Brigham and Women's Hospital
Founding Member, Mass General Brigham

Evidence-based Management of COPD

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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Disclosures

None

Outline

- Quick review of GOLD COPD staging
- Inhaled corticosteroids for COPD
- When NOT to prescribe oxygen in COPD
- Non-invasive ventilation for STABLE COPD?
- Antibiotic stewardship in COPD exacerbations
- Bonus topics!
  - High flow nasal oxygen

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

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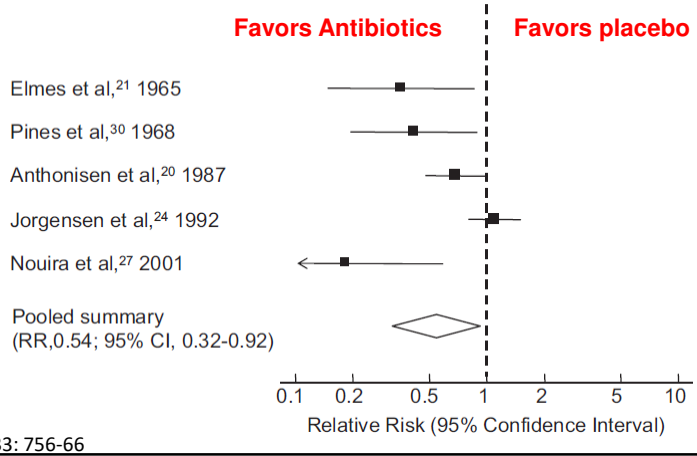
AE-COPD: Antibiotics

Meta-analysis:

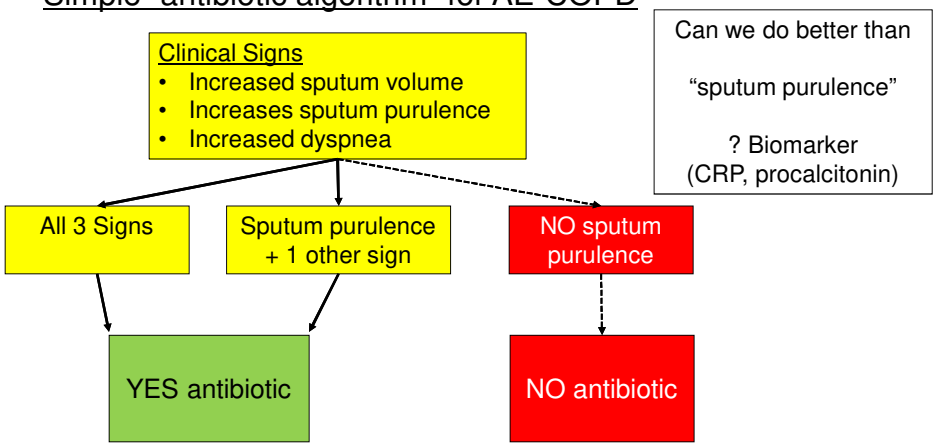
- Antibiotics reduce treatment failures
- When studies stratified by treatment setting antibiotics reduce treatment failures only in hospitalized patients



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***

Procalcitonin in COPD Exacerbations: NOT so fast…

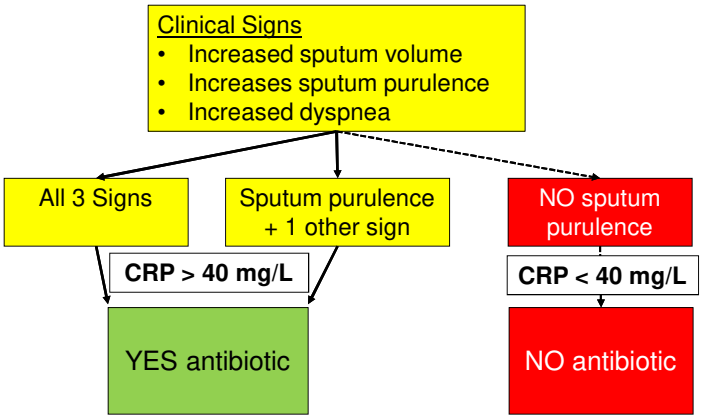
- Meta analysis of 8 trials examining procalcitonin in COPD exacerbations Mathioudakis, AG et al. *Eur Resp Rev* 2017 **26**: p160073
  - Procalcitonin-guided decision making reduced antibiotic exposure
  - No definitive difference in outcomes, ***BUT there was a trend toward increased RE HOSPITALIZATION rate in the procalcitonin group***

