Missouri ACP Meeting 2019
Updates in COPD
B.O.A.T.S (based on a true story)

Movie – The Princess Bride

HELLO. MY NAME IS INIGO MONTOYA. YOU KILLED MY FATHER. PREPARE TO DIE.

INIGO’S GUIDE TO NETWORKING SUCCESS

1. POLITE GREETING
2. NAME
3. RELEVANT PERSONAL LINK
4. MANAGE EXPECTATIONS
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• Division of Pulmonary, Critical Care and Sleep Medicine
• Saint Louis University
• Division of Critical Care medicine
• Mercy Hospital Saint Louis
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Disclosures

• Speakers Bureau for Sunovion, Boehringer Ingelheim

• Consultant and speaker for Biodesix (Genestrat/Verastrat), Cheetah

• https://www.medscape.com/viewarticle/915834_2

• Images are from images.google.com

• 10000 foot overview
Patient scenario

• 63 y/o male; has been a patient for 5 years; Smoker; Known COPD; Last FEV1 in Feb 2019 was 18%.

• Sig SOB; cough; No night time or exertional O2; Quit smoking after last PFTs done; multiple exacerbations

• On multiple inhalers through the years. Now on ICS/LABA and LAMA.

• Asking for more options for treatment...
Which of the following is the next best option for the treatment of this patient's COPD?

- Using blood Eosinophil levels to guide treatment.
- Using combination therapy (LABA/LAMA/ICS).
- Adding Theophylline.
- Focusing on Exacerbation reduction.
- Bronchoscopic Lung Volume Resection/Reduction.
Agenda

- *Eosinophils*
- Combination therapy
- Theophylline
- Exacerbation reduction
- Bronchoscopic Lung Volume Resection
COPD exacerbation phenotypes and responsiveness to steroids

- This observational, 1-year study of 182 exacerbations in 86 patients identified four distinct biologic COPD exacerbation phenotypes
  - Eosinophil-predominant phenotype is most responsive to corticosteroid treatment

COPD = chronic obstructive pulmonary disease

Bafadhel et al. Am J Respir Crit Care 2011
Eosinophils are a marker of response to ICS in COPD

Effect on lung function

A baseline blood eosinophil count of ≥2% identifies a group of COPD patients with slower rates of decline in FEV1 when treated with ICS.

Relationship between blood Eos and ICS response tends to be linear. Threshold of 150-300 cells/mm³ (or a differential count of 2%) has been used as decision point.

Barnes N et al. ERJ 2016
Post-hoc analysis suggests that blood eosinophils are a potential biomarker of ICS effectiveness in reducing exacerbation rates.

Further research is required to help establish blood eosinophilia as a biomarker for treatment response.

**COPDGene**

- COPD Eosinophil ≥ 300/µL
- Eosinophil < 300/µL

- COPD Gene
- ACO
- FF/VI all doses
- VI 25 µg

29% difference
p < 0.0001

10% difference
p = 0.283

0.79
n=795

0.91
n=1,583

1.28
n=500

**ECLIPSE**

- COPD Eosinophil ≥ 300/µL
- Eosinophil < 300/µL

- ECLIPSE
- ACO
- FF/VI all doses
- VI 25 µg

54
130

47
120

• Mechanism of increased ICS effect in COPD patients with higher blood Eos is not completely known.

• Effect of ICS containing regimens is higher in patients with high exacerbation risk (≥ 2 exac and/or 1 hosp in the previous year)

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30095-X/fulltext
Blood Eos and ICS Effect – Positives

• Blood Eos predict the magnitude of effect of ICS (added on top of regular maintenance BD Rx) in preventing future exacerbations.

• Higher effects at higher counts (Continuous relationship)

• Minimal effect of ICS at < 100 cells/μL. (? identify patients who wont respond)

• Highest effect at > 300 cells/μL. (? identify patients with greatest Rx benefit)

• Possible use as a biomarker in conjunction with clinical assessment

Blood Eos and ICS Effect – “Not so positive”

- Studies have differing results with regard to the ability of blood Eos to predict future exacerbation outcomes.
- Either no relationship or a positive relationship.
- There is insufficient evidence to recommend that blood Eos should be used to predict future exacerbation risk on an individual basis in COPD patients.

