

## Evidence-based Management of COPD

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## Disclosures

None

## Outline

- Quick review of GOLD COPD staging
- Antibiotic stewardship in COPD exacerbations
- Inhaled corticosteroids for COPD
- Anti-eosinophil biologics (Mab's) for COPD
- When NOT to prescribe oxygen in COPD
- Non-invasive ventilation for STABLE COPD
- Lung volume reduction for COPD

## Case #1

A 64 y/o M is admitted for acute COPD exacerbation. Symptoms include increased dyspnea and productive cough. Procalcitonin is 0.15 ng/mL. C-reactive protein is 65 mg/L. Chest X-ray is clear without consolidation.

Scheduled albuterol/ipratropium via nebulization and prednisone 40mg PO daily is initiated.

What is the best next step in management?

- A) Continue current management and monitor respiratory status closely
- B) Stop PO prednisone and initiate methylprednisolone IV
- C) Obtain a chest CT to assess for pneumonia
- D) Initiate azithromycin PO x 5 days
- E) Initiate levofloxacin PO x 14 days
- F) Initiate cefepime IV x 5 days

## Case #1

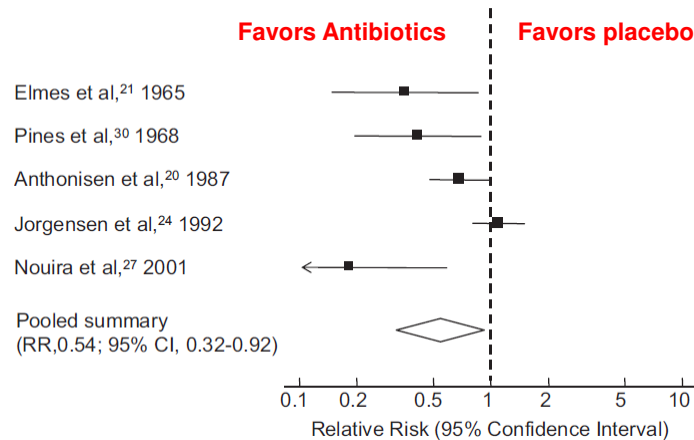
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## AE-COPD: Antibiotics

### Meta-analysis:

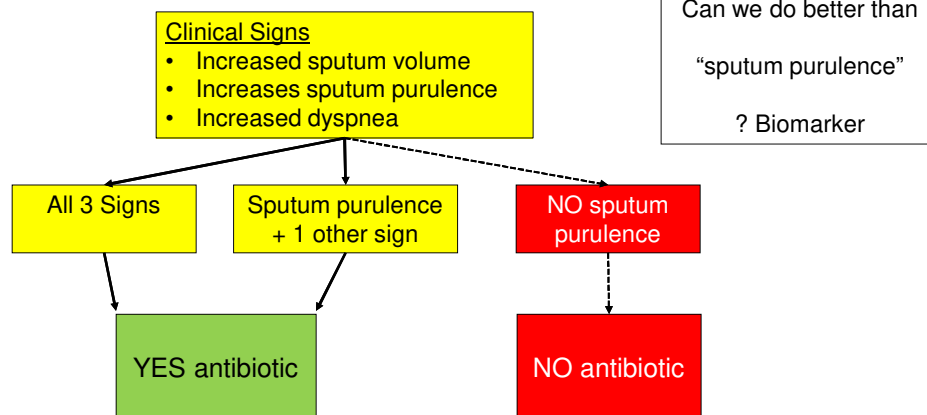
- Antibiotics reduce treatment failures
- When studies stratified by treatment setting antibiotics reduce treatment failures only in hospitalized patients



Chest 2008; 133: 756-66

## AE-COPD: Antibiotics

### Simple “antibiotic algorithm” for AE-COPD



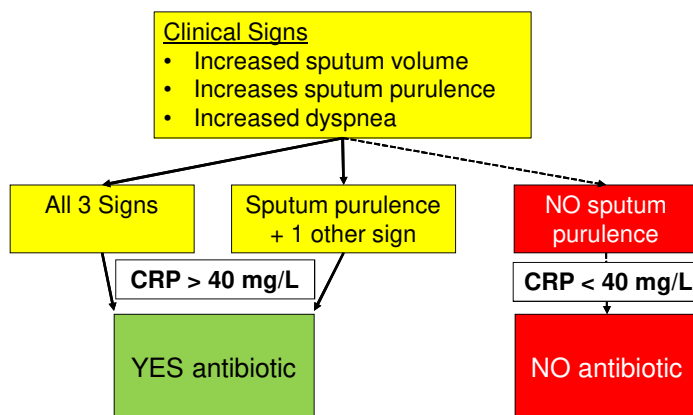
Chest 2008; 133: 756-66

## CRP: marker for antibiotic response in COPD?

- In-hospital RCT of CRP in COPD exacerbations Prins HJ et al. *Eur Resp J* 2019 **53**: p1802014
  - 220 patients treated with antibiotics per clinical (Anthonisen) criteria versus antibiotics for CRP > 50 mg/L
  - CRP measured at admit and 24 H; if CRP > 50 mg/L at 24H, then antibiotics started
  - **ANTIBIOTIC USE DECREASED from 46% of patients to 31% using CRP**
  - **No difference in outcomes: acute treatment failure, hospital LOS, time to next exacerbation, change in QOL score**
- Ambulatory RCT of CRP in COPD exacerbations Butler CC et al. *N Engl J Med* 2019 **381**: p111
  - 653 patients treated with antibiotics per clinical criteria versus CRP-guided decision
    - CRP < 20 mg/L NO antibiotics, > 40 mg/L antibiotics advised (20-40, clinical criteria)
  - **ANTIBIOTIC USE DECREASED from 69% to 47% using CRP**
  - **No difference in outcomes: including treatment failures and 6 month hospitalization rate, or incidence of pneumonia**

## AE-COPD: Antibiotics

### Simple “antibiotic algorithm” for AE-COPD



## COPD Exacerbation: *antibiotic selection*

- For inpatients, consider a sputum culture
- No history of prior resistant bacteria / pseudomonas or additional structural lung disease, such as bronchiectasis:
  - Consider azithromycin, respiratory quinolone, or 3<sup>rd</sup> generation cephalosporin
- History of pseudomonas, resistant gram-negative rods, consider:
  - Cefepime, ceftazidime, or piperacillin-tazobactam
- Total treatment course: 5-7 days
- Treatment failure -> consider repeat chest imaging and follow-up sputum cultures

## Case #2

A 58 y/o F admitted for acute exacerbation of COPD has progressive respiratory distress, tachypnea despite corticosteroids, antibiotics, and nebulized albuterol/ipratropium. Her mental status is normal.

