

Updates on Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Central Texas Society of Health-System Pharmacists Fall Seminar
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Financial Disclosures

- No conflicts to disclose

Pharmacist Learning Objectives

1. Describe the initial treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD).
2. Explore recent literature supporting a shorter duration of steroid treatment for acute exacerbations of COPD.
3. Recommend antibiotic therapy based on patient-specific factors for appropriate patients with acute exacerbations.
4. Assess patient risk and symptoms to determine if changes to the COPD maintenance regimen are warranted.

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Pharmacy Technician Learning Objectives

1. Discuss the initial treatment of acute exacerbations of COPD.
2. Explain recent evidence supporting a shorter duration of steroid treatment for acute exacerbations of COPD.
3. Identify which patients with an acute exacerbation of COPD should receive antibiotics.
4. Re-evaluate a patient's maintenance regimen for COPD after an acute exacerbation.

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Acute Exacerbations of COPD

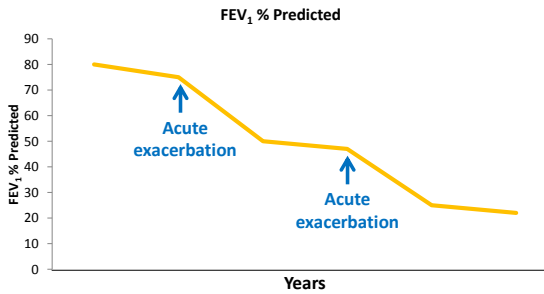
What is an Acute Exacerbation of COPD?

- An **acute** event characterized by
 - Worsening of respiratory symptoms
 - Beyond normal day-to-day variation
- Leads to a change in medication
- Largest predictor of risk of exacerbations is a **history of exacerbations**

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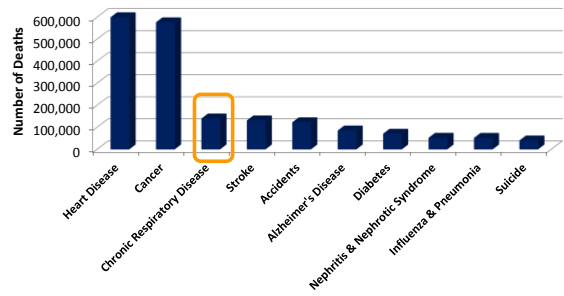
Exacerbations and Decline in Lung Function



FEV₁: forced expiratory volume in 1 second

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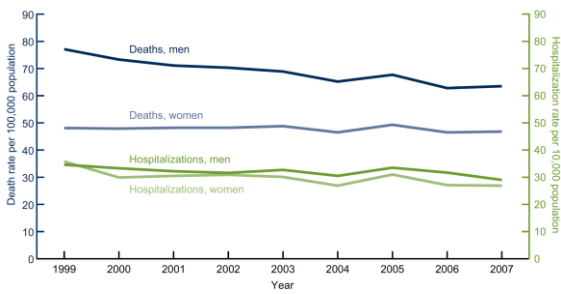
COPD Is the 3rd Leading Cause of Death in the U.S., 2010



<http://www.cdc.gov/nchs/fastats/deaths.htm>

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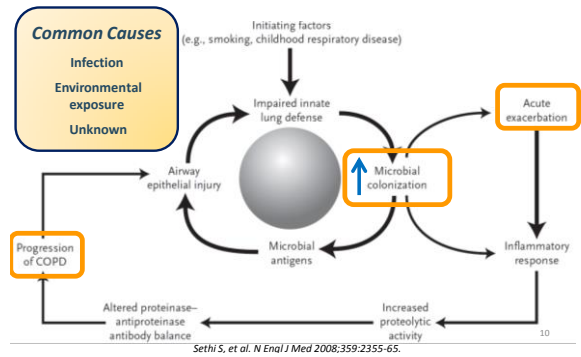
Deaths due to COPD among U.S. Adults, 1999-2007



Akinbami L, et al. National Center for Health Statistics, Centers for Disease Control, 2011

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Common Causes



Sethi S, et al. N Engl J Med 2008;359:2355-65.

