BREATHING NEW AIR INTO THE TREATMENT OF COPD AND ASTHMA

ANNUAL CONVENTION AND SCIENTIFIC SESSIONS
ACOI 2019

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• NO DISCLOSURES
THE CHANGING PARADIGM

- Asthma and COPD are the most common of the obstructive lung diseases
- Chronic airway inflammation and airway obstruction
- Affects millions of people worldwide
- COPD is the third leading cause of death worldwide
- Years of life lost increased 13.2% from 2007 to 2017
- Healthcare burden in US: 17 million exacerbations/700,000 hospitalizations/122,000 deaths/$30 billion annually
- Understanding the inflammatory pathways and disease phenotypes is imperative in targeting treatment

THE CHANGING PARADIGM

• COPD is THE most common of the obstructive lung diseases
• Worldwide prevalence 10.1%

OBJECTIVES

• Inflammatory basis of COPD and Asthma
  • Disease phenotypes
  • Targets for treatment
• Current evidence-based treatment recommendations
• Immunomodulatory biologic therapies
• Dual-bronchodilator therapy for COPD
• Role of NIV in COPD
• Inhaler technology
• Phenotype “what can be observed”
  • Morphology, development, biochemical or physiological properties
  • Resulting from expression of an organism’s genes, influences of environmental factors and interactions between the two
  • No agreed upon definition
    • Symptoms, imaging, physiology, biomarkers
  • **Phenotype can change over time**

• Endotype “cellular and molecular pathway”
  • Not well understood
  • Does not change over time

• Both important in targeting treatment
• “One size does not fit all”

ASTHMA
ASTHMA

- Definition:
  - Chronic inflammatory disorder of the airways triggered by various sensitizing stimuli resulting in reversible airflow obstruction

- Key Components:
  - Airway hyperresponsiveness
  - Airflow limitation
    - Bronchoconstriction, mucus plugs, inflammation, thickening of the basement membrane, increased smooth muscle mass

- Symptoms: episodic or persistent
  - Dyspnea, wheezing, cough, chest tightness
  - Diurnal variation (night and early morning)

- Genetic factors: no single derangement, sex and obesity

- Environmental factors:
  - Allergens (dust, pollen, dander, mold), viruses, occupational exposures, tobacco smoke, air pollution, biomass fuel
ASTHMA CLASSIFICATION

ALLERGIC
• Atopic (extrinsic)
• Most common form
• Peak age 2nd decade
• Stronger family history
• IgE to specific antigens
  • Dust, pollen, dander, mold
• Immunomodulators

NON-ALLERGIC
• Non-atopic (intrinsic)
• Less common (10%)
• Later age of onset
• Greater inflammatory cell infiltrate
• Triggers not allergy related
  • Exercise, cold/dry air, smoke, viruses, fumes, medications
• Bronchial thermoplasty
Innate immune system
• Nonspecific defense mechanism when an antigen is presented:
  • Physical barriers
  • Chemicals in the blood
  • Immune system cells

Adaptive immune system
• Antigen specific immune response
• More complex mechanism
• Antigen must first be processed and recognized
  • Cells that attack
  • Memory cells

THESE DISTINCTIONS ARE NOT MUTUALLY EXCLUSIVE
MAJOR CONTRIBUTORS

• **TH2 LYMPHOCYTE**
  • IL5, IL4, IL13
  • Promote IgE and eosinophils

• **EOSINOPHIL**

• **MAST CELL**

• **NEUTROPHIL**
**ASTHMA DIAGNOSIS**

- Pattern of symptoms + objective data + response to therapy
  - Nocturnal symptoms
  - Diurnal variation
- Spirometry
  - Airflow obstruction
    - FEV1/FVC, FEV1, PEF, TLC, DLCO
  - Reversibility
    - 12% or 200 cc increase
- CXR/CT chest

- Laboratory data
  - IgE, serum eosinophils
  - Allergy testing
- Bronchial hyperreactivity
  - Methacholine challenge testing
    - 20% decline in FEV1
    - Sensitive, not specific
- feNO
  - Levels are high (due to eosinophils)
  - Assessment, management, long term monitoring
ASTHMA TREATMENT

• Shift in our approach
  • No longer based on severity
  • Based on treatment response/control

• Goals
  • Improve quality of life with less daytime/nighttime symptoms
  • Avoid exacerbations
  • Minimize side effects/cost, minimize use of rescue medications

• Toolbox
  • Inhaled corticosteroids, bronchodilators, and anticholinergics
  • Oral agents: corticosteroids, LTRA
  • Immunomodulatory biologic therapy
  • Bronchial thermoplasty
  • Allergy immunotherapy

• Environmental control
• Monitoring (symptoms/lung function/action plan)
• Ongoing education/partnership
<table>
<thead>
<tr>
<th>SEVERITY COMPONENTS</th>
<th>INTERMITTENT</th>
<th>PERSISTENT ASTHMA: daily medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MILD</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Less than once a week</td>
<td>More than twice per week but not daily</td>
</tr>
<tr>
<td>Nocturnal Symptoms</td>
<td>Less than twice a day per month</td>
<td>Three-four times per month</td>
</tr>
<tr>
<td>Interference with activity</td>
<td>Brief exacerbations</td>
<td>Exacerbations may cause minor limitation of activity and sleep</td>
</tr>
<tr>
<td>SABA use</td>
<td>≤ 2 days per week</td>
<td>&gt;2 days per week, but not daily and not more than once on any day</td>
</tr>
<tr>
<td>Pulmonary Function Test</td>
<td>Normal FEV₁ between exacerbations</td>
<td>FEV₁ &gt;80% predicted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FEV₁/FVC: normal</td>
</tr>
<tr>
<td>Recommended Treatment Strategy</td>
<td>Preferred: SABA PRN</td>
<td>Preferred: Low-dose ICS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternative: Cromolyn, LTRA, Medecrom, or Theophylline</td>
</tr>
</tbody>
</table>

**Each Step:** patient education, environmental control, and management of comorbidities.

**Steps 2-4:** Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.

Quick-relief medication for all patients:
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIA) generally indicates inadequate control and the need to step up therapy.