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
   - Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - Place patient in box corresponding to current treatment & follow indications
   - Assess response, adjust and review
   - These recommendations do not depend on the ABCD assessment at diagnosis

- **DYSPNEA**
  - LABA or LAMA
    - LABA + LAMA
      - Consider switching inhaler device or molecules
      - Investigate (and treat) other causes of dyspnea
    - LABA + ICS
      - LABA + LAMA + ICS

- **EXACERBATIONS**
  - LABA or LAMA
    - LABA + LAMA + ICS
      - LABA + LAMA
        - Consider if eos < 100
        - Consider if eos ≥ 100
      - LABA + LAMA + ICS
        - LABA + LAMA
          - Roflumilast FEV₁ < 50% & chronic bronchitis
            - Azithromycin

*eos = blood eosinophil count (cells/μL)*
* Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
* Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*
Agenda

• Eosinophils
• *Combination therapy*
• Theophylline
• Exacerbation reduction
• Bronchoscopic Lung Volume Resection
Types of Handheld Inhalers

- **MDIs** (Metered Dose Inhalers) → Use propellant, not breath-actuated
- **DPIs** (Dry Powder Inhalers) → Do not use propellant, breath-actuated
- **SMIs** (Slow Mist Inhalers) → Do not use propellant, not breath-actuated
10 (and counting) handheld inhalers

<table>
<thead>
<tr>
<th>MDIs</th>
<th>DPIs</th>
<th>SMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Aerosphere</td>
<td>- Diskus</td>
<td>- Respimat</td>
</tr>
<tr>
<td>- HFA</td>
<td>- Inhub</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Handihaler</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Pressair</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Aerolizer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Ellipta</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Neohaler</td>
<td></td>
</tr>
<tr>
<td>LABA</td>
<td>LAMA</td>
<td>Inhaler</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Olodaterol</td>
<td>Tiotropium</td>
<td>Respimat Soft Mist</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>Glycopyrronium</td>
<td>Breezhaler</td>
</tr>
<tr>
<td>Vilanterol</td>
<td>Umeclidinium</td>
<td>Ellipta</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Aclidinium</td>
<td>Genuair</td>
</tr>
</tbody>
</table>

**Abbreviations:** LABA, long-acting $\beta_2$-adrenoceptor agonists; LAMA, long-acting muscarinic receptor antagonists.
Which combination is better for patients with COPD?

LABA/ICS

LABA/LAMA
LABA/LAMA vs monotherapy

- Most studies with LABA/LAMA combinations have been performed in patients with a low rate of exacerbations.

- (SPARK) Wedzicha et al. 2013 → In patients with a history of exacerbations, a combination of LA BD is more effective than LA monotherapy for preventing exacerbations.

- (1+1=2)

- (DYNAGITO) Calverley et al. 2018 → combining LABA + LAMA did NOT reduce exacerbation rate as much as expected compared with a LAMA alone.

- (1+1≠2)
Annualized Rate of Moderate or Severe Exacerbations: SPARK

- Glycopyrronium 50 µg once daily
- Tiotropium 18 µg once daily
- Indacaterol/glycopyrronium 110/50 µg once daily

12% reduction, \( P = .038 \)
10% reduction, \( P = .096 \)

DYNAGITO Study Design: Tiotropium and Olodaterol in the Prevention of COPD Exacerbations (cont)

Rate of Moderate-to-Severe Exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Tiotropium 5 μg</th>
<th>Tiotropium/Olodaterol 5/5 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of treated patients, n</td>
<td>3941</td>
<td>3939</td>
</tr>
<tr>
<td>Adjusted rate of events, per patient-year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.97</td>
<td>0.90</td>
</tr>
<tr>
<td>99% CI</td>
<td>0.90, 1.03</td>
<td>0.84, 0.96</td>
</tr>
</tbody>
</table>

Rate ratio of events vs tiotropium 5 μg

<table>
<thead>
<tr>
<th></th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.93</td>
</tr>
<tr>
<td>99% CI</td>
<td>0.85, 1.02</td>
</tr>
</tbody>
</table>

RR = 0.93
P = .0498

Figure 5 Cumulative risk of first moderate-to-severe COPD exacerbation by treatment group.