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Pollution May Lead to Exacerbation



<http://www.theatlantic.com/infocus/2013/01/chinas-toxic-sky/100449/>

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Management

Patient Case

WR is a 62 year-old-male presenting to the emergency room with ↑ shortness of breath, an increase in sputum production, and a change in sputum color over the past 2 days. He has been using albuterol 6 to 8 times daily for the past several days. He had one acute exacerbation of COPD this winter. His grandson recently had the flu.

Medical History: 43-year smoking history
15-year history of COPD, angina, & depression

Current COPD regimen: salmeterol 2 puffs BID
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Post-bronchodilator PFT: Obtained at last clinic visit 3 months ago
FEV₁ of 1.3 liters (46% of predicted)
FVC of 2.2 liters
FEV₁ /FVC ratio of 59%

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Clinical Presentation

- **Diagnosis based solely on change in symptoms**

- ↑ shortness of breath
 - ↑ sputum production
 - Sputum purulence
- } **Cardinal Symptoms**

- **Evaluate**

- Severity of COPD
- Duration or worsening of symptoms
- Previous exacerbations
- Co-morbidities
- Current treatment regimen

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Assessment of Severity

Potential Indications for Hospital Admission

- ↑ intensity of symptoms (ex: new resting dyspnea)
- Severe underlying COPD
- Onset of new physical signs
 - Central cyanosis
 - Peripheral edema
 - Paradoxical chest wall movements & use of accessory muscles
 - Hemodynamic instability
 - Deteriorated mental status
- ↓ response to initial management
- High risk comorbidity or new arrhythmia
- Frequent exacerbations
- Older age
- Insufficient home support

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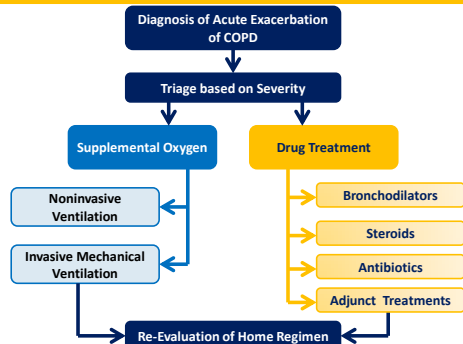
Patient Case

WR is very short of breath with a respiratory rate of 26 breaths/minute and an oxygen saturation of 84%. What is the **FIRST** intervention you would like to initiate?

- Albuterol
- Ipratropium
- Supplemental oxygen
- Intubate and start on invasive mechanical ventilation

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Initial Management



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Initial Management

- **Bronchodilator Therapy**

- Mainstay of treatment
- ↑ dose or frequency of short-acting bronchodilator
- Combine short-acting β-agonist and short-acting anticholinergic
- Use spacers or nebulizers

- **Adjunctive Therapy**

- DVT prophylaxis
- Treatment of associated conditions
 - Example: diuretics for volume overload secondary to heart failure

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Wedzicha JA, et al. Clin Chest Med 2014;35:157-163.

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Description of Levels of Evidence in GOLD Guidelines

Evidence Category	Sources of Evidence
A	Randomized controlled trials Rich body of data (i.e., several studies with consistent findings)
B	Randomized controlled trials Limited body of data (i.e., fewer or smaller studies, may have inconsistent results)
C	Nonrandomized trials Observational studies
D	Panel consensus judgement

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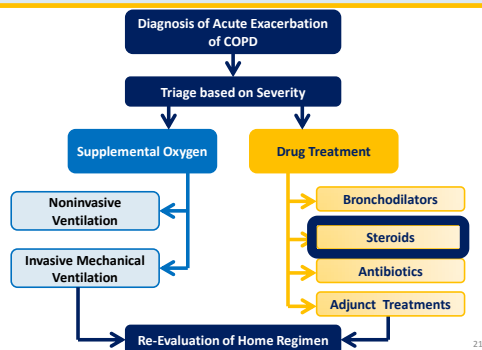
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Patient Case

Which of the following medications would you like to initiate in WR for treatment of the COPD exacerbation?