# Levels of Asthma Control

(Assess patient impairment)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (All of the following)</th>
<th>Partly controlled (Any present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>Twice or less per week</td>
<td>More than twice per week</td>
<td></td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td>3 or more features of partly controlled asthma present in any week</td>
</tr>
<tr>
<td>Nocturnal symptoms / awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for rescue / “reliever” treatment</td>
<td>Twice or less per week</td>
<td>More than twice per week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV₁)</td>
<td>Normal</td>
<td>&lt; 80% predicted or personal best (if known) on any day</td>
<td></td>
</tr>
</tbody>
</table>

**Assessment of Future Risk**: (risk of exacerbations, instability, rapid decline in lung function, side effects)
TRADITIONAL PHARMACOLOGIC ASTHMA TREATMENT

- Direct bronchodilators (short/long)
  - B2 agonists (increases cAMP)
    - Albuterol, levalbuterol
    - Salmeterol, vilanterol
  - Anti-cholinergics (M3 receptor)
    - Ipratropium bromide
    - Tiotropium, glycopyrylronium, umeclidium, aclidinium
  - Methylxanthines
    - Aminophylline, theophylline
  - Adrenergic agonists
    - Epinephrine

- Anti-inflammatory medications
  - Corticosteroids (inhaled, PO, IV, IM)
    - Fluticasone, beclomethasone
    - Prednisone
  - Mast cell stabilizers (inhibits histamine and tryptase)
    - Cromolyn sodium
    - Nedocromil (not for acute attacks)
  - Leukotriene antagonists
    - 5 lipoxygenase synthesis inhibitor
      - zileuton
    - Leukotriene receptor antagonist
      - montelukast
TRADITIONAL PHARMACOLOGIC ASTHMA TREATMENT

• Benefits of LABA
  • Improve lung function/symptoms
  • Decrease in exacerbations when used with ICS

• DO NOT USE LABA WITHOUT ICS

• ICS/LABA superior to higher dose ICS
• Step down therapy once control achieved
• Inform patients of concerns seen in asthma

• SMART Trial
  • Double blind, randomized observational trial 28 wk in 26K pts
  • Salmeterol v placebo added to “usual care”
  • Salmeterol was associated with greater asthma related deaths and life threatening exacerbations in AA population (no difference in Caucasian)

LAMA FOR THE TREATMENT OF UNCONTROLLED ASTHMA

- 2 replicate, randomized controlled study 912 patients
- Inclusion criteria
  - FEV1<80%, Mean FEV1 62%
  - >1 severe exacerbation in prior year
  - Mean age 53
- Add on tiotropium or placebo
- Result
  - Tiotropium associated with
    - Longer time to first exacerbation
    - More sustained bronchodilation

Kerstjens, HAM. NEJM. 2012(367):1198-1207
What is the role of tiotropium in asthma?: a systematic review with meta-analysis.

Rodrigo GJ¹, Castro-Rodríguez JA².

Author information

Abstract

BACKGROUND: The role of tiotropium for the treatment of asthma has not yet been clearly defined. The aim of this systematic review was to assess the efficacy and safety of tiotropium in patients with asthma.

METHODS: Randomized placebo-controlled trials were included. Primary outcomes were peak and trough FEV1 and morning and evening peak expiratory flow (PEF).

RESULTS: Thirteen studies (4,966 patients) were included. Three different therapeutic protocols were identified. Tiotropium as an add-on to inhaled corticosteroids (ICSs) showed statistically and clinically significant increases in PEF (22-24 L/min) and FEV1 (140-150 mL). Additionally, tiotropium decreased the rate of exacerbations (number needed to treat for benefit [NNTB], 36) and improved asthma control. The use of tiotropium in patients poorly controlled despite the use of medium to high doses of ICS was not inferior to salmeterol. Finally, the use of tiotropium as an add-on to ICS/salmeterol combination increased pulmonary function to a clinically significant magnitude, reduced asthma exacerbations (relative risk, 0.70; 95% CI, 0.53-0.94; P < .02; I² = 0%; NNTB, 17), and improved asthma control compared with ICS/salmeterol. Tiotropium was well tolerated, and no potential safety signals were observed.

CONCLUSIONS: Tiotropium resulted noninferiorly to salmeterol and superiorly to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/salmeterol. Major benefits were concentrated in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations.

Many studies have demonstrated the efficacy of LAMA add on therapy irrespective of allergic or inflammatory components

Tiotropium FDA approved (asthma)
  • adults 2015
  • children (>6y) 2017
Can be used as add on therapy
  • ICS/LABA + LAMA
  • ICS/LAMA
Ongoing research
  • LAMA monotherapy??

