survey (NHANES) 2011;(63):1-8
COPD was more prevalent in older age groups

Third National Health and Nutrition Examination Survey (NHANES) 2011;(63):1-8
COPD was more prevalent among Puerto Rican and non-Hispanic white adults than among non-Hispanic black and Mexican-American adults, and among adults with family income below the poverty level (8.3%) than those with income at least 200% of the poverty level (4.3%).

Third National Health and Nutrition Examination Survey (NHANES) 2011;(63):1-8
Prevalence of COPD was almost twice as high in the East South Central U.S. Census division (7.5%) as in the Pacific division (3.9%)

Third National Health and Nutrition Examination Survey (NHANES) 2011;(63):1-8
From 1999 through 2007, COPD hospitalization rates declined for both men and women, but COPD death rates declined only for men.

Third National Health and Nutrition Examination Survey (NHANES) 2011;(63):1-8
Direct Medical Cost of COPD

- The annual median cost of health care is estimated to be 3.4 times higher compared to non-COPD pts.
- COPD is the third most frequent reason for hospital readmission.
- Hospitalization costs increase with more acute symptoms and co-morbidities.
- COPD exacerbations nearly double medical costs, with severe exacerbations incurring 2.6 fold greater total medical costs compared to non-sever exacerbations.

US department of health and human services
November, 2013
Natural history and prognosis
Risk Factors for COPD

- Tobacco smoke
- Occupational exposure to organic and inorganic dust
- Genes
- Lung growth and development
- Respiratory infections
- Socioeconomic status
- Gender, Age
- Oxidative stress
- Poor nutrition and other co-morbidities
Risk Factors for COPD
Pathogenesis overview

1. Increase in air space inflammation
2. Oxidative stress: Oxidant/antioxidant imbalance
3. Increase protease burden/decreased antiprotease function
4. Defective repair
Changes in Large Airways in COPD Patients

- Mucus hypersecretion
- Neutrophils in sputum
- Squamous metaplasia of epithelium
- No basement membrane thickening
- Goblet cell hyperplasia
- Mucus gland hyperplasia
- Macrophages
- CD8+ lymphocytes
- Little increase in airway smooth muscle
Mucous Metaplasia

Epithelial lining and goblet cells.
Mechanism of Airflow Limitation

Normal

Airway held open by alveolar attachments (elastin fibers)

COPD

Disrupted alveolar attachments (emphysema)

Mucus hypersecretion

Mucosal inflammation, fibrosis

Airway obstructed by
- Loss of alveolar attachments
- Mucosal inflammation + fibrosis
- Lumenal obstruction with inflammatory exudate and mucus

Air Trapping in COPD

ERS review O’Donnell et al. 2006;15:100, 61=67:
Changes in the Lung Parenchyma in COPD Patients

Source: Peter Barnes MD
Pathology of Airflow Limitation

Emphysema

Small airway remodeling

Mechanism of COPD Symptoms

- Emphysema and small airway obstruction
- Lung hyperinflation (↑ Trapped air)
- Dyspnea
- ↓ Exercise tolerance
- Deconditioning
  - Cough and sputum
  - Poor health status

- Mucus hypersecretion
How does tobacco smoke cause COPD
Patho-biologic mechanism
Protease-Antiprotease Imbalance in COPD
Increase protease burden/decreased antiprotease function

1. MMP: Matrix Metalloproteinases
2. SLPI: Secretory Leukoprotease Inhibitor
3. TIMP: Tissue inhibitor of MMP
Inflammation in COPD: overview

Cigarette smoke (and other irritants)
- CXCL9
- CXCL10
- CXCL11

Epithelial cells
- TGF-β

Fibroblast
- T_H1 cell
- T_C1 cell

Macrophage
- CXCL1
- CXCL8
- CCL2

Neutrophil
- CXCR2
- CXCR2

Monocyte
- CCR2

Proteases
- Neutrophil elastase
- MMP-9

Fibrosis (small airways)

Alveolar wall destruction (emphysema)