- Prednisone 40 mg PO daily x 5 days
- Prednisone 40 mg PO daily x 14 days
- Methylprednisolone 32 mg IV daily x 5 days
- Methylprednisolone 32 mg IV daily x 10 days
- Methylprednisolone 125 mg IV Q 6 hours X 5 days

Initial Management



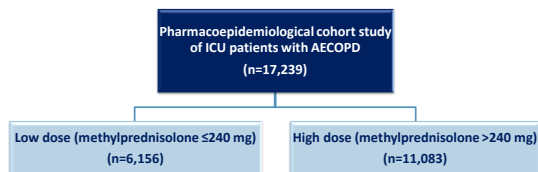
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Questions regarding Corticosteroid Use

- What dose should I use?
- What route of steroid administration is preferred?
- How long should I treat with steroids?

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High vs Low Dose Corticosteroids



Results

- Low dose steroid was not associated with mortality reduction vs high dose (OR 0.85 [95% CI 0.71-1.01, p=0.06])
- Low dose steroid was associated with ↓ hospital and ICU length of stay, hospital costs, length of invasive ventilation, need for insulin therapy, and fungal infections

Kiser TH, et al. *Am J Resp Crit Care Med* 2014;189:1052-64.
ICU: intensive care unit; AECOPD: acute exacerbation of COPD

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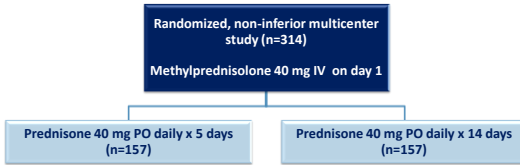
Route of Steroid Administration

- Prospective evaluation of 210 patients**
 - Compared 5 days of prednisolone 60 mg orally (n=103) vs intravenously (n=107)
 - No difference in overall, early, or late treatment failure or length of stay
- Pharmacoepidemiological study of 79,985 patients**
 - Groups:
 - High dose (120-800 mg prednisone equivalent), intravenous (n=73,765)
 - Low dose (20-80 mg prednisone equivalent), oral (n=6,220)
 - Propensity-matched analysis:
 - Oral, low dose steroid associated with ↓ risk of treatment failure, length of stay, and cost vs intravenous, high dose steroids

De Jong YP, et al. *Chest* 2007;132:1741-47.
Lindenaier PK, et al. *JAMA* 2010;303:2359-67.

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Reduction in the Use of Corticosteroids in Exacerbated COPD The REDUCE Trial



- Population**
 - Mean age 70 years, 60% male, all past or current smokers
 - Predominantly GOLD Grade 3 or 4
- Outcomes**
 - Primary:** time to next exacerbation within 180 days
 - Secondary:** all-cause mortality, change in FEV₁, cumulative steroid dose, duration of hospital stay, need for mechanical ventilation, glucocorticoid-associated adverse events

Leuppi JD, et al. JAMA 2013;309:2223-31.

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Duration of Steroid Therapy

Outcome	Conventional Treatment (n=155)	Short-Term Treatment (n=156)	Comparison Measure	p value
Time to next exacerbation within 180 days	57 (36.8%)	56 (35.9%)	HR 0.95 (90% CI 0.70-1.29)	0.006
Death	13 (8.4%)	12 (7.7%)	HR 0.93 (95% CI 0.40-2.20)	0.87
Need for mechanical ventilation	21 (13.6%)	17 (11%)	OR 0.78 (95% CI 0.37-1.63)	0.49
Cumulative prednisone dose (mg)	560 (IQR, 560-773)	200 (IQR 200-310)		<0.001

