BRIGHAM AND WOMEN'S HOSPITAL
| The Lung Center |

**Evidence-based Management of COPD (and other related pearls!)**

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HARVARD MEDICAL SCHOOL

## Outline

- Quick review of GOLD COPD staging
- Inhaled corticosteroids for COPD – new evidence…
- When NOT to prescribe oxygen in COPD
- Non-invasive ventilation for STABLE COPD?
- Antibiotic stewardship in COPD exacerbations
- Bonus topics!
  - High flow nasal oxygen
  - COVID-19 and pre existing lung disease



## Scott Schissel, MD, PhD

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## COPD



## Disclosures

None



## 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 10-14 days
F) Initiate cefepime IV x 5 days

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## CRP: marker for antibiotic response in COPD?

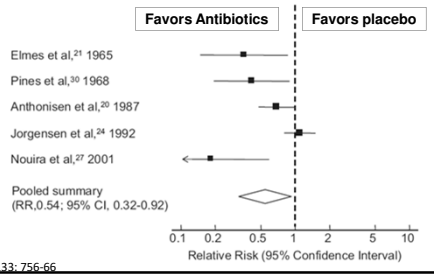
- In-hospital RCT of CRP in COPD exacerbations Prins HJ et al. *Eur Resp J* 2019 **53**: p1802014
  - 220 patients treated with antibiotics per clinical (Anthonisen) criteria versus antibiotics for CRP > 50 mg/L
  - CRP measured at admit and 24 H; if CRP > 50 mg/L at 24H, then antibiotics started
  - ***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

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

## Procalcitonin in COPD Exacerbations: NOT so fast…

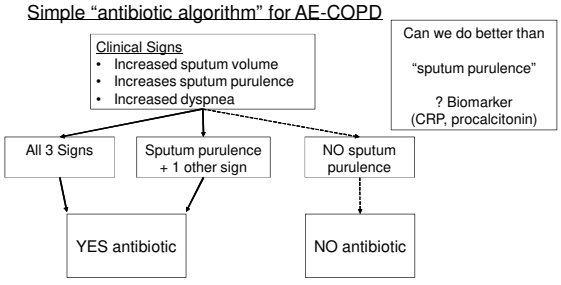
- Meta analysis of 8 trials examining procalcitonin in COPD exacerbations Mathioudakis, AG et al. *Eur Resp Rev* 2017 **26**: p160073
  - Most trials with procalcitonin cut offs: <0.25 = No antibiotics, > 0.5 antibiotics encouraged
  - Procalcitonin-guided decision making reduced antibiotic exposure
  - 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***
  - ***Antibiotic use only modestly decreased in procalcitonin group***

**More studies are needed before procalcitonin is used in COPD exacerbations**

# AE-COPD: Antibiotics

Simple "antibiotic algorithm" for AE-COPD

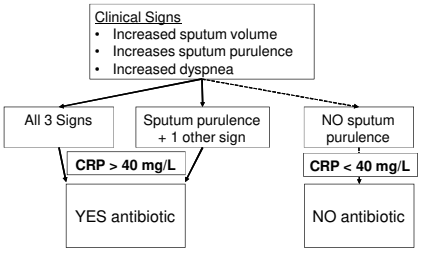



Chest 2008; 133: 756-66



# AE-COPD: Antibiotics

Simple "antibiotic algorithm" for AE-COPD



## 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?

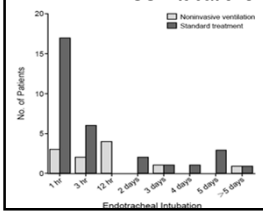
A) urgent anesthesia and ICU consultation for intubation / ventilation.
B) initiation of Hi Flow nasal cannula oxygen
**C) initiation of bilevel positive airway pressure (BiPAP)**
D) initiation of theophylline IV



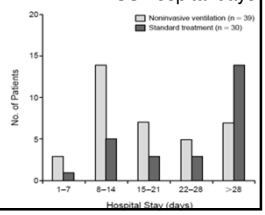
## NIPPV for Severe AE-COPD NEJM 1995 333: p817

- 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



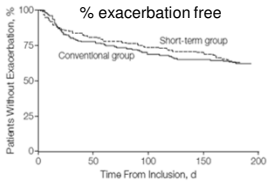
## Case #3

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

# 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**



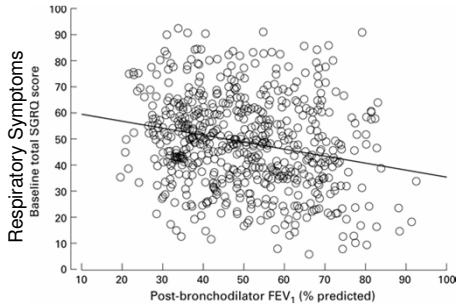
# GOLD COPD Classification Guides Treatment Selection

(including inhaled steroids!)