Management of severe asthma

- Optimize dose of ICS/LABA
  - Complete resistance to ICS is rare
  - Consider therapeutic trial of higher dose
- Consider low dose maintenance oral corticosteroids
- Monitor for and manage side-effects, including osteoporosis
- Add-on treatments without phenotyping
  - Tiotropium - reduces exacerbations (history of exacerbations, age ≥12 years)
  - Theophylline, LTRA – limited benefit
- Phenotype-guided treatment
  - Severe allergic asthma: add-on omalizumab (anti-IgE)
  - Severe eosinophilic asthma: add-on mepolizumab or reslizumab (anti-IL5)
  - Sputum-guided treatment to reduce exacerbations and/or steroid dose
  - Aspirin-exacerbated respiratory disease: consider add-on LTRA
- Non-pharmacological interventions
  - Consider bronchial thermoplasty for selected patients
  - Comprehensive adherence-promoting program
- For detailed guidelines, see Chung et al, ERJ 2014
IMMUNOMODULATORS

- Anti-IgE
  - omalizumab
- Anti-IL5
  - Mepolizumab
  - Benralizumab
  - Reslizumab
- Anti-IL4 and IL13
  - Dupilumab
- New on the horizon
  - Anti-IL5, IL4, and IL13

- When do you use them?
  - Moderate to severe allergic asthma
  - Refractory to traditional therapy

- What do they do?
  - Decrease exacerbations
  - Decrease steroid use
  - Improve lung function
  - Improve QOL

• Indication
  • Moderate/severe persistent allergic asthma
  • High IgE, +/- high eosinophil
  • Positive allergy skin testing

• Dosing
  • Based on IgE level and weight/subcutaneous injection; frequent dosing
  • Approved for adults and children >12y (2003), age >6y (2016)
  • Don’t need to follow IgE levels

• Data
  • Moderate/severe asthma: decreased exacerbations, decreased steroid dosing
  • Severe asthma: conflicting results but improved QOL

• Caution
  • Monitor patients after administration: Anaphylaxis rare
  • Slight increase in risk of malignancy (<1%), cardio and cerebrovascular disease, parasitic infections

• Cost
  • $12,000/y v $2500/y ICS/LABA
Omalizumab

Anti-IgE

Mepolizumab
Benralizumab
Reslizumab

dupilumab

IL-3, IL-5, GM-CSF

Airway inflammation

Vasodilation → edema
Goblet cell hyperplasia → mucus production
Bronchial smooth muscle contraction

Inflammation and Bronchiol contraction
**ANTI-IL5: MEPOLIZUMAB, BENRALIZUMAB, RESLIZUMAB**

- **Indication**
  - Severe allergic asthma with eosinophilia refractory to traditional therapy

- **Dosing**
  - Monoclonal antibody binds and inactivates IL-5
  - Mepolizumab: fixed dose 100 mg, subcut, q4wk
  - **Benralizumab**: fixed dose 30 mg, subcut, q8wk
  - Reslizumab: weight based 3 mg/kg, IV, q4wk

- **Caution**
  - Risk of opportunistic infection: herpes zoster
  - Monitor patients after administration: Anaphylaxis rare
  - Pregnancy category not assigned

- **Cost**
  - $35,000 annually/$1000 per vial reslizumab

www.fda.gov; www.drugs.com
ANTI-IL4 AND IL13: DUPILUMAB

- Indication
  - Moderate/severe allergic asthma, atopy, eosinophilia
- FDA approval
  - Atopic dermatitis: March 2017
  - Asthma: Approved 2018
- Data
  - QUEST and VENTURE trials
  - LIBERTY ASTHMA PROGRAM

- Cost
  - $38,000 annually
- Biggest advantage
  - AT HOME ADMINISTRATION

# Anti-IL4 and IL13: Dupilumab Phase 3 Trials

## QUEST Data Summary

<table>
<thead>
<tr>
<th>Placebo-adjusted reduction in annualized rate of severe asthma exacerbations over 52 weeks</th>
<th>Placebo (n=317)</th>
<th>200 mg Dupixent (n=631)</th>
<th>300 mg Dupixent (n=633) vs. Placebo (n=321)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>48 percent</td>
<td>46 percent</td>
<td></td>
</tr>
</tbody>
</table>

| Patients with 300 eosinophils/μl or greater | 66 percent | 67 percent |

## VENTURE Data Summary, Continued

<table>
<thead>
<tr>
<th>Change in annualized rate of severe asthma exacerbations over 24 weeks</th>
<th>Placebo (n=313)</th>
<th>300 mg Dupixent (n=610)</th>
<th>Difference between 300 mg DUPIXENT (n=107) vs. Placebo (n=103) (Overall population)</th>
<th>Placebo (n=41)</th>
<th>300 mg DUPIXENT (n=48) vs. Placebo (n=41) (Patients with 300 eosinophils/μl or greater)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>140 mL</td>
<td>130 mL</td>
<td>59 percent reduction</td>
<td>71 percent reduction</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Absolute (percent) change in FEV₁ from baseline to 24 weeks</th>
<th>Placebo (n=139)</th>
<th>300 mg Dupixent (n=266)</th>
<th>220 mL (15 percent) improvement</th>
<th>320 mL (25 percent) improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with 300 eosinophils/μl or greater</td>
<td>210 mL</td>
<td>240 mL</td>
<td>13 percent</td>
<td>18 percent</td>
</tr>
</tbody>
</table>
BRONCHIAL THERMOPLASTY