2012 Cochrane Database Review

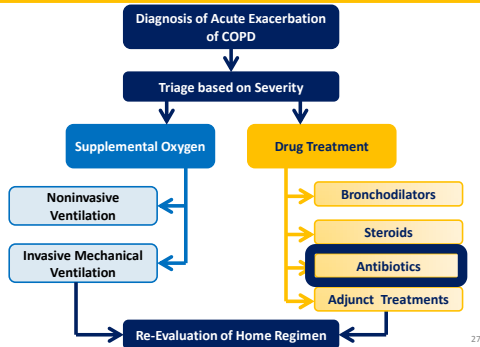
- Evaluated efficacy of shorter course (≤ 7 days) vs longer course (>7 days) steroids
- 7 studies of 288 patients
- No difference in risk of treatment failure, FEV₁, or adverse events

A dose of 40 mg prednisone per day for 5 days is recommended (Evidence B).

Leuppi JD, et al. JAMA 2013;309:2223-31.
Walters JAE, et al. Cochrane Database of Systematic Reviews 2011:CD006897.

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Initial Management



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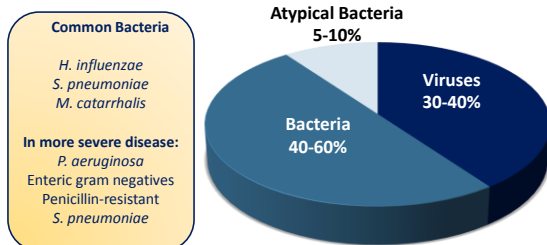
Patient Case

Should WR be initiated on antibiotic therapy for treatment of his acute exacerbation of COPD?

- Yes
- No

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Common Pathogens



Miravittles M, et al. Am J Respir Crit Care Med 2013;188:1052-7.
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Who Should Receive Antibiotics?

- Retrospective cohort study of 84,621 patients**
 - Early antibiotic treatment (within 2 days) associated with:
 - ↓ need for mechanical ventilation, inpatient mortality, readmission for an acute exacerbation
 - ↑ readmission with *C. difficile*
- 2012 Cochrane Review**
 - High quality data to support mortality reduction in severe COPD exacerbations
 - Benefit controversial in mild to moderate exacerbations

Antibiotics should be given to patients who:

- Have all 3 cardinal symptoms (Evidence B)
- Have 2 cardinal symptoms and one is sputum purulence (Evidence C)
- Require invasive or non-invasive mechanical ventilation (Evidence B)

Rothberg MB, et al. JAMA 2010;303:2035-42.
Vollenweider DJ, et al. Cochrane Database of Systematic Reviews 2012:CD10257.
GOLD Guidelines, 2014 Update, www.goldcopd.org

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Use of Procalcitonin

Single center, randomized controlled trial (n=208)

Outcome	Result	p value
Antibiotic prescription	Procalcitonin: 40% Standard: 72%	<0.0001
Antibiotic exposure	RR 0.56 (95% CI 0.43 – 0.73)	<0.0001

- **No difference**
 - Background therapy of AECOPD
 - Clinical outcome, FEV₁ improvement at 14 days or 6 months
 - Exacerbation rate, rehospitalization rate, or mean time to next exacerbation
- Stolz D, et al. Chest 2007;131:9-19.*

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Stability Parameters for Discharge

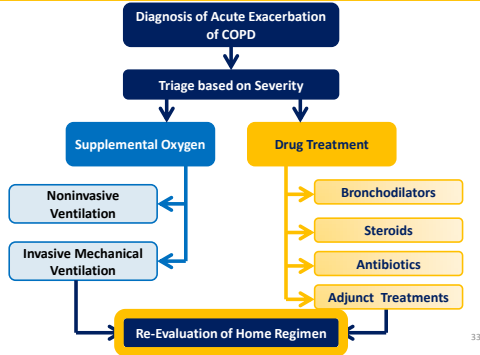
Discharge Criteria

- Able to use long-acting bronchodilators with or without inhaled corticosteroids
- Use of short-acting bronchodilators no more than every 4 hours
- Ambulatory (if was previously able)
- Able to eat and sleep without frequent dyspnea
- Clinically stable for 12-24 hours
- Arterial blood gases stable for 12-24 hours
- Patient, family, and physician are confident that the patient can manage successfully at home
- Follow-up and home arrangements in place