A 4 slide review of the GOLD Classification



# FEV1 Correlates Poorly with COPD Symptoms




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

FEV1 (% predicted)



# 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**<br>Few Exacerbations<br>Less Dyspnea | **So… do we care about $FEV_1$?** | 1 | ≥80% |
| **Group B:**<br>Few Exacerbations<br>More Dyspnea | **Not too much, but we add it in…** | 2 | ≥50% and <80% |
| | | 3 | ≥30% and <50% |
| **Group C:**<br>More Exacerbations<br>Less Dyspnea | **FEV1 in this case 80% → "grade 1"** | 4 | <30% predicted |
| **Group D**<br>More Ex<br>More Dyspnea | **Final COPD Stage: *GROUP C (grade 1)*** | | – Severe MRC) |



## 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*** ?✓

Inhaled corticosteroids beneficial ✓



## 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



## 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)



## Case #5

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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**



## COPD Therapy: putting it together by GOLD Stage

| GOLD GROUP | Initial Pharmacotherapy of COPD |
|---|---|
| **A** | Short acting anti-cholinergic PRN<br>or<br>Short acting Beta agonist PRN |
| | |
| | |
| | |

## COPD Therapy: putting it together by GOLD Stage

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

## Higher Potency LAMAs

## versus

## Inhaled Corticosteroids for Stable COPD



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

Tiotropium (QD)

Aclidinium (BID)

Umeclidinium (QD)

Glycopyrrolate (QD)



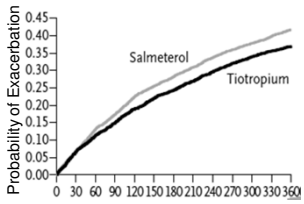
## Fluticasone / Salmeterol / tiotropium *versus* salmeterol / tiotropium alone

- WISDOM trial, NEJM 2014
- 2400 subjects with severe COPD, FEV1 <50%
  - Randomized to
    - Salmeterol/Fluticasone (50/500ug) bid + Tiotropium 18 ug QD
    - Salmeterol 50 ug bid + Tiotropium 18 ug QD
      - *NOTE: fluticasone tapered over 12 weeks; abrupt ICS withdrawal is a risk factor for acute exacerbations*
- Outcomes at 52 weeks
  - *No difference in overall exacerbation rate*
  - However – with corticosteroid withdrawal:
    - Small decline in FEV1 from 18 -> 52 weeks
    - Early increase in severe COPD exacerbations
    - Small decline in health related QOL



## 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

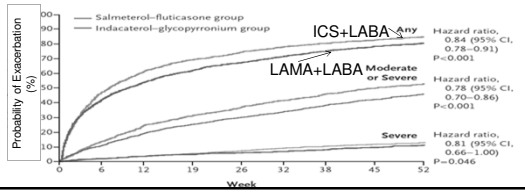



- *Tiotropium more effective than salmeterol in preventing moderate and severe exacerbations*
- *Effect independent of concomitant ICS use*



## 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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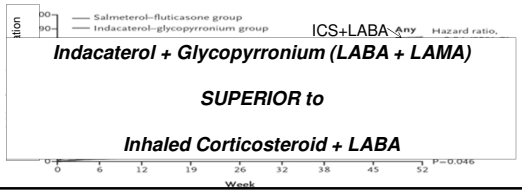



***Indacaterol + Glycopyrronium (LABA + LAMA)***

***SUPERIOR to***

***Inhaled Corticosteroid + LABA***

## TORCH – results

- Combination therapy significantly reduced exacerbations
- *LABA, ICS's, and ICS / LABA combination treatment did NOT reduce rate of decline in lung function*
- Probability of pneumonia increased in subjects receiving fluticasone (from 2% to 5%)

N Engl J Med 2007; 356: 775-89



## Stepping back…

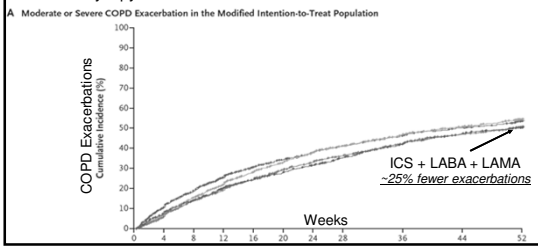
Inhaled corticosteroids do *decrease* exacerbation rate in COPD

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



## 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




## Combined ICS and LABA (Fluticasone / Salmeterol) in COPD: Towards a Revolution in COPD Health "TORCH" Trial *2007*!


Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*

*TORCH (and other trials) support using ICS / LABA combination treatment over ICS monotherapy*

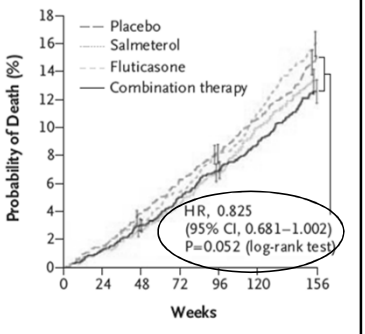


## Mortality trends favor inhaled corticosteroids in COPD

*Definitely intriguing…*

## TORCH trial 2007 – mortality

Decreased mortality with combination therapy but did not reach statistical significance