Abbreviations: OLO, olodaterol; TIO, tiotropium.
ICS/LABA vs LABA/LAMA

• (FLAME) Wedzicha et al. 2014 → In patients with a h/o exacerbations, combination LABA/LAMA decreased exacerbations to a greater extent than ICS/LABA combination. (LABA+LAMA > ICS/LABA)

• (IMPACT) Lipson et al. 2018 → High exacerbation risk population (≥ 2 exac and/or 1 hosp in the previous year); ICS/LABA decreased exacerbations to a greater extent than a LABA/LAMA combination (at higher blood eosinophil concentrations). (ICS/LABA > LABA/LAMA)
**FLAME: Indacaterol-Glycopyrronium (LABA+LAMA) versus Salmeterol-Fluticasone (LABA+ICS) for COPD**

Randomized, double-blind, double-dummy, noninferiority trial

**Objective:** To compare LABA + LAMA with LABA + ICS for reducing COPD exacerbations in patients with COPD and mMRC dyspnea grade ≥2 symptoms

3,362 patients (≥40 years) who are current or former smokers
Stable COPD per GOLD 2011 criteria on a stable medication

Indacaterol+glycopyrronium (LABA + LAMA) vs Salmeterol+fluticasone (LABA + ICS)

**Primary Outcomes**
Treatment continued for 52 weeks

3.59

Annual rate of COPD exacerbations
RR 0.88; 95% CI 0.82-0.94; P<0.001

4.09

**Secondary Outcomes**
Annual rate of moderate or severe exacerbations
RR 0.83; 95% CI 0.75-0.91; P<0.001

**Conclusion:** Indacaterol+glycopyrronium (LABA+LAMA) is associated with a 11% reduction in the rate of annual COPD exacerbations when compared to salmeterol+fluticasone (LABA+ICS)

## Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD - The IMPACT Trial

**Randomized Trial Involving 10,355 Patients with COPD**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>N</th>
<th>Rate of COPD Exacerbations per year</th>
<th>Incidence of Pneumonia per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS + LABA</td>
<td>4151</td>
<td>0.91 (P&lt;0.001)</td>
<td>7% (P&lt;0.001)</td>
</tr>
<tr>
<td>ICS + LABA</td>
<td>4134</td>
<td>1.07</td>
<td>6%</td>
</tr>
<tr>
<td>LAMA + LABA</td>
<td>2070</td>
<td>1.21</td>
<td>4%</td>
</tr>
</tbody>
</table>

**TRIPLE THERAPY > DUAL THERAPY IN TERMS OF COPD EXACERBATIONS BUT LEADS TO INCREASED RATES OF PNEUMONIA**

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Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Helga Magnusson, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tetzlaff, M.D., Lesley Towse, B.Sc., Helen Finnigan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chanez, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D., for the WISDOM Investigators*

ABSTRACT

BACKGROUND
Treatment with inhaled glucocorticoids in combination with long-acting bronchodilators is recommended in patients with frequent exacerbations of severe chronic obstructive pulmonary disease (COPD). However, the benefit of inhaled glucocorticoids in addition to two long-acting bronchodilators has not been fully explored.

The authors’ affiliations are listed in the Appendix. Address reprint requests to Dr. Magnusson at the Pulmonary Research Institute at Lung Clinic Grosshansdorf, Woehrendamm 80, D-22927 Grosshansdorf, Germany, or at magnussen@
ICS withdrawal did not increase exacerbations in moderate to severe COPD or severe COPD. ICS withdrawal lead to a small significant decrease in FEV1.
1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
   - Consider the predominant treatable trait to target (dyspnea or exacerbations)
   - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - Place patient in box corresponding to current treatment & follow indications
   - Assess response, adjust and review
   - These recommendations do not depend on the ABCD assessment at diagnosis

**DYSPNEA**

- LABA or LAMA
  - LABA + LAMA
    - Consider switching to LABA + ICS
    - Consider switching inhaler device or molecules
  - LABA + ICS

