Update in Asthma and COPD: the Hospitalized Patient

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Disclosures

- Genentech: research grant (completed)
- Merck: consultant
- Boehringer-Ingleheim: consultant
Acute Exacerbations of Asthma
Case 1

- 24 yo woman with asthma maintained on fluticasone/serevent (250/50)
- Exacerbation ongoing for 3 days
- Not relieved in ED by continuous albuterol nebs and 60 mg prednisone
- RR 24 sat 92% HR 110 BP 125/90
- Dyspneic at rest, interferes with conversation
- PEFR 40% of predicted
- Clear sputum
- Prior hx hospitalization

- PEFR drops to <25% predicted, too dyspneic to speak, perspiring
Asthma exacerbations
Pathophysiology

- Occlusion of the bronchial lumen by mucus, cells, thickened/contracted smooth muscle, bronchial wall inflammation and edema.

- Leads to:
  - low V/Q ratios
  - increased work of breathing
  - dynamic hyperinflation
Asthma exacerbations
Patterns of deterioration

- "Type 1" - Slow deterioration
  - inspissated mucus and inflammatory cells
  - slow to respond to therapy

- "Type 2" - Rapid deterioration
  - may not have mucus inspissation,
  - rapid response to therapy
  - much less common (~15% of exacerbations)

Woodruff PG Acad Emerg Med 1998
Barr RG Eur Resp J 2000
Asthma exacerbations
Initial therapy

- Oxygen
- Aerosolized albuterol, 2.5mg q 15 mins or continuously
- Systemic corticosteroids
Corticosteroids in asthma exacerbations

- No good way to synthesize the poorly comparable studies
- NAEPP recommends
  - Prednisone 40–80 mg/day in 1 or 2 divided doses, total course 3–10 days
  - IV corticosteroids if poor response to initial therapy, no guidance on dose

*NAEPP Expert Panel Report 3, 2007*
Asthma exacerbations

Other possible therapies

- Levalbuterol
- Antibiotics
- Methylxanthines
- Aerosolized ipratropium
- Heliox
- Magnesium
Levalbuterol: background

- Albuterol is racemic
- (equimolar mixture of stereoisomers)

**FIG 3.** Three-dimensional molecular conformation of (S)-albuterol and (R)-albuterol (also called levalbuterol).
Levalbuterol: rationale

- (R)-albuterol is the active drug
  - bronchodilator and bronchoprotective

- (S)-albuterol may not be simply inert
  - intensifies bronchoconstriction?
  - induces hypersensitivity?
  - promotes activation of eosinophils?
Levalbuterol: weakness in rationale

- Structure of the β-receptor/ligand interaction predicts that only (R)-albuterol should bind
- On direct comparison:
  - R- and RS-albuterol have similar dose-related effects on FEV1, HR, K+ in laboratory setting
  - Neither S-albuterol nor placebo have any effects

Lotvall JACI 2001
Levalbuterol: non-supportive adverse effects data

“In the clinical trials, a slightly greater number of serious adverse events and clinically significant ECG changes were reported in patients who received Xopenex 1.25mg as compared to the other active treatment groups.”

Xopenex® package insert
Conflicting Reviews to date

PRO


CON


Asthma exacerbations

Other possible therapies

- Levalbuterol
- Antibiotics
- Methylxanthines
- Aerosolized ipratropium
- Heliox
- Magnesium
Antibiotics

Not generally recommended except:

- To treat “comorbid conditions”
  - Pneumonia
  - Sinusitis
- Presence of fever and purulent sputum

*NAEPP Expert Panel Report 3, 2007*
Asthma exacerbations
Other possible therapies

- Levalbuterol
- Antibiotics
- Methylxanthines
- Aerosolized ipratropium
- Heliox
- Magnesium
Methylxanthines

- Not recommended at all
  - Does not improve lung function in hospitalized adults
  - Poor ratio of efficacy to toxicity

- Parmeswaman 2000
Asthma exacerbations

Other possible therapies

- Levalbuterol
- Antibiotics
- Methylxanthines
- Aerosolized ipratropium
- Heliox
- Magnesium
Ipratropium: con

- Not recommended for hospitalized patients by the NAEPP EPR because
  - No benefit seen in two RCTs of hospitalized children
  - No data on hospitalized adults

...but I use it because

- Craven 2001
- Goggin 2001
Ipratropium: pro

- Meta-analysis of ipratropium in emergency management of adults with acute asthma

- Eligible studies
  - RCT, double blind, placebo controlled
  - ipratropium as adjunctive therapy to beta-agonists