ABG: pH 7.32 PaCO<sub>2</sub> 65 PaO<sub>2</sub> 88 on 2 L/minute supplemental oxygen by nasal cannula

What is the best next step in the management of acute respiratory failure in this patient?

- A) urgent anesthesia and ICU consultation for intubation / ventilation.
- B) initiation of Hi Flow nasal cannula oxygen
- C) initiation of bilevel positive airway pressure (BiPAP)
- D) initiation of theophylline IV

## Case #2

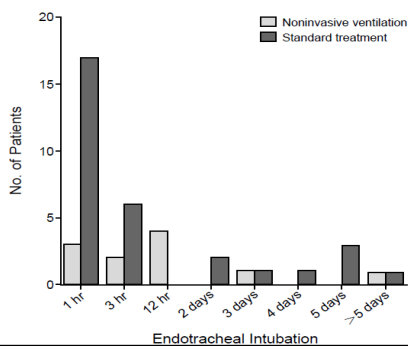
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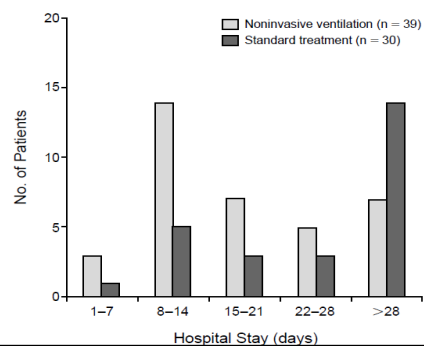
### NIPPV for Severe AE-COPD NEJM 1995 333: p817

- All patients with severe AE-COPD and evidence of respiratory failure
  - RR > 25 - 30
  - Acute hypercarbia and respiratory acidosis (pH < 7.35)
- Should be considered for non-invasive positive pressure ventilation (NIPPV)
- *NIPPV likely not an option for severe respiratory failure: pH < 7.3, poor mental status, complicating shock*

#### NIPPV = LESS intubations



#### NIPPV = LESS hospital days



## Case #3

A 72 y/o M is now improving from an acute COPD exacerbation after pulse prednisone, empiric antibiotics, and nebulized bronchodilators and is now ready for discharge on hospital day #4.

How long should systemic corticosteroids be continued?

- A) until symptoms begin to improve
- B) 5 days total
- C) 5 days at 40mg followed by an individualized taper
- D) 14 days

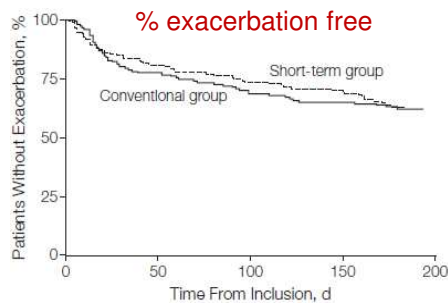
## Case #3

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- D) 14 days

## AE-COPD: using *less* corticosteroid

- REDUCE: 314 COPD pts
- FEV1 ~32% predicted
- 80% GOLD C + D
- RCT of prednisone 40 mg QD x 5 DAYS versus 14 DAYS



- Prednisone for 5 days NOT inferior to 14 days of treatment
- 14 days of treatment NOT associated with increased corticosteroid – related adverse events

- *Consider:*
- *Prednisone 40 mg daily x 5 days only for AE-COPD*

JAMA 2013. 309(21): 2223

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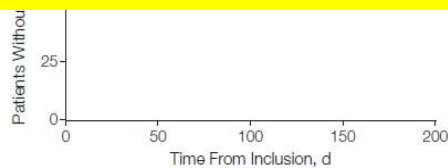
- Prednisone for 5 days NOT inferior to 14 days of treatment

\*\*\*

**Based on patient-specific factors, a prednisone starting dose > 40 mg daily may lead to fewer early treatment failures:**

**Chest, 2021-11-01, Volume 160, Issue 5, Pages 1660-1669**

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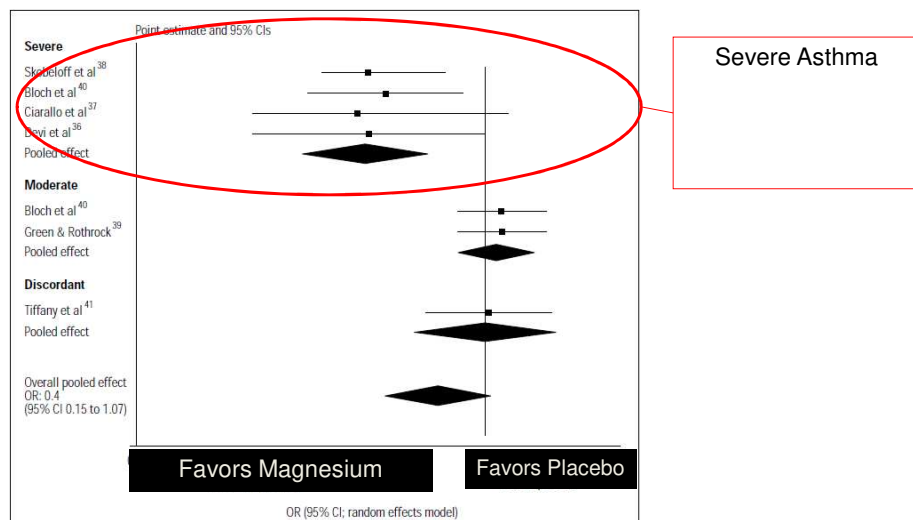
*5 days only for AE-COPD*