**EXACERBATIONS**

- LABA or LAMA
  - LABA + LAMA
    - LABA + LAMA + ICS
      - Consider if eos < 100
      - Consider if eos ≥ 100
  - LABA + ICS
    - LABA + LAMA + ICS
      - Roflumilast
      - Azithromycin

\(\text{eos} = \text{blood eosinophil count (cells/µL)}\)

* Consider if eos \(\geq 300\) or eos \(\geq 100\) AND \(\geq 2\) moderate exacerbations / 1 hospitalization
** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS

FIGURE 4.3

© 2019 Global Initiative for Chronic Obstructive Lung Disease
Agenda

- Eosinophils
- Combination therapy
- *Theophylline*
- Exacerbation reduction
- Bronchoscopic Lung Volume Resection

[https://medimoon.com/2013/04/counseling-parameters-for-theophylline/](https://medimoon.com/2013/04/counseling-parameters-for-theophylline/)
Best matches for theophylline and copd:

**Doxofylline is not just another theophylline!**

**Association of pre-hospital theophylline use and mortality disease patients with sepsis.**

**Therapeutic approaches of asthma and COPD overlap.**

Search results
Items: 1 to 20 of 964

https://memegenerator.net/instance/67668635/exorcism11-i-did-cocaine-and-theophylline
Increased clearance

P450 enzyme induction by drugs (rifampicin, phenobarbitone, carbamazepine, ethanol)
Smoking (tobacco, marijuana)
High-protein, low-carbohydrate diet
Barbecued meat
Childhood

Decreased clearance

P450 enzyme inhibition by drugs (cimetidine,* erythromycin, † fluoroquinolone antibiotics, allopurinol, zileuton, fluvoxamine, phenytoin, fluconazole, ketoconazole, acyclovir, ritonavir, diltiazem, verapamil, interferon-α, estrogens, pentoxifylline)
Congestive heart failure
Liver disease
Pneumonia
Viral infection
Vaccination (influenza immunization)
High carbohydrate diet
Old age

* Not ranitidine.
† Also clarithromycin but not azithromycin.
TWICS (theophylline with ICS) Trial

• Double-blind, placebo-controlled, randomized
• ≥ 2 exacerbations (Rx with Abx, OCS, or both) last year & on ICS (~80% ICS/LABA/LAMA)

<table>
<thead>
<tr>
<th></th>
<th>Theo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 1578 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose theo (200 mg)</td>
<td>791 pts</td>
<td>787 pts</td>
</tr>
<tr>
<td>For conc 1-5 mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on IBW and smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3430 exacerbations</td>
<td>1727 (mean 2.24 exac/yr)</td>
<td>1703 (mean 2.23 exac/yr)</td>
</tr>
</tbody>
</table>

CONCLUSION - Addition of low-dose theo, did not reduce the number of COPD exac over a 1-year period

• Outside of areas where cost and access to healthcare and drugs is problematic, use of low-dose theophylline
Agenda

• Eosinophils
• Combination therapy
• Theophylline
• *Exacerbation reduction*
• Bronchoscopic Lung Volume Resection
Etiology of COPD Exacerbations

- Infectious
  - Viral (~40-50%)
  - Atypical
    - Purulent Sputum (~40-50%)

- Noninfectious
  - ~20% Mucoid Sputum
  - Allergies, smoking, pollution, stress; undertreatment or nonadherence in established COPD

~5-10% Bacterial-viral co-infection may occur

Figure 4.

Risk of

Severe exacerbation

Severe exacerbation + death

Hazard function of successive hospitalized COPD exacerbations (per 10,000 per day) from the time of their first ever hospitalization for a COPD exacerbation over the follow-up period. For further explanations, see text. Reproduced from Thorax with permission from BMJ Publishing Group, Ltd. 

58
Figure 1. Fletcher–Peto diagram modified: lung function decline is not a constant, stable process.

Notes: It is the accumulated result of mild losses during steady state and sharp losses, due to acute exacerbations that accelerate as exacerbations become more frequent and more severe over time, during the natural course of the disease.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FEV\textsubscript{1}, forced expiratory volume in 1 second; HrQoL, health-related quality of life.