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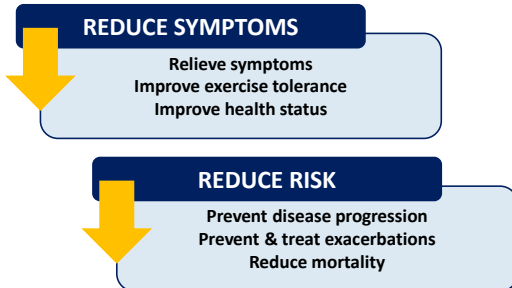
Initial Management



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MAINTENANCE THERAPY

Goals of Treatment of Stable COPD



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Classifying Severity of Airflow Limitation

Classification of Severity of Airflow Limitation in COPD	
Stage	Characteristics (POST-bronchodilator)
In patients with FEV ₁ /FVC < 70%:	
GOLD 1: Mild	FEV ₁ ≥80% predicted
GOLD 2: Moderate	FEV ₁ 50-79% predicted
GOLD 3: Severe	FEV ₁ 30-49% predicted
GOLD 4: Very Severe	FEV ₁ <30% predicted

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COPD Assessment Test (1 of 2)

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

COPD Assessment Test
www.catestonline.org

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COPD Assessment Test (2 of 2)

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

COPD Assessment Test
www.catestonline.org

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The Modified Medical Research Council (MMRC) Dyspnea Questionnaire

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

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Patient Classification

Association between Symptoms, Breathlessness, Spirometric Classification, and Risk of Exacerbations					
RISK GOLD Classification of Airflow Limitation	4	(C) High Risk, Less Symptoms	(D) High Risk, More Symptoms	≥2 or ≥1 leading to hospital admission	RISK Exacerbation history in last 12 months
	3	(A) Low Risk, Less Symptoms	(B) Low Risk, More Symptoms	1	
	2			0	
	1			0	
SYMPTOMS					
CAT < 10		CAT ≥ 10			
BREATHLESSNESS					
mMRC 0-1		mMRC ≥ 2			

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Patient Case

What changes, if any, should be made to WR's maintenance regimen for his COPD?

- Add theophylline
- Change salmeterol to combination salmeterol + fluticasone
- Add roflumilast
- Add acclidinium

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Treatment Options

Long-Acting Beta Agonists Formoterol Arformoterol Indacaterol Salmeterol Olodaterol	Long-Acting Anticholinergics Tiotropium Acclidinium
Inhaled Corticosteroids Beclomethasone Budesonide Ciclesonide Flunisolide Fluticasone Mometasone	Combination Products Vilanterol + Umeclidinium Mometasone + Formoterol Budesonide + Formoterol Fluticasone + Salmeterol Fluticasone + vilanterol
Methylxanthines Theophylline	Phosphodiesterase-4 Inhibitors Roflumilast

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Initial Pharmacologic Management of COPD

Patient Group	Recommended 1 st Choice
A Low Risk, Less Symptoms	SA-ACh PRN or SABA PRN
B Low Risk, More Symptoms	LA-ACh or LABA
C High Risk, Less Symptoms	ICS + LABA or LA-ACh
D High Risk, More Symptoms	ICS + LABA and/or LA-ACh
Other Possible Treatments	Roflumilast Theophylline

SABA: short acting β_2 -agonist
ICS: inhaled corticosteroid
SA-ACh: short-acting anticholinergic

LABA: long acting β_2 -agonist
LA-ACh: long-acting anticholinergic

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Medical History: 43-year smoking history
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Post-bronchodilator PFT: Obtained at last clinic visit 3 months ago
FEV₁ of 1.3 liters (46% of predicted)
FVC of 2.2 liters
FEV₁/FVC ratio of 59%

Patient Case

What medications, if any, would NOT be appropriate to initiate or continue for WR?