## Therapies for COPD versus ASTHMA Exacerbations

Treatment	ASTHMA	COPD
Albuterol and ipratropium	YES	YES
Corticosteroids	YES	YES
Oxygen and NIV (as indicated)	YES	YES
Antibiotics	No	YES*
Magnesium sulfate 2G IV x 1	YES	<b>YES</b>

## Mg++ for AE – asthma: the evidence mounts...

- Meta-analysis: Ann of Emerg Med 36 (3): p181  
– Mg++ IV x 1 most affective in SEVERE ASTHMA



## Mg++ for AE – COPD: new for 2022

Ni H, Aye SZ, Naing C.

Magnesium sulfate for acute exacerbations of chronic obstructive pulmonary disease.

*Cochrane Database of Systematic Reviews* 2022, Issue 5. Art. No.: CD013506.

- Intravenous magnesium, 2G IV x 1, associated with:
  - *Lower hospital admission rate for emergency department patients*
  - *Lower hospital length of stay*
  - *Improved dyspnea scores*
- NO benefit from NEBULIZED magnesium
- Consider early IV magnesium in severe COPD exacerbations and in cases of asthma / COPD overlap

## Case #4

A 77 y/o M admitted for acute COPD exacerbation is now improved and ready for discharge, this is his third admission for COPD in 18 months.

At baseline, he gets SOB walking “steep hills.”

Baseline pulmonary function tests notable for:

FEV1 2.2 L (80%) corresponding to mild obstruction

FEV1 / FVC 80%

What is the most important information in determining his optimal discharge regimen?

- A) FEV1
- B) FEV1 / FVC
- C) Number of exacerbations per year
- D) Exercise capacity
- E) A + B
- F) C + D

## Case #4

What is the most important information in determining his optimal discharge regimen?

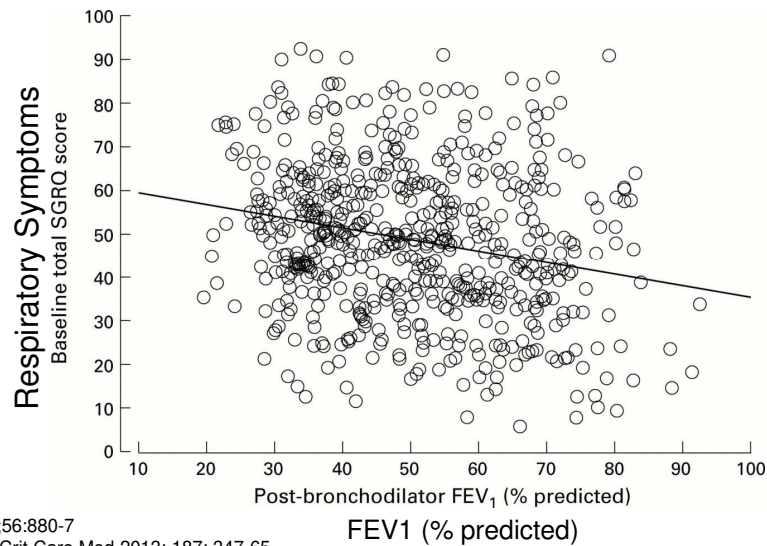
- A) FEV 1
- B) FEV 1 / FVC
- C) Number of exacerbations per year
- D) Exercise capacity
- E) A + B
- F) **C + D**

## GOLD COPD Classification Guides Treatment Selection

(including inhaled steroids!)

A 4 slide review of the  
GOLD Classification

## FEV1 Correlates Poorly with COPD Symptoms



Thorax 2001;56:880-7

Am J Respir Crit Care Med 2013; 187: 347-65

## New GOLD COPD Classification

Patient Group	Exacerbations	Dyspnea
<b>Group A</b> Few Exacerbations Less Dyspnea	0 to 1 per year	Mild ( $< 2$ MMRC) Do family/friends have to stop on level ground to wait for you? No - Yes +

## New GOLD COPD Classification

Patient Group	Exacerbations	Dyspnea
<b>Group A</b> Few Exacerbations Less Dyspnea	0 to 1 per year	Mild ( $< 2$ MMRC)
<b>Group B:</b> Few Exacerbations More Dyspnea	0 to 1 per year	Moderate-severe ( $> 2$ MMRC)
<b>Group E:</b> +Exacerbations (E)  <i>Additional Factors*</i>	$\geq 2$ per year or, 1 Hospital Admit /yr  <i>*Blood eosinophils <math>&gt; 300</math> or hospital admissions?</i>	N/A

## New GOLD COPD Classification

Patient Group	Exacerbations	Grade	FEV <sub>1</sub>
<b>Group A</b> Few Exacerbations Less Dyspnea	<b>So... do we care about FEV<sub>1</sub>?</b>	1	$\geq 80\%$
		2	$\geq 50\%$ and $< 80\%$
	<b>Not too much, but we add it in...</b>	3	$\geq 30\%$ and $< 50\%$
<b>Group E:</b> More Exacerbations	<b>FEV1 in this case 80% → "grade 1"</b>	4	$< 30\%$ predicted
<b>Final COPD Stage: GROUP E (grade 1)</b>			

## Case #5

A 65 yo M admitted for acute COPD exacerbation is now improved and ready for discharge.

At baseline, he gets SOB with limited level walking, and this is his first exacerbation this year consistent with GOLD group B

His home COPD regimen includes budesonide / formoterol + albuterol / ipratropium, he but has been only on albuterol / ipratropium for 1 year due to cost of therapy.