- Measurements
  - improvement in FEV1
  - hospital admission

Results

- Ipratropium provides an additional 7.3% improvement in FEV1 (approximately 100 ml)
- Associated with a decreased risk of hospitalization (RR=0.73, 95% CI 0.53-0.99)
- Not associated with any additional adverse effects

Asthma exacerbations
Other possible therapies

- Levalbuterol
- Antibiotics
- Methylxanthines
- Aerosolized ipratropium
- Heliox
- Magnesium
Heliox: background

- Helium: low MW => density 4-fold less than air
- Lower Reynolds number => laminar flow
- Heliox: a mixture of helium and oxygen available with helium concentrations ranging from 60-80%
Heliox: example of a clinical study

- 23 adults presenting to the ED with severe acute asthma (poor response to albuterol x 2)
- Randomization
  - heliox (70%/30%), or
  - 30% oxygen
- Measurements
  - PEFR, dyspnea score, HR, RR at 20-480 mins

*Kass et al. Chest 1999*
PEF, % Predicted

* - $p$ for heliox < 0.001 compared with baseline
# - $p$ for oxygen < 0.05 compared with baseline
$\theta$ - $p$ for heliox < 0.01 compared with 20 minutes

Time from Initiation of Treatment
Other RCTs have found no benefit

2 recent systematic reviews/meta-analyses:

- Slight benefit in first hour of use
- Insufficient data on harder clinical outcomes such as intubation, ICU admission rates, duration of hospitalization, or mortality

- *Ho AM Chest 2003*
- *Rodrigo GJ Chest 2003*
Asthma exacerbations

Other possible therapies

- Levalbuterol
- Antibiotics
- Methylxanthines
- Aerosolized ipratropium
- Heliox
- Magnesium
Intravenous magnesium

- 2 RCTs in adults demonstrate improved lung function in subjects with severe obstruction (FEV1 < 25% predicted) when used as adjunct to albuterol and steroids
- Adult dose: 2 gms IV MgSO₄ in 50ml NS infused over 10-15 mins

- Silverman RA, Chest 2002
- Bloch H, Chest 1995
Asthma exacerbations
Ventilator management

- Controlled modes
- Typically, high FiO2 is not required
- Permissive hypercapnia - well tolerated
- Increase expiratory time – slow respiratory rate
Fig. 3. Flow-time waveform showing persistence of flow at end-expiration in a patient with intrinsic positive end-expiratory pressure (auto-PEEP). In most patients with obstructive lung disease, failure to reach zero flow at the end of a relaxed expiration signifies that lung volume is above functional residual capacity and indicates dynamic hyperinflation.
Asthma exacerbations the pregnant patient

- Goal PaCO2 = 28-35 mmHg (as acidosis reduces uteroplacental flow)
- Standard asthma therapies are not contraindicated
Case 1

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Case 1

24 yo woman with asthma maintained on fluticasone/serevent (250/50)
Not relieved in ED by continuous albuterol nebs and 60 mg prednisone
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Dyspneic at rest, interferes with conversation
PEFR 40% of predicted
Clear sputum

Which of the following are recommended therapy?
- A. Antibiotics
- B. Systemic corticosteroids
- C. IV magnesium sulfate
- D. All of the above
Asthma exacerbations

Other therapies: review

- Levalbuterol value over albuterol is uncertain
- Antibiotics only in certain circumstances
- Methyloxanthines NO
- Aerosolized ipratropium I use it
- Heliox may have short term value
- Magnesium YES, if severe (PEFR<25% predicted)
Acute Exacerbations of COPD
Case 2

- 74 yo man with COPD maintained on albuterol/ipratropium and tiotropium
- Exacerbation ongoing for 3 days
- Not relieved in ED by continuous albuterol nebs and 60 prednisone
- RR 22 sat 92% on 2L O2 HR 110 BP 125/90
- Dyspneic at rest, interferes with conversation
- Green sputum
- Prior hx hospitalization

- Later: Paradoxical breathing
COPD exacerbations
Pathophysiology

- Occlusion of the bronchiolar lumen by mucus, cells, thickened/contracted smooth muscle, bronchial wall inflammation and edema.