- Single center RCT of procalcitonin in 302 ICU-level COPD exacerbations Daubin C et al. *Intensive Care Med* 2018 **44**: p428
  - ***3 month mortality HIGHER in procalcitonin group (31% v 12%)***
  - ***Mortality effect mostly in patients where INITIAL antibiotics held per procalcitonin***

More studies are needed before procalcitonin is used in COPD exacerbations

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 3rd 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 PaCO2 65 PaO2 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

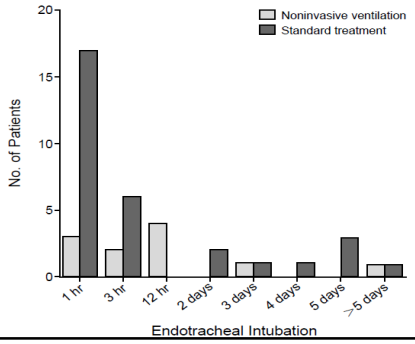
What is the best next step in the management of acute respiratory failure in this patient?

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

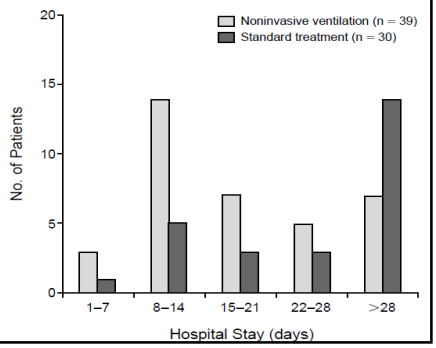
NIPPV for Severe AE-COPD NEJM 1995 333: p817

- 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

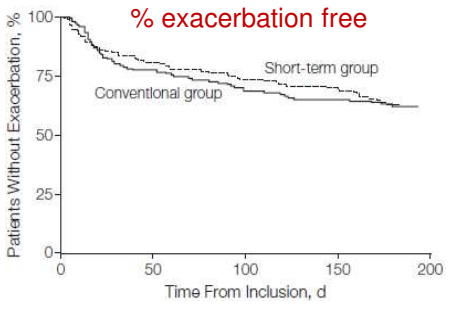
Case #3

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

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*

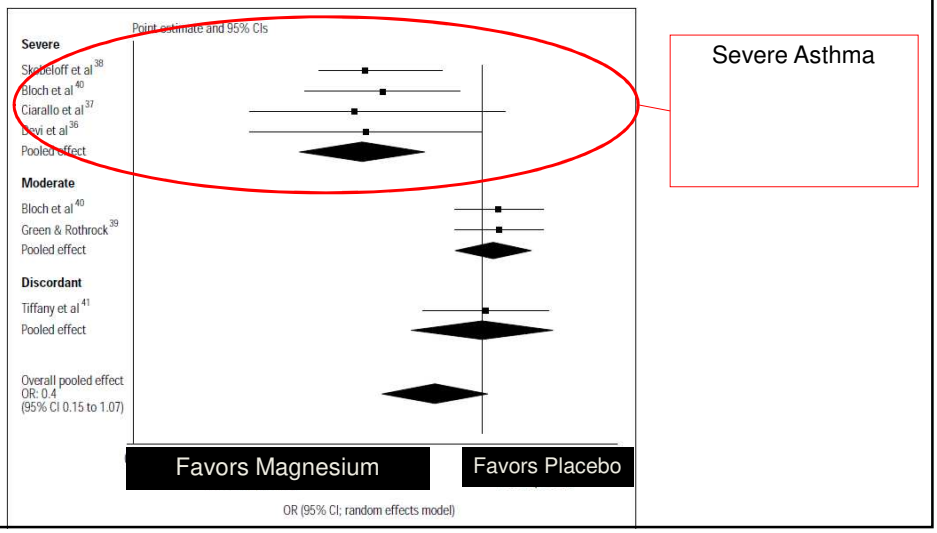
JAMA 2013. 309(21): 2223

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	?