What is the optimal discharge regimen for this patient?

- A) RESUME a cheaper ICS / LABA (use albuterol / ipratropium prn)
- B) START tiotropium (use albuterol prn)
- C) Resume budesonide / formoterol and add tiotropium (use albuterol prn)
- D) Refer to pulmonary rehabilitation
- E) B + D

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- D) Refer to pulmonary rehabilitation
- E) **B + D**

## Goals of COPD Treatment

- Reduce symptoms
  - Relieve dyspnea, cough, and congestion
  - Improve exercise tolerance
  - Improve health status
- Reduce risk
  - Prevent disease progression
  - Prevent exacerbations
  - Reduce mortality

## Treatment of Stable COPD

- Primary and Secondary Prevention
  - Smoking Cessation / Exposure Reduction
  - Vaccinations: Influenza, COVID-19, RSV, and pneumococcal
- Nonpharmacologic Treatment
  - Oxygen Supplementation
  - Nocturnal positive pressure ventilation (for chronic hypercapnia)
  - Regular Exercise and / or Pulmonary Rehabilitation
- Pharmacologic Treatment
  - Remember, treats symptoms with little / no effect on long term lung function or mortality
- Surgical Treatment
  - Lung volume reduction, bullectomy, lung transplantation

## Pharmacologic Treatment of Stable COPD

- Short acting bronchodilators
- Long acting bronchodilators (BID)
  - Beta agonists: salmeterol, formoterol
  - Muscarinic antagonists: aclidinium
- Ultra long acting bronchodilators (QD)
  - Beta agonists: vilanterol, indacaterol, olodaterol
  - Muscarinic antagonists: tiotropium, umeclidinium, glycopyrrolate
- Inhaled corticosteroids
- Other anti-inflammatories: azithromycin, roflumilast (PDE4 inhibitor)
- Anti eosinophil – directed biologics (e.g dupilumab)

## COPD Therapy: putting it together by GOLD Stage

GOLD GROUP	Initial Pharmacotherapy of COPD
A	Short acting anti-cholinergic PRN or Short acting Beta agonist PRN

## COPD Therapy: putting it together by GOLD Stage

GOLD GROUP	Initial Pharmacotherapy of COPD
<b>A</b>	Short acting anti-cholinergic PRN or Short acting Beta agonist PRN
<b>B</b>	Long Acting Beta Agonist (LABA) or, Long Acting Anti-Muscarinic (LAMA)
<b>E</b>	LAMA + LABA or <b><i>Inhaled corticosteroid if exacerbations persist</i></b>
<b>E*</b>	LAMA + LABA + <b><i>Inhaled corticosteroid</i></b> <ul style="list-style-type: none"> <li>• <i>If exacerbations persist and no evidence of eosinophilia or asthma overlap</i> <ul style="list-style-type: none"> <li>➢ CONSIDER adding a MACROLIDE or ROFLUMILAST (FEV1 &lt;50%).</li> </ul> </li> <li>• <i>If exacerbations persist and there is evidence of eosinophilic airway inflammation (exhaled NO &gt; 50 ppb, blood eos &gt; 300)</i> <ul style="list-style-type: none"> <li>➢ CONSIDER targeted anti-eosinophil treatment</li> </ul> </li> </ul>

## The Evidence for Long Acting Anti-Muscarinic Antagonists (LAMA)

Tiotropium (QD)

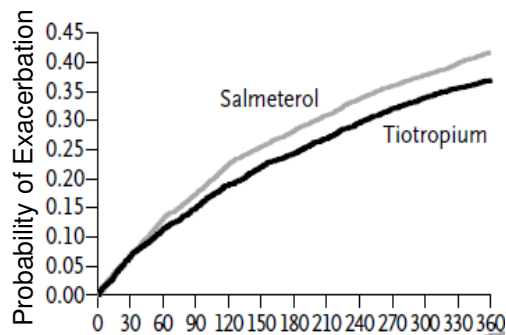
Aclidinium (BID)

Umeclidinium (QD)

Glycopyrrolate (QD)

## Prevention of Exacerbations with Tiotropium in COPD (POET-COPD): NEJM 2011: 364 p1093

- 7376 patients with severe COPD (FEV1 1.4 49%) and at least 1 exacerbation in year prior randomized:
  - Tiotropium 18 mcg QD v Salmeterol 50 mcg BID x 1 year
  - The majority of patients were on an ICS +/- methylxanthine



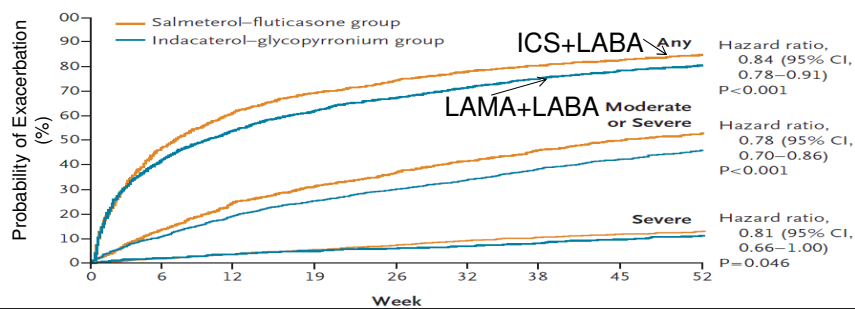
- *Tiotropium more effective than salmeterol in preventing moderate and severe exacerbations*