Mucus hypersecretion

James Crapo, ed Atlas of COPD 2009
Oxidative Stress in COPD

- Cigarette smoke
- Inflammatory cells

- Antiproteases
  - SLPI, α₁-AT
  - ³↑ Proteolysis

- O₂⁻, H₂O₂, OH⁻, ONOO⁻

- Steroid resistance
- ↑ Mucus secretion
- Isoprostanes → Plasma leak
- Bronchoconstriction

- NF-κB
- CXCL8 ← TNF-α
- Neutrophil recruitment

Atlas of COPD
Other mechanisms in COPD

• Cell death
  Alveolar cell apoptosis

• Aging
  Cellular Senescence: DNA damage/repair
  Telomere shortening
  Fewer stem cells for alveolar maintenance

• Adaptive immune system/autoimmunity
Proposed model of COPD
MacNee et al. Proc Am Thorac Soc 2009; 527-31
COPD Assessment

It's a matter of breath and death!
COPD diagnostic criteria according to GOLD 2013

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context; the presence of a post-bronchodilator FEV1/FVC < 70% confirms the presence of persistent airflow limitation and thus of COPD.
Signs and Symptoms of COPD

- Easily fatigued
- Frequent respiratory infections
- Use of accessory muscles to breathe
- Orthopnea
- Wheezing
- Pursed-lip breathing
- Chronic cough
- Barrel chest
- Dyspnea
- Prolonged expiratory time
- Digital clubbing
- Cor pulmonale (late in disease)
- Thin in appearance
Differential Diagnosis

Asthma
CHF
Bronchiectasis
α-1 AT deficiency

Tuberculosis
Obliterative Bronchiolitis: Young, non-smoker; occupational exposure; collagen vascular disease;
Diffuse Panbronchiolitis: Male; non-smoker; sinusitis; centrilobular nodules
Classification of COPD Severity

FEV1/FVC <0.70
FEV1>80% predicted

FEV1/FVC <0.70
30%≤FEV1<50%
0% Predicted

FEV1/FVC <0.70
FEV1<30% Predicted
Or
FEV1<50% predicted
Plus Chronic Respiratory Failure
Chest X-Ray

- Flattened diaphragms
- Reduced lung markings
- Narrow cardiac silhouette
- Cachexia
Chest CT

No evidence of bolus emphysema but show mosaic attenuation consistent with severe small airway disease.

Heterogeneity in COPD
Hersh et al. COPD, 2007; 4:331-7
Other useful tests

• Lung volumes; diffusing capacity
  - hyperinflation
• Respiratory muscle forces
• Arterial Blood Gas
  - Recommended in sever COPD
  - O2 sats give no information about PCO2
• 6-minute walk test
  - Evaluate disability, and rehab assess
Management: Goals of Therapy
Stable COPD

• Relieve Symptoms
• Improve exercise tolerance
• Improve health status
• Prevent disease progression
• Prevent and treat exacerbations
• Reduce Mortality
Effective therapies available for patients with stable COPD

<table>
<thead>
<tr>
<th>Improve survival</th>
<th>May improve survival</th>
<th>Improve patient centered outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Smoke cessation</td>
<td>• Pharmacotherapy with salmeterol and fluticasone</td>
<td>• Pharmacotherapy Short acting Bronchodilators Long acting anti-muscarinics Long acting beta agonists Inhaled corticosteroids Theophylline Alpha-1-antitrypsin for selected patients Antibiotics for selected patients</td>
</tr>
<tr>
<td>• Lung volume reduction surgery for selected patients</td>
<td>• Pulmonary rehabilitation</td>
<td>• Oxygen therapy</td>
</tr>
<tr>
<td>• Noninvasive ventilation for acute chronic hypercapnic respiratory failure</td>
<td></td>
<td>• Surgery Lung volume reduction surgery Lung transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pulmonary rehabilitation</td>
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</tbody>
</table>
Therapeutic Options: Key Points

• Smoke cessation has the greatest capacity to influence the natural history of COPD
• Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates
• All COPD patients benefit from regular physical activity and should repeatedly be encouraged to remain active
Therapeutic Options: Key Points

- Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.
- None of the existing medications for COPD has been shown to modify the long-term decline in lung function.
- Influenza and pneumococcal vaccination should be offered depending on local guidelines.
Prevention of COPD Progression: Smoking Cessation