- FDA approved 2010
- Nonpharmacologic therapy for adults with severe asthma refractory to available medical therapy
- Catheter delivered radio frequency energy which heat the lining of the lung to 65°C
- Targets airway remodeling by reducing airway smooth muscle mass which is responsible for
  - Bronchoconstriction
  - Mucus hypersecretion
  - Airway hyperresponsiveness
• Repeated procedures several weeks apart targeting different lobes

• Benefit data
  • 40% reduction in asthma exac
  • 80% reduction in ER visits
  • 65% reduction days lost work/school
  • 70% reduction in hospitalizations

• Risks
  • Bronchospasm following procedure
  • Hemoptysis, atelectasis, infection
  • Avoid with pacemaker/AICD
  • Avoid FEV1<65%

Chupp G. ERJ 2017 Aug; Castro AJRCCM 2010; Wechler ME. J Allergy Clin Immunol 2013 (132)
COPD
COPD PHENOTYPES

- Non-exacerbator
- Exacerbator with emphysema
  - MOLT (Multiorgan loss of tissue)
- Exacerbator with chronic bronchitis
- Frequent exacerbator
- Alpha 1 Antitrypsin deficiency
- ACOS
- BCOS

COPD RISK FACTORS

- Cigarette smoking
- Occupational exposures
  - Silica, formaldehyde, toluene, nickel, cadmium, cotton, dust
- Air pollution
- Biomass fuel
- Hyperresponsive airway
- Asthma
- Genetic factors
Figure 3-13. Macrophages are activated by cigarette smoke and recruit neutrophils and CD+ lymphocytes to cause elastolysis and emphysema. Similarly, cigarette smoke activates airway epithelium to trigger airway remodeling. Both of these processes result in airflow obstruction.

CXCR3, chemokine CXC receptor 3; CXCR2, chemokine CXC receptor 2; EGF, epidermal growth factor; IL-8, interleukin 8; CXCL, CXC chemokine ligand; CCL, CC chemokine ligand; LTB4, leukotriene B4; MMPs, matrix metalloproteinases; PDGF, platelet-derived growth factor; TGF β, transforming growth factor β.
INFLAMMATION

Small Airway Disease
- Airway inflammation
- Airway remodeling

Parenchymal Destruction
- Loss of alveolar attachments
- Decreased elastic recoil

AIRFLOW LIMITATION
Upper Lobe

Lower Lobe

Alpha 1 AT def
<table>
<thead>
<tr>
<th>Feature</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inciting factor</td>
<td>Allergen or irritant</td>
<td>Smoking or irritant</td>
</tr>
<tr>
<td>Major cell types</td>
<td>Epithelial cells, T_{h}2 cells (CD4+)</td>
<td>T_{h}1 and T_{c}1 cells (CD8+) Neutrophils, macrophages</td>
</tr>
<tr>
<td></td>
<td>Mast cells, eosinophils</td>
<td></td>
</tr>
<tr>
<td>Mediators</td>
<td>IL-4, IL5, IL-13</td>
<td>LTB4, TNFα, IL-8</td>
</tr>
<tr>
<td>Airway and parenchymal</td>
<td>Mainly large airway</td>
<td>Small airway fibrosis</td>
</tr>
<tr>
<td>involvement</td>
<td>No parenchymal involvement</td>
<td>Parenchymal destruction</td>
</tr>
<tr>
<td>Pathological changes</td>
<td>Subepithelial fibrosis</td>
<td>Peribronchial fibrosis</td>
</tr>
<tr>
<td></td>
<td>Smooth muscle hyperplasia+++</td>
<td>Smooth muscle hyperplasia+</td>
</tr>
<tr>
<td></td>
<td>Mucous metaplasia</td>
<td>Mucous metaplasia</td>
</tr>
<tr>
<td></td>
<td>Basement membrane thickening</td>
<td>Alveolar destruction</td>
</tr>
</tbody>
</table>

| Airflow limitation            | Reversible                                                             | Airflow limitation                                                   | Partially reversible                                               |

ATS Pulmonary Board Review 2015
COPD DIAGNOSIS

- Clinical presentation
- Risk Factors
- Pulmonary function testing
- Imaging
- Resting/ambulatory pulse ox
- ABG
- Alpha 1 antitrypsin deficiency screen
**Normal**

- FEV1  > 80%
- FVC  > 80%
- FEV1/FVC  > 90%

**Obstruction**

- FEV1/FVC  < LLN OR < 70%
- Long expiratory time
- coving
COPD DIAGNOSIS

- CAT (COPD Assessment Test)
  - Numeric scale relating 8 functional parameters
    - Cough, sputum, walking, sleeping, energy, etc.
  - Lower score=fewer symptoms
  - Higher score=more symptoms

- mMRC Questionnaire (Modified Medical Research Council)
  - Degree of breathlessness using 0-4 scale
  - Higher values indicating decreasing exercise tolerance
**CAT/MMRC SCORE**

Modified Medical Research Council (mMRC) Questionnaire for Assessing Severity of Breathlessness

<table>
<thead>
<tr>
<th>Score</th>
<th>Description of Dyspnea</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I get breathless only with strenuous exercise</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying on level ground or walking up a slight hill</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>On level ground, I walk slower than other people my age because of breathlessness, or I have to stop for breath when walking at my own pace</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>I stop for breath after walking approximately 100 yards or after a few minutes on level ground</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>I am too breathless to leave the house, or breathless when dressing</td>
<td>Very severe</td>
</tr>
</tbody>
</table>
**CHANGING PARADIGM**