- *Effect independent of concomitant ICS use*

Higher Potency LAMAs  
versus  
Inhaled Corticosteroids for Stable  
COPD

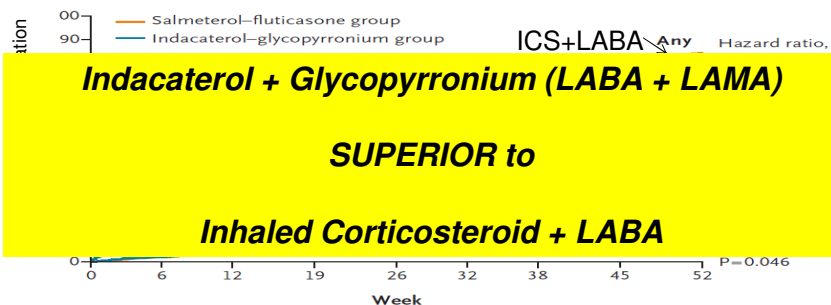
## Fluticasone / Salmeterol *versus* indacaterol / glycopyrronium

- FLAME trial, NEJM 2016
- 1680 subjects with severe COPD, FEV1 44%, GOLD D (75% of patients)
  - Randomized to
    - Salmeterol/Fluticasone (50/500ug) bid or,
    - Indacaterol 110 ug QD + glycopyrronium 50 ug QD
  - LABA + LAMA only
- Outcomes at 52 weeks: *COPD exacerbation rate*



## Fluticasone / Salmeterol *versus* indacaterol / glycopyrronium

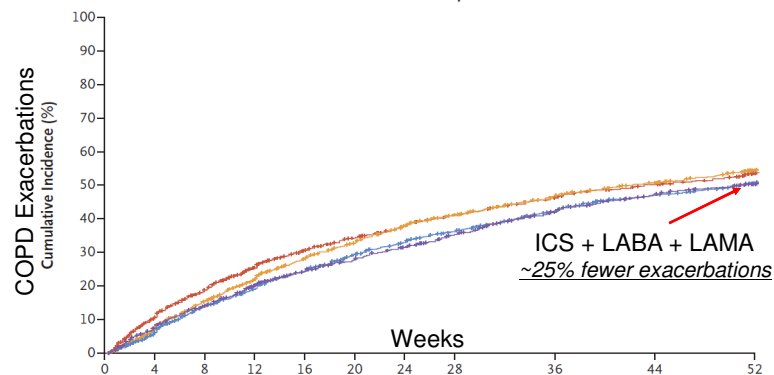
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## Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD

- ETHOS trial: *NEJM* 383 (1) July 2020
  - Budesonide (high or low dose) + glycopyrrolate + formoterol - versus
  - Budesonide + formoterol – versus
  - Glycopyrrolate + formoterol

A Moderate or Severe COPD Exacerbation in the Modified Intention-to-Treat Population



Stepping back...

Inhaled corticosteroids do decrease  
exacerbation rate in COPD,  
*But increase the risk of pneumonia*

OK to start after failing LABA/LAMA therapy and/or there  
is evidence of eosinophilic airway inflammation

## Case #6

- 58 yo F with COPD GOLD E on high dose ICS, a LABA, a LAMA and still requires prednisone 3-4 x year due to exacerbations: she is now admitted for another COPD exacerbation
- Labs revealed:
  - Peripheral Eos 8% absolute count 750
  - IgE total ~ 110 (mildly elevated)
  - RAST + for seasonal pollens only

What additional treatment can be considered at discharge for this patient?

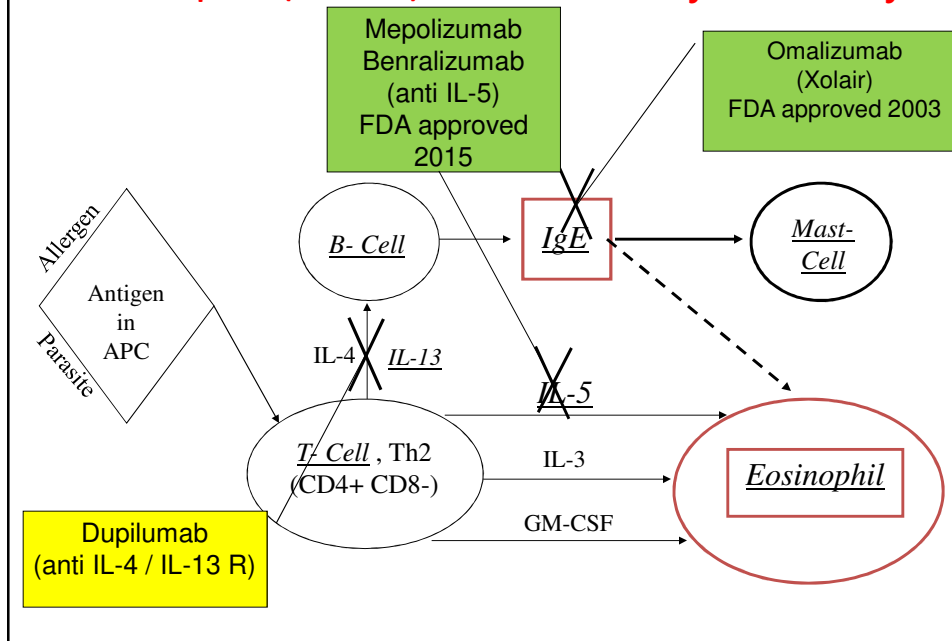
- A) Standing oral prednisone
- B) Dupilumab
- C) Theophylline
- D) Change to a NEBULIZED inhaled corticosteroid

## Case #6

What additional treatment can be considered at discharge for this patient?