N Engl J Med 2007; 356: 775-89

## COPD Therapy by GOLD Stage: no change in ICS role

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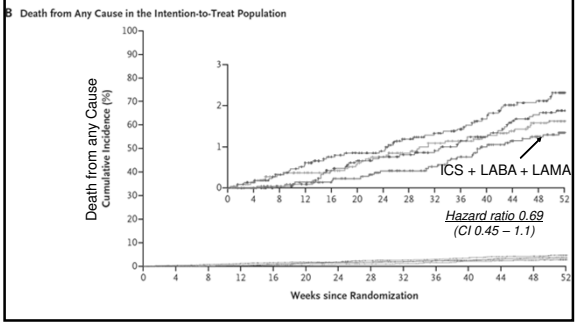
- ETHOS trial: *NEJM* 383 (**1**) July 2020
- Mortality Findings… trend benefits ICS use, but not conclusive




## 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.

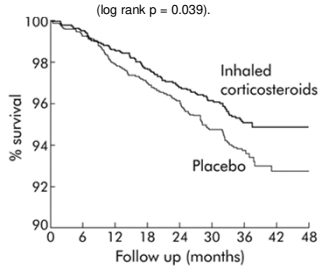
His nurse obtains pulse oximetry on room air which is 94% at rest and 85% with ambulation, improving to 95% with 3 L/minute nasal cannula oxygen.

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



## Do ICSs Improve Survival in COPD?

Kaplan-Meier Survival Curves Between COPD Patients Treated with ICS and Placebo (log rank p = 0.039).




Number of study participants 5085 4410 3429 3023 2951 2893 2331 867 221

Sin, D D et al. Thorax 2005;60:992-997



## Case #6

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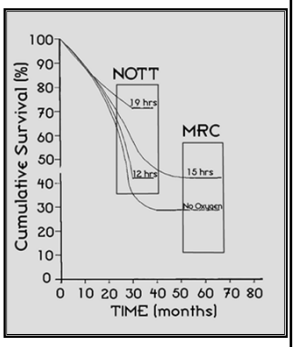
## Oxygen Supplementation in COPD

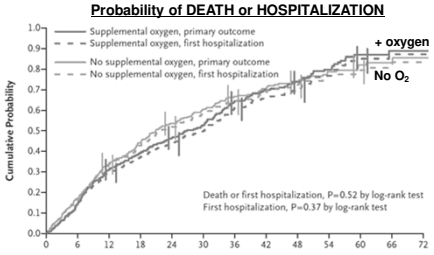
- In the 1970s…
- 290 COPD patients with *SEVERE RESTING* hypoxemia studied +/- oxygen
- Criteria:
  - **$SaO_2$ ≤88% at REST**
  - **$SaO_2$ ≤90% with R-sided CHF or polycythemia**
- Long-term oxygen therapy decreased mortality and improved QOL




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

## Oxygen Supplementation: 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




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

## 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

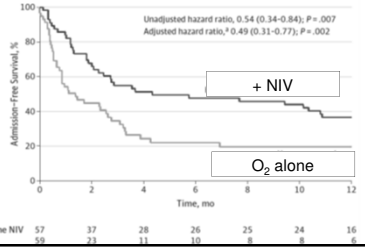
- The current evidence supports supplemental $O_2$ when:
  - The $SaO_2$ is ≤88% ***AT REST***
  - And likely, when the $SaO_2$ is ≤90% with cor pulmonale or polycythemia (hematocrit >55%)
- The current evidence does **NOT** support supplemental $O_2$ with:
  - Exertional hypoxemia – even to an $SaO_2$ 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%)**

## 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

## 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!



## Oxygen Delivery Systems

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



## 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



## 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)

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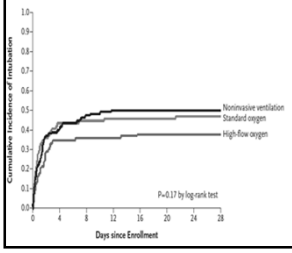
## Hi Flow O2 versus NIPPV

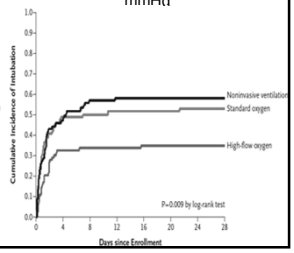
NEJM 2015 372: p2185

- 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

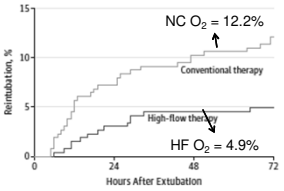



Intubations: PaO2/FiO2 < 200 mmHg



## 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



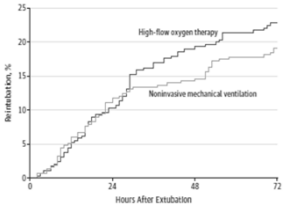

- *Re-intubation rate < with HF $O_2$*
- ICU LOS, mortality rates not significantly different
- At baseline, only 16% of patients had primary respiratory failure (majority of patients surgical or neuro)

*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


- Wedzicha, JA et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med.* 2016. **374**: p2222-34
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- 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
- Daubin C et al. Procalcitonin algorithm to guide initial antibiotic therapy in acute COPD exacerbations admitted to the ICU. *Intensive Care Med.* 2018. **44**: p428-437