**GOLD GUIDELINES**

**Chronic Obstructive Pulmonary Disease (COPD)**

**GOLD I:** Mild, FEV₁ ≥ 80% predicted  
**GOLD II:** Moderate, 50% ≤ FEV₁ < 80% predicted

**Mild**
- SABA  
  - when necessary  
  - or Anti-cholinergic

**Moderate**
- LABA  
  - or Anti-cholinergic

**Severe**
- LABA  
  - or Anti-cholinergic  
  - + ICS

**Very Severe**
- LABA  
  - and/or Anti-cholinergic  
  - + ICS

**Non-Pharmacologic:**
- Smoking cessation, pulmonary rehabilitation and physical activity;  
- Add long-term oxygen if chronic respiratory failure;  
- Consider surgical treatments for selected patients (lung volume reduction surgery or lung transplantation)

*Source: Cowen Report, March 2017; American Lung Association; Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.*
Table 2.4. Classification of airflow limitation severity in COPD (Based on post-bronchodilator FEV₁)

<table>
<thead>
<tr>
<th>GOLD</th>
<th>FEV₁/FVC ≤ 0.70:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:</td>
<td>FEV₁ ≥ 80% predicted</td>
</tr>
<tr>
<td>2:</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>3:</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>4:</td>
<td>FEV₁ &lt; 30% predicted</td>
</tr>
</tbody>
</table>

Figure 2.4. The refined ABCD assessment tool

- Spirometrically confirmed diagnosis
- Assessment of airflow limitation
- Assessment of symptoms/risk of exacerbations

### Post-bronchodilator FEV₁/FVC < 0.7

<table>
<thead>
<tr>
<th>GOLD</th>
<th>FEV₁ (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:</td>
<td>≥ 80</td>
</tr>
<tr>
<td>2:</td>
<td>50-79</td>
</tr>
<tr>
<td>3:</td>
<td>30-49</td>
</tr>
<tr>
<td>4:</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>

- mMRC 0-1
  - CAT < 10
  - mMRC ≥ 2
  - CAT ≥ 10

A       | B
---|---
C       | D

www.goldcopd.org 2017
Higher Risk

GOLD 3 or 4 criteria for lung function

Less Symptoms

GOLD 1 or 2 criteria for lung function

Lower Risk

mMRC 0-1 CAT < 10

mMRC ≥ 2 CAT ≥ 10

More Symptoms

≥ 2 Exacerbation/yr OR
≥ 1 Exacerbation w/hospital

≤ 1 Exacerbation/yr

CAT = COPD Assessment Test; mMRC = modified Medical Research Council Dyspnea Scale
Llama Love
• 4 year multicenter RCT, 6K pts
• Primary outcome-spirometry
• LAMA v placebo
• Results
  • No change in rate of FEV1 decline
  • Reduced number of exacerbations
  • No mortality difference
  • Improved QOL
• Adverse cardiovascular effects of LAMA refuted
• 3 year multicenter RCT, 6K patients
• Primary outcome: mortality
• Results
  • No mortality difference
  • Fewer annual exacerbations
    • ICS/LABA vs placebo
  • Fewer severe exacerbations
    • ICS/LABA and LABA
  • More pneumonia with ICS
FLAME TRIAL 2016

- 1 year multicenter RCT double blind, randomized, noninferiority trial
- 3300 patients
- Primary outcomes: exacerbations
- Results
  - No mortality difference
  - LAMA-LABA
    - Decreased exacerbation rate (11%)
    - Increased time to first exacerbation
  - More pneumonia with ICS/LABA
    - (5% v 3%)
The Impact of Tiotropium on Mortality and Exacerbations When Added to Inhaled Corticosteroids and Long-Acting β-Agonist Therapy in COPD

Philip M. Short, MBChB; Peter A. Williamson, MBChB; Douglas H. J. Elder, MBChB; Samuel I. W. Lapiworth, BSc; Stuart Shenbri, MD; and Brian J. Lapiworth, MD

Background: Tiotropium has been shown to improve lung function, quality of life, and exacerbations and reduce mortality when compared with placebo in COPD. It remains unclear whether benefits are seen when tiotropium is used in conjunction with inhaled corticosteroids (ICSs) plus long-acting β-agonists (LABAs).

Methods: We performed a retrospective cohort study using a National Health Service database of patients with COPD in Tayside, Scotland, between 2001 and 2010 that is linked with databases regarding hospital admissions, pharmacy prescriptions, and death registries. The impact of the addition of tiotropium (Tio) to ICS + LABA therapy on all-cause mortality, hospital admissions for respiratory disease, and emergency oral corticosteroid bursts was evaluated. Adjusted hazard ratios (HRs) were calculated by Cox regression after inclusion of the following covariates: cardiovascular and respiratory disease, diabetes, smoking, age, sex, and deprivation index.

Results: A total of 1,857 patients were given ICS + LABA + Tio, and 996 were given ICS + LABA. Mean follow-up was 4.65 years. The adjusted HR for all-cause mortality for ICS + LABA + Tio vs ICS + LABA was 0.65 (95% CI, 0.57-0.73; P < .001). Adjusted HRs for hospital admissions and oral corticosteroid bursts were 0.95 (95% CI, 0.73-0.99; P = .04) and 0.71 (95% CI, 0.63-0.80; P < .001), respectively.