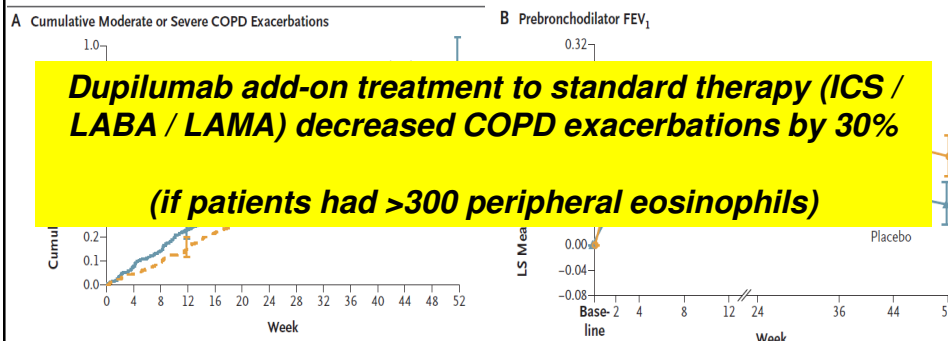
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- B) Dupilumab**
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## Eosinophil ("Th2") Inflammatory Pathway



## Dupilumab (IL4 / IL13R Mab) for COPD with Peripheral Eosinophilia

- NEJM 2023: DOI: 10.1056/NEJMoa2303951
- 939 subjects with COPD, FEV1 1.4 50%, GOLD E
  - Randomized to
    - ICS / LABA / LAMA + Placebo or DUPILUMAB 300 mg SC q 2 weeks
  - Outcomes at 52 weeks: *exacerbation rate and FEV1*



## COPD Therapy: putting it together by GOLD Stage

GOLD GROUP	Initial Pharmacotherapy of COPD
A	Short acting anti-cholinergic PRN or Short acting Beta agonist PRN
B	Long Acting Beta Agonist (LABA) or, Long Acting Anti-Muscarinic (LAMA)
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## Case #7

A 75 y/o M with GOLD group B, grade 4 COPD (FEV 1 0.8 L 30%, dyspnea with limited level walking and < 1 exacerbation per year) and no cardiac disease is ready for discharge after admission for cellulitis.

His nurse obtains pulse oximetry on room air which is 94% at rest and 85% with ambulation, improving to 95% with 3 L/minute nasal cannula oxygen.

What is the best option for management of his ambulatory hypoxemia?

- A) Discharge on O<sub>2</sub> 3L/min with exertion and sleep
- B) Discharge on O<sub>2</sub> 3L/min with exertion only
- C) Discharge with NO supplemental oxygen
- D) Discharge on O<sub>2</sub> 3L/min 24 h / day

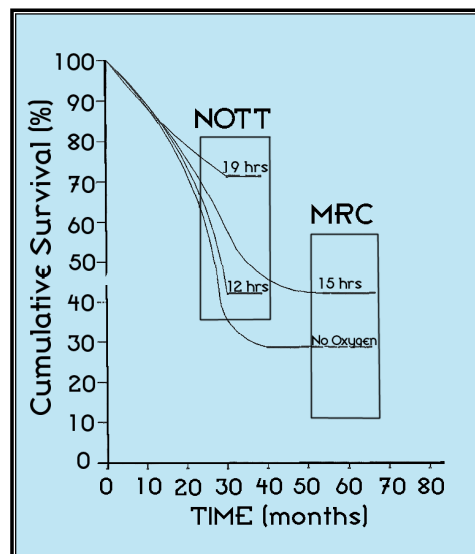
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## Oxygen Supplementation in COPD

- In the 1970s...
- 290 COPD patients with SEVERE RESTING hypoxemia studied +/- oxygen
- Criteria:
  - SaO<sub>2</sub> ≤88% at REST
  - SaO<sub>2</sub> ≤90% with R-sided CHF or polycythemia
- Long-term oxygen therapy decreased mortality and improved QOL



Ann Intern Med 1980; 93: 391-8  
Lancet 1981; 1: 681-6  
Clin Chest Med 1990; 11: 505-21

## Oxygen Supplementation: before 2016

- Indications for supplemental O<sub>2</sub>:
  - SaO<sub>2</sub> ≤88% AT REST
  - SaO<sub>2</sub> ≤90% with R-sided CHF or polycythemia
- Supplemental O<sub>2</sub> is of unclear benefit with:
  - MODERATE hypoxemia at REST = SaO<sub>2</sub> 88 - 90%
  - Hypoxemia with EXERTION ONLY, SaO<sub>2</sub> ≤88%
    - O<sub>2</sub> costs > \$2 Billion / year!

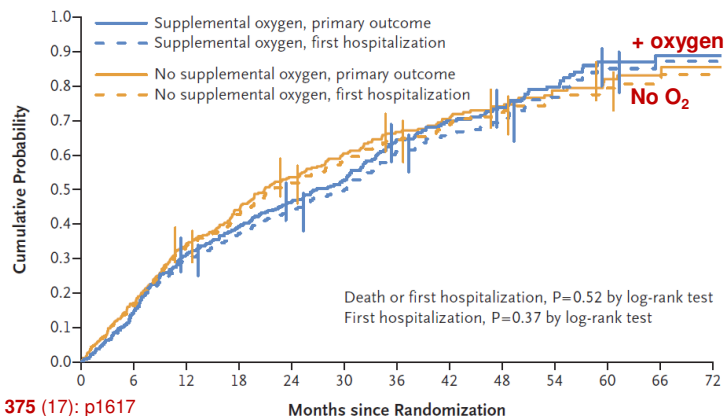
## Oxygen Supplementation: 2016 LOTT Study

- NEJM 2016 **375** (17): p1617
- 738 COPD patients with:
  - SaO<sub>2</sub> 89 - 93% AT REST or,
  - SaO<sub>2</sub> 80 - 90% with exertion
    - 30% of patients had a SaO<sub>2</sub> < 86% !
- Interventions:
  - O<sub>2</sub> titrated for SaO<sub>2</sub> > 90%
    - x 24h / day for patients with RESTING hypoxemia
    - with exertion and sleep for patients with only exertional hypoxemia
- Outcomes:
  - Primary = composite of death and first hospitalization for any cause
  - Secondary = QOL, dyspnea, 6 min walk distance, depression

## Oxygen Supplementation: LOTT Study *Results*

- No Benefit to supplemental oxygen when:
  - Resting  $\text{SaO}_2$  is  $> 88\%$  or,
  - When  $\text{SaO}_2$  is  $> 80\%$  with exertion
- No Benefit even with secondary endpoints: dyspnea, 6 min walk