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:
FEV 1 2.2 L (80%) corresponding to mild obstruction
FEV / 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?

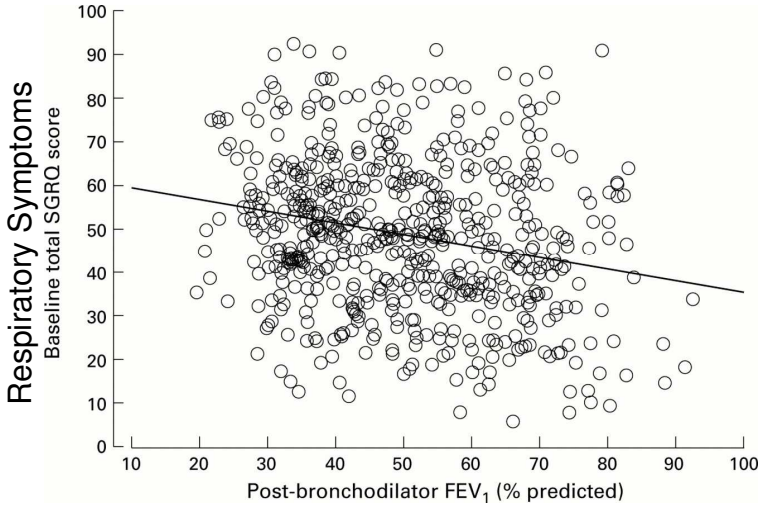
A) FEV 1
B) FEV 1 / FVC
C) Number of exacerbations per year
D) Exercise capacity
E) A + B
F) C + D

GOLD COPD Classification Guides Treatment Selection

(including inhaled steroids!)

A 4 slide review of the GOLD Classification

FEV1 Correlates Poorly with COPD Symptoms



FEV1 (% predicted)

Thorax 2001;56:880-7
Am J Respir Crit Care Med 2013; 187: 347-65

GOLD COPD Classification

Patient Group	Exacerbations	Dyspnea
Group A 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
Group A Few Exacerbations Less Dyspnea	0 to 1 per year	Mild (< 2 MMRC)
Group B: Few Exacerbations More Dyspnea	0 to 1 per year	Moderate-severe (> 2 MMRC)
Group C: More Exacerbations Less Dyspnea	≥2 per year or, ≥ 1 Hospital Admit /yr	Mild (< 2 MMRC)
Group D: More Exacerbations More Dyspnea	≥2 per year or, ≥ 1 Hospital Admit /yr	Moderate – Severe (> 2 MMRC)

New GOLD COPD Classification

Patient Group	Exacerbations	Grade	FEV_1
Group A Few Exacerbations Less Dyspnea	**So… do we care about FEV_1?**	1	≥80%
	Not too much, but we add it in…	2	≥50% and <80%
		3	≥30% and <50%
Group C: More Exacerbations Less Dyspnea	**FEV1 in this case 80% → "grade 1"**	4	<30% predicted

Final COPD Stage:
GROUP C (grade 1)

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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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

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)

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

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A	Short acting anti-cholinergic PRN or Short acting Beta agonist PRN
B	Long Acting Beta Agonist (LABA) or, Long Acting Anti-Muscarinic (LAMA)
C	LAMA -> then LAMA+ LABA or ***Inhaled corticosteroid if exacerbations persist***
D	LAMA + LABA → ***Inhaled corticosteroid if exacerbations persist*** -> CONSIDER adding a MACROLIDE or ROFLUMILAST (FEV1 <50%), if exacerbations persist

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

Tiotropium (QD)