- The only therapy proven to slow the decline in lung function
- Reduces all cause mortality by 27%
- Difficult to achieve

Long-term abstinence rates can be as high as 25% in patients with early COPD

Prevention of COPD Progression
Smoking Cessation

Mean FEV1(L)

Years of follow up

Smoking Cessation

- 70-80% of smokers want to quit
- Strong direct relationship between the intensity of counseling and results
Smoking Cessation

The 5A Strategy

- **Ask**: All pts should be asked at every visit on their smoking status
- **Advice**: Should strongly urge every smoker to quit
- **Assess**: Should ask the pt if willing to attempt quitting in the next 30 days
- **Assist**: Should help the pt with quit plan
- **Arrange**: Should schedule follow up visit or phone contact
Smoking Cessation

• Nicotine replacement therapy and counseling: 25% sustained quit rate
• Bupropion (Zyban) and counseling: 25-29% sustained quit rate
• Varencliline (Chantix) and counseling: 43% sustained quit rate
# Pharmacological Options for COPD

<table>
<thead>
<tr>
<th>Category</th>
<th>Options</th>
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</thead>
<tbody>
<tr>
<td>Beta$_2$-agonists</td>
<td></td>
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<tr>
<td>Short-acting beta$_2$-agonists</td>
<td></td>
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<tr>
<td>Long-acting beta$_2$-agonists</td>
<td></td>
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<tr>
<td>Anticholinergics</td>
<td></td>
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<tr>
<td>Short-acting anticholinergics</td>
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<tr>
<td>Long-acting anticholinergics</td>
<td></td>
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<tr>
<td>Combination short-acting beta$_2$-agonists + anticholinergic in one inhaler</td>
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<tr>
<td>Methylxanthines</td>
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<tr>
<td>Inhaled corticosteroids</td>
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<tr>
<td>Combination long-acting beta$_2$-agonists + corticosteroids in one inhaler</td>
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<tr>
<td>Systemic corticosteroids</td>
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<tr>
<td>Phosphodiesterase-4 inhibitors</td>
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<tr>
<td>Macrolide antibiotics</td>
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</table>
β2-Agonists

- Activation of β2 receptors
- Activation of Adenylate Cyclase and increase in c-AMP
- Activation of protein kinase A (PKA)
- Phosphorylation of several target proteins within the cell resulting in:
  - Increase in intracellular Ca
  - Increase membrane K conductance
  - Inhibition of myosin kinase light chain activity

Smooth muscle relaxation and bronchodilation
• The normal airway has a certain degree of vagal cholinergic tone caused by tonic release of acetylcholine resulting in nerve-induced broncho-constriction.
• This effect may be exaggerated in patients with COPD because of fixed narrowing of the airways.
Anticholinergics

- No blocking effect on the direct effect of inflammatory mediators such as histamine and Leukotrienes on bronchial smooth muscle.
- Little or no effect on mast cells, microvascular leak, or chronic inflammatory response.

<table>
<thead>
<tr>
<th>Muscarinic Receptor Subtype</th>
<th>Locations</th>
<th>Action When Stimulated With Agonist</th>
<th>Receptor-Drug Complex Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Parasympathetic ganglia, exocrine glands, mucous glands</td>
<td>Cholinergic neurotransmission</td>
<td>Ipratropium: 0.11</td>
</tr>
<tr>
<td>M2</td>
<td>Postganglionic cholinergic nerves, airway (smooth muscle)</td>
<td>Negative feedback to reduce acetylcholine release</td>
<td>Ipratropium: 0.035</td>
</tr>
<tr>
<td>M3</td>
<td>Airway (smooth muscle), mucous glands</td>
<td>Bronchoconstriction, mucus secretion</td>
<td>Ipratropium: 0.26</td>
</tr>
</tbody>
</table>

Theophylline

• A non-selective Phosphodiesterase inhibitor leading to an increased intracellular cAMP concentration.
• Adenosine receptor antagonist.
• Stimulation of catecholamine release.
• Mediator inhibition.
• Inhibition of intracellular calcium release.
• Increased histone deacetylase activity.
Histone Deacetylases