Proposed time-course patterns of COPD exacerbations: (a) usual pattern, (b) treatment failure (c) recurrence. For further explanations, see text. Reproduced with permission from Informa Healthcare, copyright ©2010, Informa Healthcare.
Which of the following medications is the BEST for reducing exacerbations in COPD?

- Roflumilast (Daliresp)
- Azithromycin
- N-acetyl cysteine
- Statins
## Table 2. Efficacy of Different Approaches to Decreasing Risk for Exacerbations

<table>
<thead>
<tr>
<th>Approach</th>
<th>Efficacy</th>
<th>Support</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-pharmacologic Interventions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>Supported</td>
<td>Large-scale observational study</td>
<td>66</td>
</tr>
<tr>
<td>Pulmonary Rehabilitation</td>
<td>Supported</td>
<td>Small-scale clinical studies</td>
<td>68, 69</td>
</tr>
<tr>
<td>Vaccination Against Pneumococcal and Influenza Virus Infection</td>
<td>Very strongly supported</td>
<td>Multiple clinical trials and meta-analyses</td>
<td>70-74</td>
</tr>
<tr>
<td><strong>Pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMA</td>
<td>Very strongly supported</td>
<td>Meta-analyses and multiple clinical trials</td>
<td>13, 76</td>
</tr>
<tr>
<td>LABA + LAMA vs. Monotherapy</td>
<td>Supported for LABA + LAMA vs LAMA</td>
<td>Clinical trial</td>
<td>132</td>
</tr>
<tr>
<td>ICS Monotherapy</td>
<td>Supported</td>
<td>Meta-analysis, benefit limited to patients with FEV₁ &lt; 50%</td>
<td>91</td>
</tr>
<tr>
<td>ICS + LABA vs ICS or LABA monotherapy</td>
<td>Very strongly supported</td>
<td>Multiple clinical trials</td>
<td>56, 94</td>
</tr>
<tr>
<td>Triple Combination Therapy vs. Components</td>
<td>Variable results</td>
<td>Small-scale clinical trials provide conflicting results; meta-analysis indicates no significant benefit; large-scale observational study supports</td>
<td>102-105, 133</td>
</tr>
<tr>
<td><strong>Systemic Treatments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roflumilast</td>
<td>Very strongly supported as add-on treatment to bronchodilators</td>
<td>Multiple large-scale clinical trials and meta-analysis</td>
<td>106-109</td>
</tr>
<tr>
<td>Macrolides/Quinolones</td>
<td>Strongly supported</td>
<td>Supported by large-scale clinical trials</td>
<td>116, 117</td>
</tr>
<tr>
<td>Statins</td>
<td>Supported</td>
<td>Supported by multiple observational studies, but no controlled trials to date</td>
<td>121, 122</td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroid, LABA = long-acting β2-agonist, LAMA = long-acting muscarinic antagonist
N-acetylcysteine (NAC)
a) Study [ref.], year | Estimate (95% CI)
--- | ---
ZHENG et al. [1], 2014 | 0.78 (0.70–0.86)
TSE et al. [20], 2013 | 0.56 (0.42–0.75)
SCHERMER et al. [26], 2009 | 1.08 (0.83–1.40)
BACHH et al. [27], 2007 | 0.67 (0.53–0.86)
DEGRAMER et al. [3], 2005 | 0.95 (0.87–1.04)
GFFFFRITS et al. [29], 2003 | 0.73 (0.58–0.93)
Pela et al. [24], 1999 | 0.57 (0.40–0.66)
HANSEN et al. [19], 1994 | 0.76 (0.48–1.19)
RASMUSSEN and OLENNOW [25], 1988 | 0.91 (0.64–1.29)
MCQAVIN et al. [22], 1985 | 0.95 (0.75–1.21)
BOMAN et al. [23], 1983 | 0.71 (0.63–0.81)
BABOLINI et al. [21], 1980 | 0.41 (0.28–0.62)
GRASSI and MORANDINI [28], 1976 | 0.72 (0.42–1.22)
Overall (I²=80%, p<0.01) | 0.75 (0.66–0.84)