- Roflumilast
- Salmeterol monotherapy
- Prednisone
- Simvastatin
- Azithromycin

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Combination Therapy

Retrospective, population-based, longitudinal cohort study (n=11,872)

New users of LABA + ICS (n=8712)

New users of LABAs alone (n=3160)

Outcome	LABAs alone (n=3160)	LABA + ICS (n=8712)	Hazard Ratio
Death and COPD hospitalization	1179 deaths (37.3%) 950 hospitalizations (30.1%)	3174 deaths (36.4%) 2420 hospitalizations (27.8%)	0.92 (95% CI 0.88-0.96)
Death and COPD hospitalization in patients with asthma	597 (66.8%)	1496 (60.4%)	0.84 (95% CI 0.77-0.91)
Death and COPD hospitalization in patients not on LA-ACh	733 (68.4%)	1695 (59.5%)	0.79 (95% CI 0.73-0.86)

Gershon AS, et al. JAMA 2014;312:1114-1121.

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Withdrawal of Inhaled Glucocorticoids The WISDOM Trial

Multicenter, randomized, double blind, active control non-inferiority study (n=2485)

6 week run in: tiotropium + salmeterol + fluticasone

Continuation of triple therapy (n=1243)

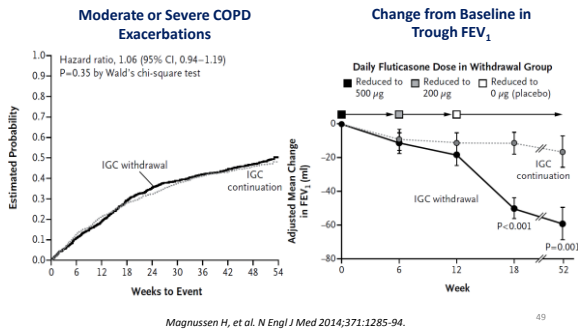
Controlled, stepwise reduction of fluticasone over 12 weeks (n=1242)

- Population**
 - Mean age 63.8 years, 82.5% men
 - 61.2% GOLD 3 and 38.1% GOLD 4 airflow limitation
- Outcomes**
 - Primary:** time to 1st moderate or severe COPD exacerbation
 - Secondary:** time for 1st exacerbation, number of moderate or severe COPD exacerbations, and change from baseline lung function

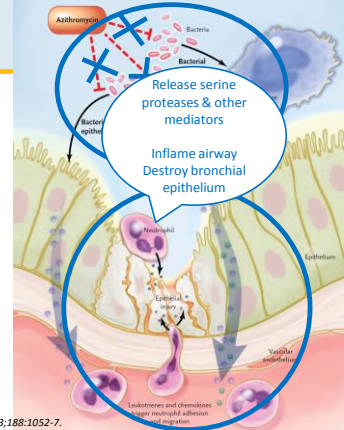
Magnussen H, et al. N Engl J Med 2014;371:1285-94.

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Withdrawal of Inhaled Glucocorticoids The WISDOM Trial



The Role of Chronic Antibiotics for Prevention of Acute Exacerbations



Wenzel RP, et al. *N Engl J Med* 2012;367:340-7.
Miravittles M, et al. *Am J Respir Crit Care Med* 2013;188:1052-7.

Azithromycin for Prevention of COPD Exacerbations

- Study Design**
 - Randomized, placebo controlled trial of 1142 patients for 1 year
 - Azithromycin 250 mg PO daily vs placebo
- Population**
 - Mean age 65 years, 59% male
 - 75% GOLD 3 or 4

Outcome	Azithromycin (n=570)	Placebo (n=572)	p value
Median time to 1 st exacerbation	266 days (95% CI 227-313)	174 days (95% CI 143-215)	<0.001
Exacerbation rate per patient year	1.48	1.83	0.83 (95%CI 0.72-0.95)
Macrolide resistance in patients not colonized at baseline	81%	41%	<0.001

The use of antibiotics, other than treating infectious exacerbations of COPD and other bacterial infections, is currently NOT indicated (Evidence B).