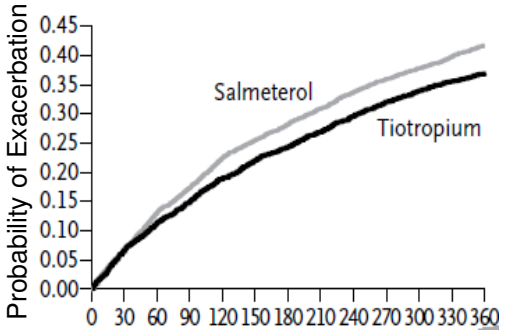
Aclidinium (BID)

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



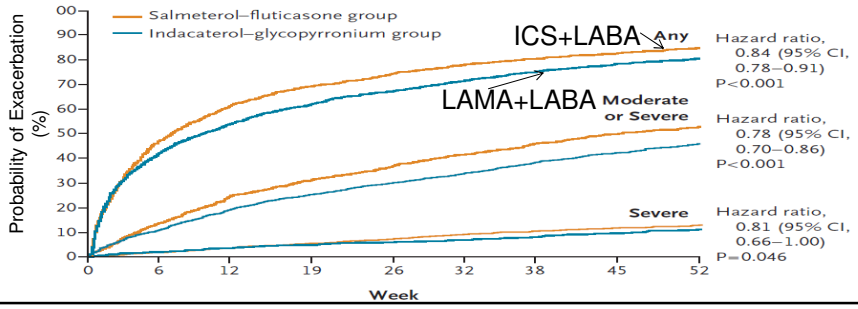
- *Tiotropium more effective than salmeterol in preventing moderate and severe exacerbations*

- *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*



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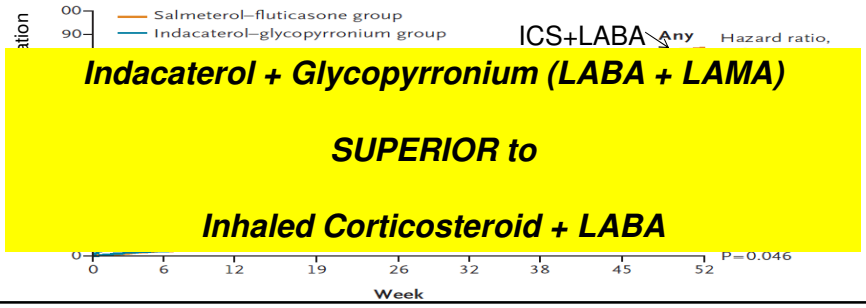


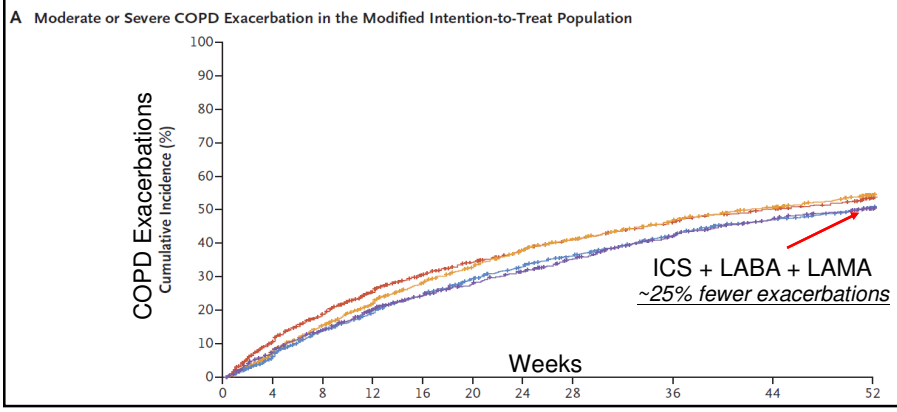
Indacaterol + Glycopyrronium (LABA + LAMA)

SUPERIOR to

Inhaled Corticosteroid + LABA

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



Stepping back…

Inhaled corticosteroids do *decrease*

exacerbation rate in COPD,

But increase the risk of pneumonia

(OK to start *after* failing LABA/LAMA therapy)