Conclusions: The study suggests that the addition of tiotropium to ICSs and LABA therapy may confer benefits in reducing all-cause mortality, hospital admissions, and oral corticosteroid bursts in patients with COPD. Triple therapy is widely used in the real-life management of COPD, with only limited scientific support. The study supports the use of triple therapy in COPD and provides a platform for randomized controlled trials specifically addressing this topic.

CHEST 2012; 141(1):81-86
IMPACT TRIAL-TRIPLE THERAPY

• Randomized trial 10K COPD pts
• 52 weeks ICS/LAMA/LABA v ICS/LABA and LAMA/LABA
• Primary outcome-exacerbations
• Results
  • ICS/LAMA/LABA-lower rates of mod-severe exacerbations than either combination (ICS/LABA 15% and LAMA/LABA 25%)
  • ICS/LAMA/LABA-lower rates of hospitalization due to COPD than LAMA/LABA (34%)
  • Higher incidence of pneumonia in ICS containing group
Maintenance therapy in COPD: time to phase out ICS and switch to the new LAMA/LABA inhalers?

Syed Mohammad Tarig¹ and Enson C Thomas²
Wisdom Trial

- 12 month double blind, parallel group study; 2485 patients
- Primary outcome: exacerbations
- ICS/LABA/LAMA vs gradual withdrawal of ICS
- Results:
  - Discontinuation of ICS was noninferior in terms of time to first exacerbation
  - FEV1 declined in ICS withdrawal group
  - No change in dyspnea
CONSIDERATION FOR ICS WITHDRAWAL

COPD patients currently treated with ICS/LABA + LAMA

Review exacerbation history, Blood eosinophil count

Exacerbation history plus elevated blood eosinophil count*

Strong recommendation for ICS continuation#

This protocol does not apply to patients with asthma

Consider switch to LABA/LAMA

History of exacerbations and no elevated eosinophil count, or elevated eosinophil counts in the absence of a history of exacerbations.ΔΔ

Discuss risks vs benefits with the individual patient and consider trial of withdrawal

COPD patients currently treated with ICS/LABA alone

Limited history of exacerbations (<2 per year), no elevated eosinophil count

ΔΔ Also consider symptoms and exacerbations prior to ICS introduction since patients with a strong history of an objective response to ICS may not benefit from withdrawal.

*Consider blood eosinophil counts as supporting evidence when discontinuing inhaled corticosteroids. A blood eosinophil count <300 cells per µL adds additional confidence that ICS is not required. Note that oral corticosteroids suppress blood eosinophil counts and so values taken during or after a recent course of oral corticosteroids may not be reliable.

#Patients with frequent exacerbations should be reviewed to include underlying co-morbidities (asthma/bronchiectasis), and to optimise treatment (pulmonary rehabilitation, inhaler technique).

CONCLUSION:
Roflumilast failed to statistically significantly reduce moderate and/or severe exacerbations in the overall population. Roflumilast improved lung function and reduced exacerbations in participants with frequent exacerbations and/or hospitalization history. The safety profile of roflumilast was consistent with that of previous studies.

SE: depression, anxiety, suicidal thoughts, weight loss; drug-drug interactions: erythromycin, ketoconazole, cimetidine

Do not use with theophylline; can use with azithromycin
Limited role in severe copd. No role in mild-moderate disease

**DO NOT USE IN ACUTE SETTING**
AZITHROMYCIN

- Azithromycin 250 mg taken daily for 1 year when added to usual treatment, decreased the frequency of exacerbations and improved quality of life
- Risk of cardiovascular death (underlying CAD)
- Check baseline QTc
- Hearing impairment
- Antibiotic resistance
- Review of 350K prescriptions to patients without severe cardiac disease vs no antibiotic use
  - Absolute increase in cardiac death in 29 (1 in 20,000)

Table 3.4. Bronchodilators in stable COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms (Evidence A).
- Regular and as-needed use of SABA or SAMA improves FEV₁ and symptoms (Evidence A).
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV₁ and symptoms (Evidence A).
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates (Evidence A).
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (Evidence A) and decrease hospitalizations (Evidence B).
- Combination treatment with a LABA and LAMA increases FEV₁ and reduces symptoms compared to monotherapy (Evidence A).
- Combination treatment with a LABA and LAMA reduces exacerbations compared to monotherapy (Evidence B) or ICS/LABA (Evidence B).
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance (Evidence B).
- Theophylline exerts a small bronchodilator effect in stable COPD (Evidence A) and that is associated with modest symptomatic benefits (Evidence B).
<table>
<thead>
<tr>
<th>Table 3.5. Anti-inflammatory therapy in stable COPD</th>
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</thead>
<tbody>
<tr>
<td><strong>Inhaled corticosteroids</strong></td>
</tr>
<tr>
<td>• An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD (Evidence A).</td>
</tr>
<tr>
<td>• Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease (Evidence A).</td>
</tr>
<tr>
<td>• Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms and health status (Evidence A) and reduces exacerbations (Evidence B) compared to ICS/LABA or LAMA monotherapy.</td>
</tr>
<tr>
<td><strong>Oral glucocorticoids</strong></td>
</tr>
<tr>
<td>• Long-term use of oral glucocorticoids has numerous side effects (Evidence A) with no evidence of benefits (Evidence C).</td>
</tr>
<tr>
<td><strong>PDE4 inhibitors</strong></td>
</tr>
<tr>
<td>• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:</td>
</tr>
<tr>
<td>» A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations (Evidence A).</td>
</tr>
<tr>
<td>» A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations (Evidence B).</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
</tr>
<tr>
<td>• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year (Evidence A).</td>
</tr>
<tr>
<td>• Treatment with azithromycin is associated with an increased incidence of bacterial resistance (Evidence A) and hearing test impairments (Evidence B).</td>
</tr>
<tr>
<td><strong>Mucolytics/antioxidants</strong></td>
</tr>
<tr>
<td>• Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations (Evidence B).</td>
</tr>
<tr>
<td><strong>Other anti-inflammatory agents</strong></td>
</tr>
<tr>
<td>• Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy (Evidence A). However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications (Evidence C).</td>
</tr>
<tr>
<td>• Leukotriene modifiers have not been tested adequately in COPD patients.</td>
</tr>
</tbody>
</table>
Figure 13: Potential targets for novel COPD therapy. Potential strategies and new therapies for chronic obstructive pulmonary disease (COPD) treatment are shown in the green boxes. EGFR, epidermal growth factor receptor; MMP9, matrix metalloproteinase 9; NE, neutrophil elastase; PDE4, phosphodiesterase type 4; PPARγ, peroxisome proliferator-activated receptor-γ; TGF-β, transforming growth factor-β; T helper; TLR, Toll-like receptor. Figure from Ref. 188, Nature Publishing Group.