- Nuclear enzymes that are recruited by corticosteroids to switch off inflammatory gene expression.
- This mechanism also accounts for the synergistic interaction with the anti-inflammatory effect of steroids.
- May lead to reversal corticosteroid resistance in severe asthma and COPD.
Phosphodiesterase-4 Inhibition

Imunomodulatory effect

Decrease the number of activated lymphocytes in the airways by blocking their trafficking from the circulation.
Reduce eosinophils in bronchial biopsy specimens and induced sputum.
Reduce neutrophils in the sputum of COPD patients.
Corticosteroids

- Inhibit recruitment of inflammatory cells by reducing chemotaxis and adhesion.
- Decrease phagocytosis
- Decrease the production of inflammatory mediators
COPD: Effectiveness of Fluticasone and Salmeterol

Mahler et al. AJRCCM 2002; 166: 1084-1091
TORCH Trial
Toward a Revolution in COPD Health

• Randomized double blind trial
• Comparing Salmeterol (50 mcg)/Fluticasone (500 mcg) BID with placebo; Salmeterol alone; or Fluticasone alone for a period of 3 yrs
• 6184 patients
• Primary outcome: all cause of mortality
• Secondary outcome: number of exacerbations, and St. George’s Respiratory Questionnaire (SGRQ).
TORCH: Rate of decline in FEV1: effect of treatment

Celli, B et al. AJRCCM; 2008; 178: 332-8
Rate of exacerbations requiring systemic corticosteroids

Mean # of exacerbations/year

43% Reduction

Calverley NEJM 2007
TORCH Trial

- Did not achieve a significant decrease in mortality \( \{ \text{HR: 0.825; 95\% CI; P < 0.052} \} \)
- The probability of death in the ICS arm was 16\% vs. 12.6\% in ICS/LABA arm.
- Increase incidence of pneumonia among patients receiving ICS treatment, both as combination treatment and as monotherapy.
UPLIFT Trial
The Understanding Potential Long Term Impact on Function and Tiotropium

• Randomized double-blind trial
• Comparing 4 years of therapy with either Tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications except anticholinergics.
• 5993 patient randomized
• Primary end points: rate of decline in mean FEV1 before and after BD beginning on day 30
• Secondary end points: Measure of FVC, changes in response on St. George’s Respiratory Questionnaire (SGRQ), COPD exacerbations and mortality.
Bronchodilator response distribution in UPLIFT

Tashkin et al. Eur Respir J 2008; 31: 742-750
UPLIFT

- No significant difference in the rate of decline in lung function.
- Significant reduction in the risk of having an exacerbation and exacerbations leading to a hospitalization.
- Survival was significantly increased in the treatment group, however when the 30 day protocol defined washout period was included the improvement in survival lost statistical significance.
TORCH

**FEV1**
92ml difference
From placebo

**Exacerbation**
25% reduction

**QOL**
3.1 points improvement
In SGRQ from placebo and baseline
UPLIFT

- **FEV1**: 110ml difference from placebo
- **QOL**: 3.3 points improvement in SGRQ from placebo and baseline
- **Exacerbation**: 16% reduction
Figure 3 Comparison of selected mortality data presented in the TORCH and UPLIFT® primary publications. Data from the individual trials have been placed on the same axes for illustrative purposes only and do not represent directly comparable data between the trials.

Abbreviations: CI, confidence interval; HR, hazard ratio; SFC, salmeterol and fluticasone in combination.
Therapeutic Options: Phosphodiesterase-4 Inhibitors

- In patients with severe and very severe COPD (GOLD 3 and 4) and a history of exacerbations and chronic bronchitis, the phosphodiesterase-4 inhibitor (PDE-4), Roflumilast, reduces exacerbations treated with oral glucocorticoids.
Therapeutic Options: Macrolide Antibiotics

• Adding Azithromycin (250mg/day) x 1 yr to usual Rx of patients with an increase risk of COPD exacerbations:
  1- Decrease the frequency of AECOPDs
  2- Improve QOL
  3- Can cause hearing impairment in a small fraction of patients

• Provisos:
  1- HR<100, no apparent risk of QTc prolongation
  2- Hearing ≥ 95th percentile for age
  3- Effect on macrolide resistance in community bacterial flora is unknown