### Probability of DEATH or HOSPITALIZATION

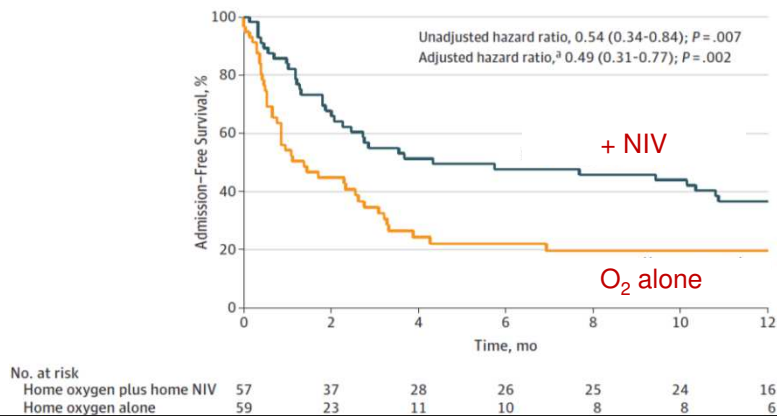


## Oxygen Supplementation: 2022

- The current evidence supports supplemental  $\text{O}_2$  when:
  - The  $\text{SaO}_2$  is  $\leq 88\%$  **AT REST**
  - And likely, when the  $\text{SaO}_2$  is  $\leq 90\%$  with cor pulmonale or polycythemia (hematocrit  $> 55\%$ )
- The current evidence does **NOT** support supplemental  $\text{O}_2$  with:
  - Exertional hypoxemia – even to an  $\text{SaO}_2$  of  $80\%$  !
  - Areas of uncertainty for supplemental  $\text{O}_2$ :
    - Exertional hypoxemia with  $\text{SaO}_2 < 80\%$
    - Exertional dyspnea responding to  $\text{O}_2$ , but with an “acceptable”  $\text{SaO}_2 (> 80\%)$

## NIPPV for STABLE COPD: evidence mounts after 2017

- JAMA. 2017; 317(21): 2177-2186
- 120 COPD patients with PaCO<sub>2</sub> > 50 mmHg and pH > 7.30
  - NIV titrated to PaCO<sub>2</sub> decrease of at least 20%
  - 12 month follow-up
  - Primary end point: time to hospital readmission or death

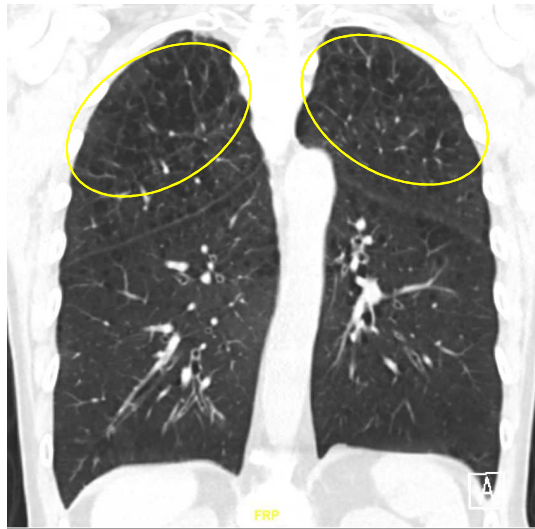


## Surgical Therapy for COPD / Emphysema

Lung Volume Reduction...

It's Back!

## Lung Volume Reduction



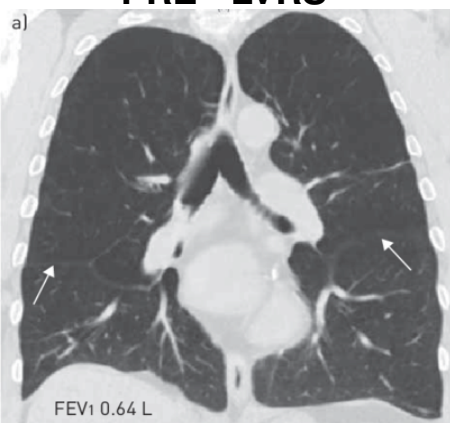
PFTs with OBSTRUCTION and HYPERINFLATION

Variable	Actual	% Pred
FVC	2.71	91
FEV1	0.88	31
FEV1/FVC	0.32	--
TLC	<u>7.92</u>	<u>148</u>
RV	<u>5.16</u>	<u>222</u>

57

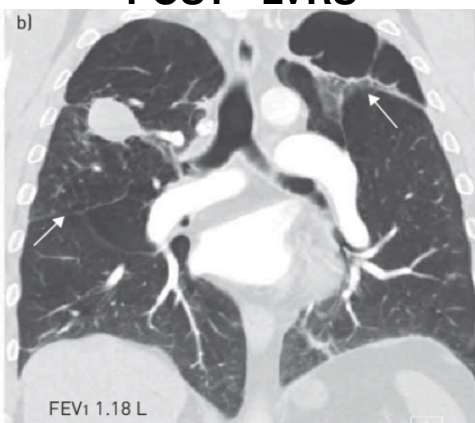
## Lung Volume Reduction: IMPROVES OBSTRUCTION