b) Study [ref.], year | Estimate (95% CI)
--- | ---
ZHENG et al. [1], 2014 | 0.70 (0.70–0.86)
TSE et al. [20], 2013 | 0.56 (0.42–0.75)
SCHERMER et al. [26], 2009 | 1.08 (0.83–1.40)
BACHH et al. [27], 2007 | 0.67 (0.47–0.97)
DEGRAMER et al. [3], 2005 | 0.95 (0.87–1.04)
Pela et al. [24], 1999 | 0.57 (0.48–0.68)
MCGAVIN et al. [22], 1985 | 0.95 (0.75–1.21)
Overall (I²=86%, p<0.01) | 0.78 (0.65–0.93)
• In COPD patients not receiving ICS, regular treatment with mucolytics such as erdosteine, carbocysteine and N-acetylcysteine may reduce exacerbations and modestly improve health status.

• Due to the heterogeneity of studied populations, treatment dosing and concomitant treatments, currently available data do not allow one to identify precisely the potential target population for antioxidant agents in COPD.
Daliresp® (roflumilast) tablets
500 mcg per tablet

ONCE-DAILY ORAL

One tablet, once a day may help adults with severe COPD experience fewer exacerbations

Dispense the accompanying Medication Guide to each patient

30 Tablets

Tablet shown not actual size.

https://images.app.goo.gl/KvvTvF4HUAEjvFwt6
EOS and HELIOS Trials

• Pts with severe COPD
• Allowed continuation of LABA and LAMA
• The preBD FEV$_1$ improved modestly when roflumilast was added to a long-acting bronchodilator
• EOS - mean preBD FEV1 ↑ by 49 mL (p<0.0001)
• HELIOS – mean preBD FEV1 ↑ by 80 mL (p<0.0001)
  • Studies ran for only 24 weeks
  • Rate of acute exacerbations was not a primary end point
  • Trend toward reduction of exacerbations

AURA and HERMES Trials

• 2009; Two 52-week placebo-controlled trials
• Patients with severe COPD with chronic bronchitis and a history of frequent exacerbations
• Maintenance therapy with LABA was continued
• ICS and LAMA were held
• Statistically significant improvements in preBD FEV$_1$ and reduction in the rate of exacerbations were observed (17% reduction, 95% CI 8–25, 1.14 v 1.37; $P < 0.0003$)

In these two studies, total incidence of diarrhea was 148 (9.6%) for DALIRESP and 55 (3.6%) for placebo.

In these two studies, total incidence of nausea was 71 (4.6%) for DALIRESP and 32 (2.1%) for placebo.

Pooled AURA and HERMES data
14% vs 11%
NNH - 35
TAK AS DIRECTED.

AZITHROMYCIN 250MG TAB (6CT)
Substituted for: ZITHROMAX 250 MG
Discard by #2/211

RPH: CM
DE: AN
NO REFILLS REMAINING
Mfg: TEVA USA

azithromycin tablets
250 mg*
For in-institution use only

https://images.app.goo.gl/gTgM6AqGnzLUPqnP9

https://images.app.goo.gl/GGbFA2z9HLrdz4Nb7
Azithromycin for Prevention of Exacerbations of COPD

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- 570 Azithro (250 mg daily) VS 572 placebo for 1 year + usual care.
- Time to first exacerbation $\rightarrow$ 266 days (95% CI, 227-313) for Azithro VS 174 days (95% CI, 143-215) for placebo ($P<0.001$).
- Frequency of exacerbations $\rightarrow$ 1.48 per pt-year for Azithro VS 1.83 per pt-year for placebo ($P=0.01$).

Figure 3. Rates of AECOPD per Person-Year, According to Study Group.
• Hazard ratio for having an AECOPD per pt-year in the Azithro group was 0.73 (95% CI, 0.63 to 0.84; P<0.001).

• Hearing decrements – more in the Azithro group than in the placebo group (25% vs. 20%, P=0.04).

• NNT to prevent one AECOPD was 2.86.
Agenda

• Eosinophils
• Combination therapy
• Theophylline
• Exacerbation reduction
• *Bronchoscopic Lung Volume Resection*
Which of the following bronchoscopic lung volume reduction modalities is approved for use in the US?