- Leads to:
  - low V/Q ratios
  - increased work of breathing
  - dynamic hyperinflation
Differences from Asthma

- Have chronic small airway disease and emphysema
- Are older, weaker, have more comorbid conditions
- More likely to have bacterial infection
COPD exacerbations
Therapeutic options

- Oxygen...judiciously... check ABG in 30 mins
- Aerosolized albuterol and ipratropium
- Corticosteroids
- Antibiotics
- Consider non-invasive ventilation
Corticosteroids
Corticosteroids in patients hospitalized for AECOPD

- Two well-done RCTs
  - In non-acidotic patients, 30 mg prednisolone every day for 14 days is superior to placebo\(^1\)
  - A higher dose regimen starting with IV solumedrol (125mg q6h) for either 2 wks or 8 wks is better than placebo, with fewer side effects with a 2 wk course\(^2\)

- GOLD guidelines recommend 30-40mg prednisone for 10-14 days but, but do not differentiate hospitalized pts from outpatients, and the evidence is “D”

- Davies, Lancet 1999
- Niehwoehner, NEJM 1999
Corticosteroids in patients hospitalized for AECOPD

- Recent RCT in JAMA
  - 40 mg prednisone for 5 days versus 14 days
  - Non-inferiority study

- Leuppi JAMA 2013
From: Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease: The REDUCE Randomized Clinical Trial


A, Proportions of patients without reexacerbation in the intention-to-treat analysis. B, Proportions of patients without reexacerbation in the per-protocol analysis. Survival curves did not differ significantly when compared by the log-rank test. Hazard ratios for the short-term vs conventional treatment group were 0.95 (90% CI, 0.70-1.29; P for noninferiority = .006) in the intention-to-treat analysis and 0.93 (90% CI, 0.68-1.26; P for noninferiority = .005) in the per-protocol analysis. P values were obtained using the Wald test.

Figure Legend:
Corticosteroids in patients hospitalized for AECOPD

- Recent RCT in JAMA
  - 40 mg methylprednisolone x 1 then 40 mg prednisone for a total of 5 days versus 14 days
  - Non-inferiority study
  - No difference in re-exacerbations or survival
  - Slightly lower hosp LOS in short-term therapy group (8 vs 9 days, p=0.04)
  - No difference in FEV1 while an inpatient
  - No difference in glucocorticoid side effects

- Leuppi JAMA 2013
Corticosteroids in patients hospitalized for AECOPD

- One person’s synthesis
  - 40 mg prednisone for 5 days likely adequate for most hospitalized COPD patients
  - Prefer a higher dose IV regimen for patients admitted to the ICU
COPD exacerbations
Therapeutic options

- Oxygen...judiciously... check ABG in 30 mins
- Aerosolized albuterol and ipratropium
- Corticosteroids
- Antibiotics
- Consider non-invasive ventilation
Antibiotics in patients hospitalized for AECOPD

- Bacterial infection during exacerbation is more common in COPD than asthma
- Antibiotics recommended by GOLD for:
  - Increased sputum volume with either increased sputum purulence or dyspnea
  - Require mechanical ventilation (invasive or non-invasive)
- GOLD recommended course is 5-10 days
- In severe illness, consider pseudomonas and even PCP
COPD exacerbations
Therapeutic options

- Oxygen...judiciously... check ABG in 30 mins
- Aerosolized albuterol and ipratropium
- Corticosteroids
- Antibiotics
- Consider non-invasive ventilation
COPD Exacerbations
Non-invasive Ventilation

- Indications
  - Acidosis (pH<7.35) and PCO₂ (>45mmHg)
  - Severe dyspnea, increased work of breathing, resp muscle fatigue (accessory muscles, retractions, paradoxical motion of the abdomen)

- Contraindications
  - Resp arrest, CV instability
  - Impaired mental status
  - Aspiration risk, recent facial, GE surgery
  - Facial trauma/abnormality
  - Extreme obesity
COPD Exacerbations
Mechanical Ventilation (intubated)

- Concerned about air trapping
Fig. 3. Flow-time waveform showing persistence of flow at end-expiration in a patient with intrinsic positive end-expiratory pressure (auto-PEEP). In most patients with obstructive lung disease, failure to reach zero flow at the end of a relaxed expiration signifies that lung volume is above functional residual capacity and indicates dynamic hyperinflation.
COPD Exacerbations
Mechanical Ventilation (intubated)

- Air-trapping: use a slow respiratory rate
- Allow permissive hypercapnia
Questions

- 74 yo man with COPD maintained on albuterol/ipratropium and tiotropium
- Not relieved in ED by continuous albuterol nebs and 60 prednisone
- RR 22 sat 92% on 2L O2 HR 110 BP 125/90
- Green sputum
- Paradoxical breathing

Which of the following are recommended?
- A. Antibiotics
- B. Systemic corticosteroids
- C. Non-invasive mechanical ventilation
- D. All of the above
COPD exacerbations
Therapeutic options: review

- Oxygen...judiciously... check ABG in 30 mins
- Aerosolized albuterol and ipratropium YES
- Corticosteroids (40mg daily, 5 day total course OK for most patients)
- Antibiotics (usually)
- Consider non-invasive ventilation early in respiratory failure