**PRE - LVRS**



**FEV<sub>1</sub> 0.64 L**

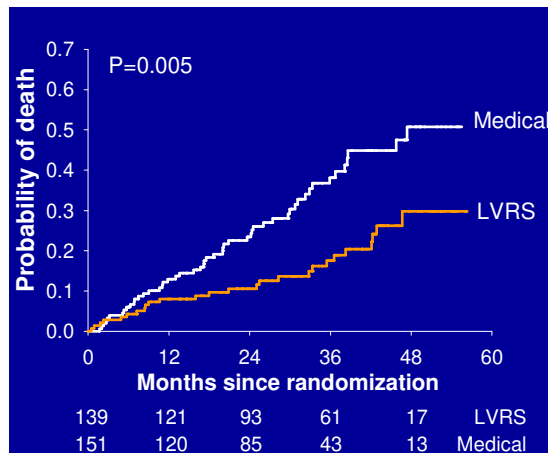
**POST - LVRS**



**FEV<sub>1</sub> 1.18 L**

## SURGICAL Lung Volume Reduction: Mortality

Upper-lobe disease and low exercise capacity

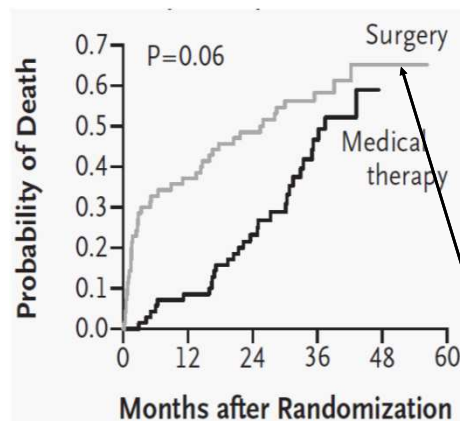


**LVRS:**  
**Mortality**  
**Decreased**

NEJM 348:2059-73, May 22, 2003

## SURGICAL Lung Volume Reduction:

NARROW patient selection / benefit -> dampened enthusiasm



Unless a patient has:

- 1) UPPER lobe emphysema and
- 2) Low baseline exercise capacity

**LVRS outcome WORSE than medical therapy**

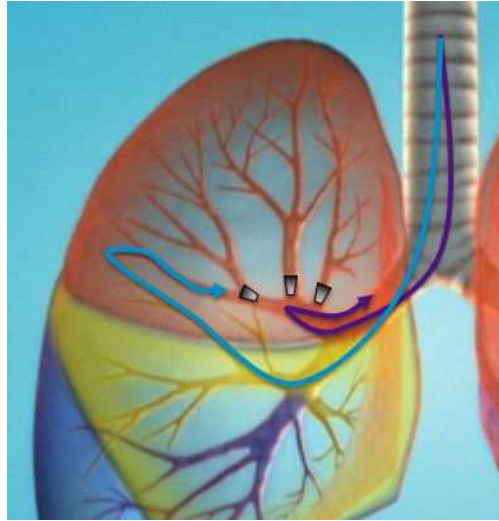
Outcome for HIGH-RISK LVRS patients:

- 1) Homogeneous emphysema
- 2)  $FEV_1 < 20\%$  predicted
- 3)  $Dlco < 20\%$  predicted

NEJM 348:2059-73, May 22, 2003

## **Bronchoscopic** Lung Volume Reduction

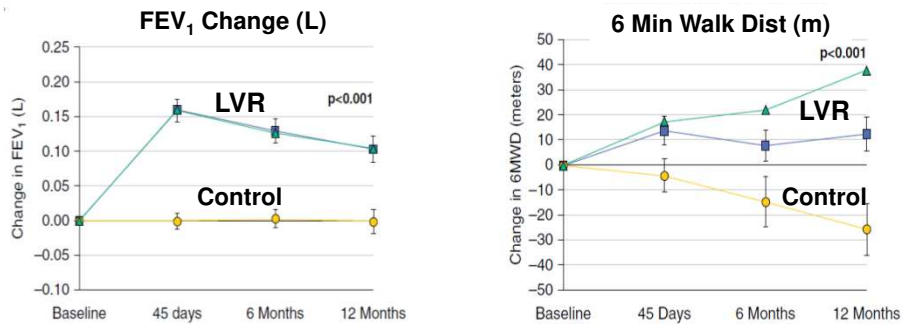
- LESS invasive
  - Lower peri-procedure morbidity/mortality?
  - Faster recovery time?
  - Same results?



## Bronchoscopic Lung Volume Reduction

- Patient Selection
  - COMPLETE smoking cessation
  - FEV<sub>1</sub> 15-45% predicted (severe)
  - Hyperinflation with TLC ≥ 100% and RV ≥ 175%
  - DLco ≥ 20%
  - Emphysema on chest CT scan
    - Homogeneous or heterogeneous
- Randomized Clinical Trial
  - *Am J Respir Crit Care Med* 2018 **198**(9): pp1151-1164
- 120 pts to valve placement
- 62 to medical therapy
- 12 month end points:
  - FEV<sub>1</sub> and lung mechanics
  - 6 minute walk distance
  - Dyspnea Score
  - Safety

## Bronchoscopic Lung Volume Reduction *It works...!*



*...But!*

~ 26% post procedure PNEUMOTHORAX rate, most require chest tube +/- valve removal

3 procedure related deaths in first 45 days (120 LVR patients)

## Key Summary Points

- COPD staging, GOLD A,B,E, incorporates only level of dyspnea and # of acute exacerbations / year
- Beta-agonists and long-acting anti-muscarinic bronchodilators are the main COPD therapies; add inhaled corticosteroids for patients with frequent COPD exacerbations
- In patients with stable COPD and oxygen desaturation with exertion only, supplemental oxygen does not clearly improve mortality
- Antibiotic treatment in COPD exacerbations should be reserved for patients with increased sputum volume / purulence

## Key Summary Points

- Avoid over treating stable COPD with inhaled corticosteroids
- Consider referral for nocturnal ventilation for COPD patients with chronic hypercarbia
- COPD patients with peripheral eosinophilia may benefit from targeted anti-eosinophil therapies
- In advanced COPD, bronchoscopic lung volume reduction using endobronchial valves may be an option for some patients

## Selected References

- Wedzicha, JA et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med.* 2016. **374**: p2222-34
- Magnussen, H et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med.* 2014. **371**: p1285 – 1294
- The long-term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med.* 2016. **375**: p1617-27
- Butler, CC et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med.* 2019. **381(2)**: p111-120