COPD Therapy by GOLD Stage: no change in ICS role

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)
C	LAMA -> then LAMA+ LABA or ***Inhaled corticosteroid if exacerbations persist***
D	LAMA + LABA → ***Inhaled corticosteroid if exacerbations persist*** -> CONSIDER adding a MACROLIDE or ROFLUMILAST (FEV1 <50%), if exacerbations persist

Case #6 *

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_2 3L/min with exertion and sleep
B) Discharge on O_2 3L/min with exertion only
C) Discharge with NO supplemental oxygen
D) Discharge on O_2 3L/min 24 h / day

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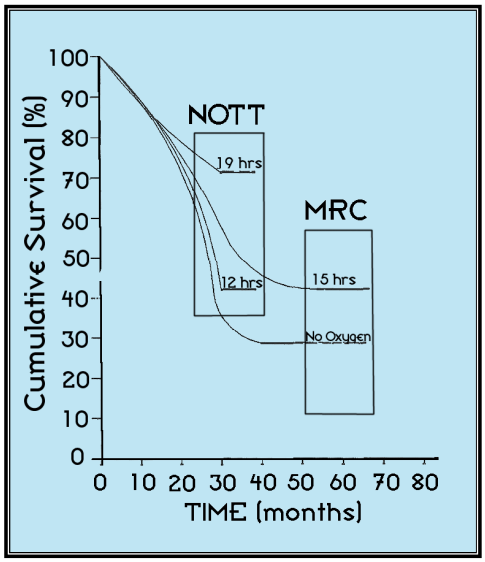
Oxygen Supplementation in COPD

- In the 1970s…
- 290 COPD patients with *SEVERE RESTING* hypoxemia studied +/- oxygen
- Criteria:
  - **SaO_2 ≤88% at REST**
  - **SaO_2 ≤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_2:
  - **SaO_2 ≤88% *AT REST***
  - **SaO_2 ≤90% with R-sided CHF or polycythemia**
- Supplemental O_2 is of unclear benefit with:
  - MODERATE hypoxemia at REST = SaO_2 88 - 90%
  - Hypoxemia with EXERTION ONLY, SaO_2 ≤88%
    - ***O_2 costs > $2 Billion / year!***

Oxygen Supplementation: 2016 LOTT Study

- NEJM 2016 **375** (17): p1617
- 738 COPD patients with:
  - SaO_2 89 - 93% ***AT REST*** ***or,***
  - SaO_2 80 - 90% with exertion
    - ***30% of patients had a SaO_2 < 86% !***

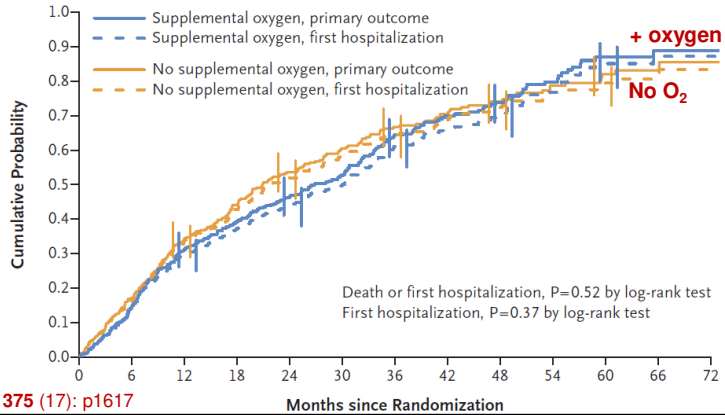
- Interventions:
  - O_2 titrated for SaO_2 > 90%
    - x 24h / day for patients with RESTING hypoxemia
    - with exertion and sleep for patients with only exertional hypoxemia

- 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 SaO_2 is > 88% or,
  - When SaO2 is > 80% with exertion
- No Benefit even with secondary endpoints: dyspnea, 6 min walk