MANAGING COPD EXACERBATIONS

- SABA, SAMA
- Steroids (PO/IV)
- Initiate maintenance therapy as soon as possible
- Avoid methylxanthines in acute setting
- Oxygen
- Initiate NIV early
- Consider nocturnal NIV
- Close monitoring
Conclusions: Three months of azithromycin for an infectious AECOPD requiring hospitalization may significantly reduce TF during the highest-risk period. Prolonged treatment seems to be necessary to maintain clinical benefits.
AZITHROMYCIN IN ACUTE SETTING

• Rationale: Azithromycin prevents acute exacerbations
• Goal: evaluate its value in the treatment of AECOPD requiring hospitalization
• Does 3 month intervention with low dose azithromycin decrease treatment failure when initiated at hospital admission and added to standard care?

• N=301
• COPD >10py, >= 1 hospitalization/y
• Azithromycin 500 mg for 3 days then 250 mg every 2 days long term x 3 months, followed for 9 months total
• Treatment failure Results (3 month)
  • Intensify treatment (47% v 60%)
  • Step up/readmission (13% v 28%)
  • All cause mortality (2% v 4%)
• Results: TF rates
  • 49% azithro v 60% placebo

Figure 3. Primary composite endpoint, treatment failure rate. The figure shows the percentage of patients who were free from treatment failure during 9 months (or 270 d) of follow-up after randomization, according to study group. Participants who did not have an event within 270 days or were terminated early were censored at Day 270 and the time of termination, respectively. CI = confidence interval; HR = hazard ratio.
NONPHARMACOLOGIC TREATMENT-COPD

• **SMOKING CESSATION**
  • Patient education
  • Medication compliance
  • Pulmonary rehabilitation
  • Vaccination
  • Nutritional support
  • Oxygen therapy
  • Consider lung volume reduction surgery
  • Consider endobronchial valve placement
  • Consider lung transplant
  • End of life/palliative care

Fletcher C. and Peto R. BMJ. 1977. 1:1645
<table>
<thead>
<tr>
<th>Abnormalities in Severe COPD</th>
<th>Benefit Conferred by Noninvasive Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive airway disease</td>
<td>Positive pressure stents open airways</td>
</tr>
<tr>
<td>Increase in inflammatory cells producing mucus, increased smooth muscle contributing to airway constriction (6)</td>
<td></td>
</tr>
<tr>
<td>Alveolar destruction</td>
<td>EPAP adjusted to overcome intrinsic PEEP to decrease respiratory muscle load</td>
</tr>
<tr>
<td>Destruction of alveoli secondary to emphysema, loss of elastic recoil contributing to hyperinflation (7)</td>
<td></td>
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<tr>
<td>Diaphragmatic dysfunction</td>
<td>High-intensity pressure support ventilation with backup rate reduces diaphragm effort and controls mechanism of breathing, resting diaphragm muscle</td>
</tr>
<tr>
<td>Atrophy from hyperinflation, limited excursion to support ventilation, increased respiratory muscle load secondary to increased airway resistance and diaphragm atrophy (8)</td>
<td></td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** COPD = chronic obstructive pulmonary disease; EPAP = expiratory positive airway pressure; PEEP = positive end-expiratory pressure.
Eligibility for NIV in the United States

The use of NIV in severe COPD is covered by the Centers for Medicare and Medicaid Services. Guidelines define the requirements to qualify for home support with a "respiratory assist device" (RAD). Both hypoxemia and hypercapnia are required, but demonstration of obstructive lung disease by spirometry is not. To qualify for home NIV, all the following criteria need to be satisfied:

1. Arterial blood gas while awake and receiving supplemental oxygen (if prescribed) demonstrating a $\text{Pa}_{\text{CO}_2}$ greater than or equal to 52 mm Hg

2. Overnight oxygen saturation less than or equal to 88% for over 5 minutes, with a minimum of 2 hours of nocturnal recording on 2 L per minute of supplemental oxygen or the patient’s prescribed level, whichever is higher