- Endobronchial blockers
- Airway bypass stents
- Endobronchial valves
- Thermal ablation vapor
- Biologic sealant
- Airway coils
NETT trial – non high risk patients

<table>
<thead>
<tr>
<th></th>
<th>Predominantly upper lobe emphysema</th>
<th>Predominantly non-upper lobe emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low exercise capacity</td>
<td>RR 0.47 p=0.005</td>
<td>RR 0.81 p=0.49</td>
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<tr>
<td>High exercise capacity</td>
<td>RR 0.98 p=0.70</td>
<td>RR 2.06 p=0.02</td>
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</tbody>
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Bronchoscopic Lung Volume Resection

- Occlude airways proximal to nonfunctioning, hyperinflated areas of lungs.

- Blocking
  - Endobronchial and intrabronchial valves

- Nonblocking
  - Coils
  - Thermal ablation

Types of Valves

• Zephyr Endobronchial Valve (Pulmonx Corporation; Redwood City, California)

• Spiration Valve System (Olympus Respiratory America; Redmond, Washington)
Typically, collateral ventilation is assessed using quantitative CT software or the Chartis System (Pulmonx Corporation)

*Endobronchial coils are not approved for use in the United States*
Thermal vapor therapies are not approved for use in the United States.
• Head-to-head comparisons between therapies are not available
• Guidelines exist*
• Both valve types improve symptoms, QOL, and lung function

• Patient Selection -
• Evidence of air trapping on lung testing (RV > 175%)
• Absence of collateral ventilation (CV) distal to the target area

<table>
<thead>
<tr>
<th>Bronchoscopic lung volume reduction modality</th>
<th>Indications</th>
<th>Common complications</th>
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<tbody>
<tr>
<td>Endobronchial blockers</td>
<td>Heterogeneous Emphysema</td>
<td>(1) Blocker migration</td>
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<tr>
<td></td>
<td></td>
<td>(2) Postobstructive pneumonia</td>
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<tr>
<td>Airway bypass stents</td>
<td>Homogenous Emphysema</td>
<td>(1) COPD exacerbation</td>
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<td></td>
<td></td>
<td>(2) Pneumonia/bronchitis</td>
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<td></td>
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<td>(3) Air leak/pneumomediastinum</td>
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<tr>
<td>Endobronchial valves</td>
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<tr>
<td></td>
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<td>(2) Pneumothorax</td>
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<tr>
<td></td>
<td></td>
<td>(3) Bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4) Pneumonia</td>
</tr>
<tr>
<td>Thermal vapor ablation</td>
<td>Heterogeneous Emphysema</td>
<td>(1) COPD exacerbation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Pneumonitis</td>
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<tr>
<td>Biological sealants</td>
<td>Both homogenous and heterogeneous emphysema</td>
<td>(1) COPD exacerbation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Pneumonia/aspiration</td>
</tr>
<tr>
<td>Airway implants/coils</td>
<td>Both homogenous and heterogeneous emphysema</td>
<td>Data not yet available</td>
</tr>
</tbody>
</table>
Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. Additionally, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown.

**Advanced COPD**

- Emphysema predominant phenotype with severe hyperinflation
  - Large bulla
    - Bullectomy
  - Heterogeneous emphysema
    - No large bulla
  - Homogeneous emphysema
    - No large bulla
      - Lung transplant

Definition of Abbreviations: BLVR, Bronchoscopic Lung Volume Reduction; EBV, endobronchial Valve; LVRS, Lung volume reduction surgery; LVRC, Lung volume reduction coil; VA, Vapor ablation.

*at some but not all centers

FIGURE 4.5
Patient scenario

• 63 y/o male; has been a patient for 5 years; Smoker; Known COPD; Last FEV1 in Feb 2019 was 18%.

• Sig SOB; cough; No night time or exertional O2; Quit smoking after last PFTs done; multiple exacerbations

• On multiple inhalers through the years. Now on ICS/LABA and LAMA.

• Asking for more options for treatment...
Which of the following is the next best option for the treatment of this patient's COPD?

- Using blood Eosinophil levels to guide treatment.
- Using combination therapy (LABA/LAMA/ICS).
- Adding Theophylline.
- Focusing on Exacerbation reduction.
- Bronchoscopic Lung Volume Resection/Reduction.
References