Time to First AECOPD

Proportion Free of AECO P(%) = Azithro (yellow line) vs Placebo (green line)

Median 266 days for Azithro
Median 174 days for Placebo

HR = 0.73 (95% CI), P < 0.0001

Other Pharmacologic Treatments

- **Influenza vaccination**: Can reduce serious illness
- **Pneumococcal Vaccination**: Polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than 65 with a FEV1 < 40% predicted
Prevention of COPD Exacerbations
Influenza Vaccination

Nichol et al. Ann Intern Med 1999; 130: 397
Other Treatment Options

- **Alpha-1 Antitrypsin Augmentation Therapy**: Not recommended for patients with COPD that is unrelated to the genetic deficiency.
- **Mucolytics**: Patients with viscous sputum may benefit from mucolytics; overall benefits are very small.
- **Antitussives**: Not recommended.
- **Vasodilators**: Nitric oxide is contraindicated in stable COPD. The use of endothelium-modulating agents for the treatment of pulmonary hypertension associated with COPD is not recommended.
Pulmonary Rehabilitation

• All COPD patients benefit from exercise training programs with improvement in exercise tolerance and symptoms of dyspnea and fatigue.
• Although an effective pulmonary rehabilitation program is weeks, the longer the program continues, the more effective the results.
• If exercise training is maintained at home the patient’s health status remains above pre-rehabilitation levels.
Efficacy of Pulmonary Rehabilitation in COPD

Quality of life CRQ score

Efficacy of Pulmonary Rehabilitation in COPD

Therapeutic Options: Oxygen Therapy

• Long term administration of oxygen ( > 15 hours per day ) to patients with chronic respiratory failure has been shown to increase survival in patients with severe, resting hypoxemia.

• Combination of noninvasive ventilation (NIV) with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in those with pronounced daytime hypercapnia.
Long Term Oxygen Therapy for COPD

Y-Axis: Proportion Surviving

Months on study

National Oxygen Therapy Trial Group
Ann Intern Med 1980;93:391

Medical Research Council Working Party
Lancet 1981;1:681
Long term Oxygen for COPD

Moderate Hypoxemia

Proportion Surviving

Months on study

Chronic Oxygen
Control

Surgical Treatment

- Lung Volume Reduction Surgery (LVRS) is more efficacious than medical therapy among patients with upper-lobe predominant emphysema and low exercise capacity.
- LVRS is costly relative to health care programs not including surgery.
- In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity.
Classification of Severity of Airflow Limitation in COPD*

In Patients with FEV1/FVC < 0.70

GOLD 1: Mild \( \text{FEV1} \geq 80\% \text{ pred} \)

GOLD 2: Moderate \( 50\% \leq \text{FEV1} < 80\% \text{ Pred} \)

GOLD 3: Sever \( 30\% \leq \text{FEV1} < 50\% \text{ Pred} \)

GOLD 4: Very Severe \( \text{FEV1} < 30\% \text{ Pred} \)

*Based on Post-Bronchodilator FEV1

2013 GOLD
Assess risk of exacerbations

Use history of exacerbations and spirometry

- Two or more exacerbations within the last year or and FEV1 < 50% of predicted value are indicators of high risk
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>FEV1/FVC Criteria</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: At Risk</td>
<td>Chronic Symptoms Exposure to risk factors Normal spirometry</td>
<td>FEV1/FVC &lt; 70% FEV1 ≥ 80% predicted With or Without symptoms</td>
<td>Avoidance of risk factors, smoking cessation program, influenza vaccination, exercise, patient education</td>
</tr>
<tr>
<td>I: Mild</td>
<td></td>
<td>FEV1/FVC &lt; 79% 50% ≤ FEV1 &lt; 80% predicted With or Without symptoms</td>
<td>Add short acting bronchodilator when needed</td>
</tr>
<tr>
<td>II: Moderate</td>
<td></td>
<td>FEV1/FVC &lt; 79% 50% ≤ FEV1 &lt; 80% predicted With or Without symptoms</td>
<td>Add regular treatment with 1 or more long-acting bronchodilator Add pulmonary rehabilitation</td>
</tr>
<tr>
<td>III: Severe</td>
<td></td>
<td>FEV1/FVC &lt; 70% 30% ≤ FEV1 &lt; 50% predicted With or Without symptoms</td>
<td>Add inhaled glucocorticoids if repeated exacerbations</td>
</tr>
<tr>
<td>IV: Very Severe</td>
<td></td>
<td>FEV1/FVC &lt;70% FEV1 &lt; 30% predicted or FEV1 &lt; 50% predicted plus chronic respiratory failure</td>
<td>Add long term oxygen therapy if: PaO2 ≤ 55mm Hg or SaO2 ≤ 88% with or w/o hypercapnia PaO2 56-60 mmHg or SaO2 ≤ 89% , if pulmonary hypertension, peripheral edema suggesting CHF, or polycythemia Consider bullectomy or lung transplantation in carefully selected patients</td>
</tr>
</tbody>
</table>
Recently approved medications and investigational drugs