3. OSA and CPAP treatment have been considered and ruled out (Formal testing is not required; this only requires clinical documentation.)
These criteria will qualify a patient for a RAD without a backup rate (i.e., a bilevel positive airway pressure or “BiPAP” device that requires the patient to initiate all breaths spontaneously). When a patient is responsible for triggering NIV, rest is not achieved. Excursion of the diaphragm is required to initiate the positive pressure support, and in the setting of hyperinflation, this increased muscle load can lead to fatigue and atrophy of the diaphragm. The studies supporting use of NIV in severe stable COPD used settings with complete ventilator control that included a backup rate. Thus, there is a disconnect between what the literature suggests to be effective therapy and what insurance coverage supports. In order for a patient to qualify for a RAD with a backup rate, failure of RAD without a backup rate has to be documented. All the following criteria have to be documented after 3 months of documented use to qualify for a RAD with a backup rate:

1. The patient is using therapy more than 4 hours per night over a 3-month period and still experiencing progression of relevant symptoms (dyspnea, cough).

2. Arterial blood gas while awake and receiving prescribed fraction of inspired oxygen demonstrates a $\text{PaCO}_2$ greater than or equal to 52 mm Hg.

3. Overnight oximetry on NIV shows oxygen saturation less than 88% for more than 5 minutes with a minimum of 2 hours of nocturnal recording on 2 L per minute of supplemental oxygen or the patient’s prescribed level, whichever is higher.
Effects of a Highly Portable Noninvasive Open Ventilation System on Activities of Daily Living in Patients with COPD

Brian W. Carlin, MD, FCCP, Kimberly S. Wiles, BS, RRT, Robert W. McCoy, BS, RRT, FAARC, Toni Brennan, RRT, Dan Easley, BS, and Richard J. Morishige, MS, RRT

Conclusions

We evaluated a new, portable noninvasive ventilator and nasal interface system to determine the effects on the performance of typical ADLs in oxygen-dependent patients in their home environment. NIOV use resulted in statistically and clinically meaningful improvements in ADL endurance, oxygenation, dyspnea, fatigue, and comfort, compared to standard oxygen therapy. Thus, the NIOV system appears to provide a practical option for increasing physical activity levels in patients who suffer from chronic respiratory insufficiency.
WHAT IS NIOV?

• A new device that provides positive pressure to augment ventilation
• Used for patients with ventilatory impairment:
  • Dyspnea that prevents activity
  • Hypoventilation syndromes
  • Hypoxemia
• Portable system
  • Early mobility
  • Activities of daily living
  • Pulmonary rehabilitation
  • Improved quality of life
Noninvasive open ventilator (NIOV) system (Breathe Model BT-V2S, Breathe Technologies Inc., Irvine, California) showing the ventilator and nasal pillow interface. The Venturi air entrainment ports are illustrated. Ventilator dimensions are: 3 3/4 (h) x 1 1/4 (d) x 7 1/2 (w) inches. Weight: 1 lb.
Tidal Volumes: 600 mL Vt; 20 BPM; 1:2 Sinusoidal

- Normal
- NIOV - 100 mL
- NIOV - 250 mL
- CFO - 2/4/6 LPM
- Pulse OCD - 2/4/6
- BiPAP 12/5

Tidal Volume (mL)

- Normal: 599
- NIOV - 100 mL: 607
- NIOV - 250 mL: 608
- CFO - 2/4/6 LPM: 606
- Pulse OCD - 2/4/6: 934
- BiPAP 12/5: 993
LVRS/VALVES

• LVRS
  • Surgically remove damaged lung
    • Reduce dead space,
    • Improve respiratory dynamics
  • No overall survival advantage, except for upper lobe disease and poor exercise capacity

• Endobronchial valves
  • Permit exhalation/drainage of secretions but no air entry with inspiration
  • Zephyr valve FDA approved 2018
  • Increased FEV1/6min walk
  • Pneumonia, AECOPD, hemoptysis

Sciurba FC NEJM 2010. 363:1233
LUNG TRANSPLANT IN COPD

• Improves exercise tolerance/QOL
• Consider referral
  • Age <70, smoke free (min 6 mo)
  • Poor functional status
  • BODE index >5
  • FEV1<25%, DLCO <25%
  • Resting hypoxemia, hypercapnia
  • PHTN
• Median survival
  • 4-7 years

• Single or double lung transplant
• Complications with transplant
  • Rejection
  • Infection
PULMONARY REHABILITATION

• UNDERUTILIZED!

INHALER TECHNOLOGY
TYPES OF INHALERS

• Pressurized metered dose inhaler (PMDI)
• Dry powder inhaler (DPI)
• Soft mist inhaler
• Nebulizer
• “SMART” technology inhaler
INHALER CONSIDERATIONS

ON THE HORIZON: “SMART” INHALER TECHNOLOGY
SMART INHALER TECHNOLOGY

• Real time data
• Frequent use v Patterned use
• Effectiveness of delivery
• Reminders/instructions
• Cost?
• Reimbursement?

• Improve drug delivery
• Improve compliance
• Boost patient engagement
• Provide integrated care
• Gain better disease control

Even newer on the horizon: wearables to detect symptoms “RESPIRATORY FITBIT”
IMPROVING ADHERENCE

• EDUCATE, EDUCATE, EDUCATE
  • Disease
  • Inhaler technique
  • Action plan
  • Resources (online, YouTube, phone apps)
• Simplify medication regimen
• Be mindful of cost to the patient
• Provide written instructions/information
• Be accessible/supportive
• Listen to the patient