Albert RK, et al. *N Engl J Med* 2011;365:689-98.
GOLD Guidelines, 2014 Update, www.goldcopd.org

Potential Candidates for Long-Term Azithromycin

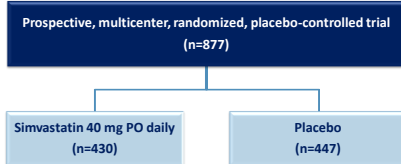
Proposed Criteria for Selecting Candidates for Azithromycin Prophylaxis

- History of COPD with ≥2 acute exacerbations in the previous year
- Compliance with current drug regimen and proper use of inhaler
- Pulse <100 beats per minute
- Corrected QT interval of <450 msec on electrocardiography
- Aminotransferase levels <3 times the upper limit of normal range
- No use of drugs known to cause QT prolongation
- No decrement in hearing on formal audiography
- No allergy to macrolides
- Sputum culture negative for mycobacteria
- No high baseline risk of cardiovascular disease

What is the collateral damage?

Wenzel RP, et al. *N Engl J Med* 2012;367:340-7.
Albert RK, et al. *N Engl J Med* 2011;365:689-98.

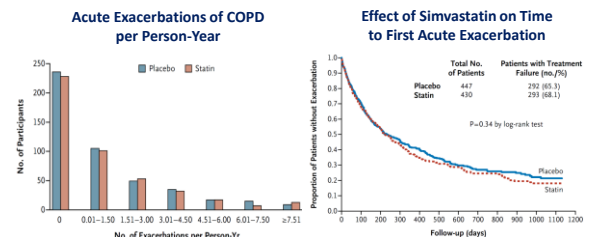
Simvastatin and Prevention of Acute Exacerbations



- Population**
 - Mean age 62.2 years, 44% women, mean FEV₁ 41.6% predicted
 - Excluded patients already on statins or with an indication for a statin
- Outcomes**
 - Primary: annual exacerbation rate (number of exacerbations per person-year)
 - Secondary: time to first exacerbation & severity of exacerbations

Criner GJ, et al. *N Engl J Med* 2014;370:2201-2210.

Simvastatin and Prevention of Acute Exacerbations



Criner GJ, et al. *N Engl J Med* 2014;370:2201-2210.

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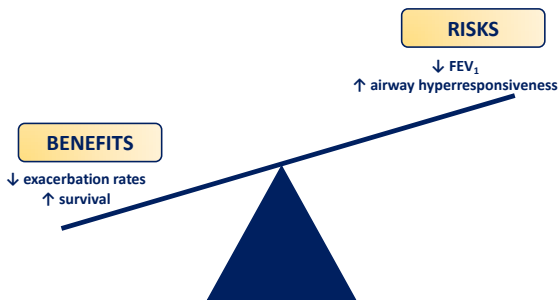
Use of Beta-Blockers in Patients with COPD

Study	Sample	Results Summary
Rutten FH, et al.	2230	32% relative reduction in mortality (only with cardio-selective agents) 29% relative reduction in exacerbations of COPD (with both selective and non-selective agents)
Short PM, et al.	5977	88% of agents used were cardio-selective 22% mortality reduction with beta-blocker use over 4 years
Quint JK, et al.	1063	50% relative reduction in mortality during hospital admission for myocardial infarction

Rutten FH, et al. Arch Intern Med 2010;770:880-7.
Short PM, et al. BMJ 2011;342:d2549.
Quint JK, et al. BMJ 2013;347:f6650.

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Use of Beta-Blockers in Patients with COPD



Rutten FH, et al. Arch Intern Med 2010;770:880-7.
Short PM, et al. BMJ 2011;342:d2549.
Quint JK, et al. BMJ 2013;347:f6650.

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Assess Before Discharge

- Smoking cessation
- Assess inhaler technique
- Education on role on maintenance regimen
- Assess vaccination status
 - *S. pneumoniae*
 - Influenza

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Updates on Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Questions?