- Nebulized formoterol (BID)
- LAMA (aclidinium)
- Once a day LABA (indacagterol, carmoterol and others)
- Once a day combination therapy
  - ICS-LABA
  - LABA-LAMA
  - ICS-LABA-LAMA
- PDE-4 inhibitors
COPD Exacerbation

“An acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications.”
Causes of COPD Exacerbation

- Infection
- Cardiovascular: CHF, MI
- Pulmonary Embolism
- Pneumothorax
- Noncompliance
Consequences of COPD Exacerbations

- Accelerated lung function decline
- Negative impact on quality of life
- Impact on symptoms and lung function
- Increased economic costs
- Increased mortality

EXACERBATIONS
Management of COPD Exacerbations

- **Oxygen**: Titrate to improve the patient’s hypoxemia with a target saturation of 88-92%.
- **Bronchodilators**: Short acting inhaled beta2-agonists with or without short acting anticholinergics are preferred.
- **Systemic Corticosteroids**: Shorten recovery time, improve lung function (FEV1) and hypoxemia, and reduce the risk of early relapse, treatment failure, and length of hospital stay. A dose of 30-40 mg prednisone per day for 10-14 days is recommended.
Systemic Steroids and COPD Exacerbations

Compared with placebo, systemic corticosteroids reduced treatment failure by 46% (95% confidence interval [CI], 0.41 to 0.71), length of hospital stay by 1.4 days (95% CI, 0.7 to 2.2), and improved FEV$_1$ by 0.13 L after 3 days of therapy (95% CI, 0.04 to 0.21).

Management of COPD Exacerbations

Antibiotics

Antibiotics should be given to patients with:

1. Three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence.
2. Those who require mechanical ventilation.
Compared with placebo, antibiotics reduced treatment failure by 46% (95% CI, 0.32 to 0.92) and in-hospital mortality by 78% (95% CI, 0.08 to 0.62). Compared with standard therapy,

Management of COPD Exacerbations
Noninvasive Ventilation (NIV)

- Improves respiratory acidosis, reduces respiratory rate, severity of dyspnea, complications and length of hospital stay.
- Decreased mortality and the need for intubation.
NPPV reduced the risk of intubation by 65% (95% CI, 0.26 to 0.47), in-hospital mortality by 55% (95% CI, 0.30 to 0.66), and the length of hospitalization by 1.9 days (95% CI, 0.0 to 3.9).
Management of Co-morbidities

COPD: Common Co-morbidities

- Cardiovascular disease
- Osteoporosis
- Pulmonary Emboli
- Lung Cancer
- Obstructive Sleep Apnea
- Depression/Anxiety
- Metabolic Syndrome and Diabetes
Co-morbidities

Systemic inflammation
- Cytokines: IL-1β, IL-6, IL-18, TNFα
- Acute phase proteins: CRP, SAA

- Genetic factors
- Cigarette smoke
- Biomass fuel
- Lung cancer
- Peripheral lung inflammation
- Hypoxia
- "spill-over"

- Skeletal muscle weakness
- Cachexia

- Cardiovascular diseases
  - IHD, CCF, hypertension

- Metabolic diseases
  - Diabetes
  - Metabolic syndrome
  - Obesity

- Bone disease
  - Osteoporosis
  - Osteopenia

- Depression