Probability of DEATH or HOSPITALIZATION



NEJM 2016 **375** (17): p1617

Oxygen Supplementation: 2022

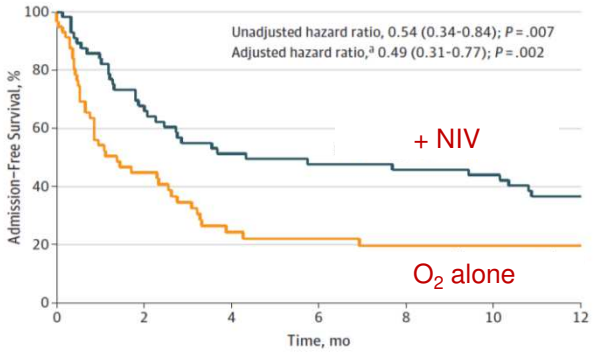
- The current evidence supports supplemental O_2 when:
  - The SaO_2 is ≤88% ***AT REST***
  - And likely, when the SaO_2 is ≤90% with cor pulmonale or polycythemia (hematocrit >55%)

- The current evidence does **NOT** support supplemental O_2 with:
  - Exertional hypoxemia – even to an SaO_2 of 80% !

  - **Areas of uncertainty for supplemental O_2:**
    - **Exertional hypoxemia with SaO_2 < 80%**
    - **Exertional dyspnea responding to O_2, but with an "acceptable" SaO_2 (>80%)**

NIPPV for STABLE COPD: evidence mounts after 2017

- *JAMA*. 2017; 317(21): 2177-2186
- 120 COPD patients with $PaCO_2$ > 50 mmHg and pH > 7.30
  - NIV titrated to $PaCO_2$ decrease of at least 20%
  - 12 month follow-up
  - Primary end point: time to hospital readmission or death



High Flow Nasal Cannula O_2

A Quick Primer!

Case #7 *

A 45 y/o M with history of hypertension is admitted with severe pneumococcal pneumonia complicated by hypoxemic respiratory failure requiring intubation for 3 days, extubated on hospital day 4.

He is transferred to your stepdown unit on high flow oxygen 40 L/min, FiO2 40% and his oxygen saturation is 97%. On 5 L/min nasal cannula oxygen his oxygen saturation is 94%

What is the best option for management of his hypoxemia?

A) Continue high flow O2 x 24 hours then transition to low flow system
B) Replace high flow O2 with BiPAP: 10/5 cmH2O of pressure
C) Transition to low flow O2 now, as O2 saturations are stable
D) Transfer back to the ICU, patients on high flow O2 should not be on the medical service

Case #7

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A) Continue high flow O2 x 24 hours then transition to low flow system

B) Replace high flow O2 with BiPAP: 10/5 cmH2O of pressure

C) Transition to low flow O2 now, as O2 saturations are stable

D) Transfer back to the ICU, patients on high flow O2 should not be on the medical service

Oxygen Delivery Systems

System	O_2 L/min	Features
Low flow	$\leq$ 10-15	Humidified, any interface (mask, NC)
High Flow	35 – 60	Heated, Humidified, nasal prongs well tolerated

High – Flow O2: why does it work?

- Hi flow -> "jet ventilation" effect in trachea and large airways -> reduction in CO_2 in these areas = REDUCED dead space -> more effective ventilation
- "CPAP effect" from pressures with hi flow…
- Interface easy for patient in respiratory distress -> improves "synchrony" -> decreases work of breathing / anxiety

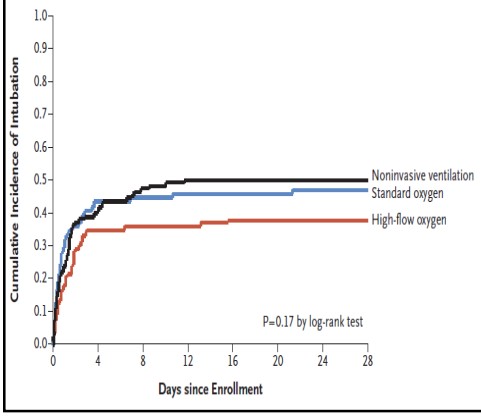
Supplemental O2, however, is NOT = *pressure*, which we often equate to *ventilation* support (i.e. BiPAP or NIPPV)

Hi Flow O2 versus NIPPV

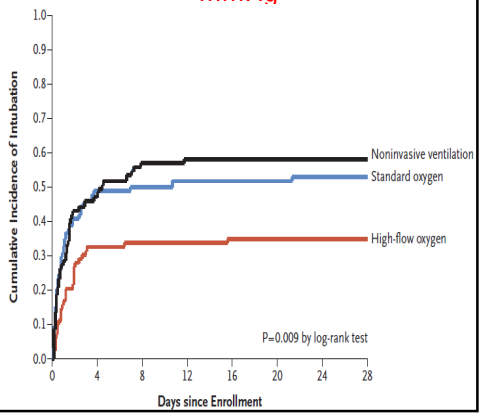
NEJM 2015 372: p2185

- RCT of 310 patients, hypoxemic respiratory failure, **normal $PaCO_2$**
- Standard O2, hi flow O2 v NIPPV
- *Primary outcome 28 day intubation rate = negative, no difference*
- *90 day mortality lower in Hi Flow group = secondary end point*

Intubations: all patients

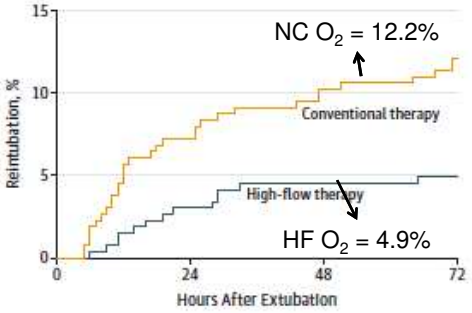


Intubations: PaO2/FiO2 < 200 mmHg



HF O_2 vs. NC O_2 Post-Extubation

- 527 patients at *low risk** of extubation failure randomized to HF O_2 vs. standard oxygen x24hrs
  - *age <65, no CHF, no COPD, APACHE-II <12 at extubation, BMI <30, no airway patency issue, able to manage secretions, simple weaning, <2 comorbidities, <7 days on vent



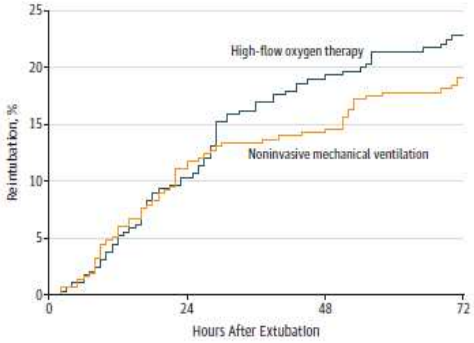
- *Re-intubation rate < with HF O_2*
- ICU LOS, mortality rates not significantly different
- At baseline, only 16% of patients had primary respiratory failure (majority of patients surgical or neuro)

JAMA 2016; 315: 1354-61

HF O_2 vs. NIPPV Post-Extubation

- Multicenter RCT; 604 patients (mixed medical / surgical)
- All *high risk* for re-intubation (age >65, +CHF, +COPD, APACHE-II >12, BMI >30, +airway problem, +secretions, >2 co-morbidities, >7 days on vent)
- Treated for 24 hours after extubation

- 19% NIV vs. 23% HFNC re-intubated at 72 hrs (NS)
- No difference in median time to re-intubation
- *43% in NIPPV group had adverse effects requiring withdrawal of therapy*



JAMA 2016; 316: 1565-74

High Flow O_2: bottom line

- HF O_2 may be as good or better than NIPPV for acute hypoxemic respiratory failure
- HF O_2 better tolerated than NIPPV
- HF O_2 may be equivalent to NIPPV at reducing post-extubation respiratory failure – *perhaps better in lower risk patients*

- *NIPPV still preferred for hypercarbic respiratory failure (or when higher "PEEP" needed)*

Summary Points

1) Every COPD patient should be staged with the new GOLD classification:
   - # of exacerbations, dyspnea score
2) Select COPD maintenance therapy based on GOLD stage, considering # of acute exacerbations
3) Supplemental O_2 guidelines for COPD now more focused
4) C-reactive protein is an emerging biomarker that can guide antibiotic use in COPD exacerbations
5) NIV has a role in hospital and ambulatory management of COPD with acute and chronic hypercarbia

Selected References

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