

Updates in the Management of COPD and Asthma

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Learning objectives

Upon completion of this activity, participants should be able to:

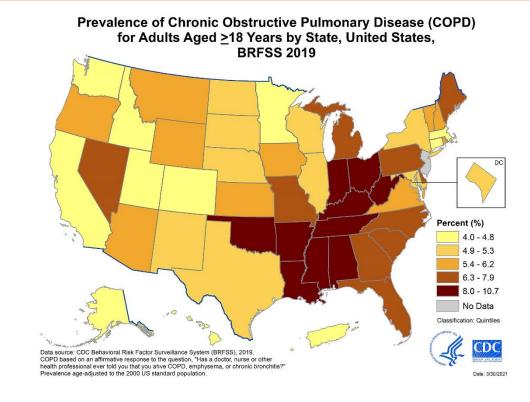
- Define appropriate initial pharmacologic therapy for COPD;
- Identify COPD patients that may benefit from inhaled corticosteroid (ICS) therapy;
- Discuss the appropriate utilization of pulmonary rehabilitation; and
- Describe the flexible treatment of mild intermittent asthma.

COPD: Clinical questions to be answered today

- How do I select the appropriate COPD maintenance therapy to initiate?
- Which COPD patients should be on inhaled steroids?
- Can I safely get COPD patients off inhaled steroids?
- Do patients with borderline hypoxemia need oxygen?
- What non-pharmacologic treatments will benefit my COPD patients?

COPD epidemiology and impact

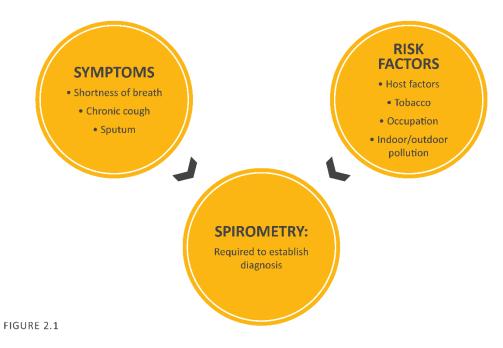
- 13 million in US have a dx of COPD but still *underdiagnosed*!
- Fourth-ranked cause of death in the United States, killing more than 120,000 individuals each year.
- Third leading cause worldwide (and increasing).



- Likelihood of underdiagnosis Black >> non-Hispanic white.
- Female smokers that visit a physician are 1/3 less likely than men to be dx with COPD than male smokers.
- 1998→2009 US prevalence increased in women, decreased in men.

COPD definition

- COPD is a common, preventable, and treatable disease characterized by **persistent respiratory symptoms** and **airflow limitation**... usually caused by significant exposure to noxious particles or gases and influenced by host factors.
- The "O" in COPD stands for Obstruction. **Demonstration of obstruction (FEV1/FVC <0.7) with spirometry** is necessary for a true COPD dx.



GOLD 2022

Assessing COPD

Goals of COPD assessment:

- 1. determine the level of airflow limitation
- 2. impact of disease on the patient's health status
- 3. risk of future events (such as exacerbations, hospital admissions, or death)

in order to guide therapy.

Asking about dyspnea

"How short of breath are you?"

"What activities cause you to be short of breath?"

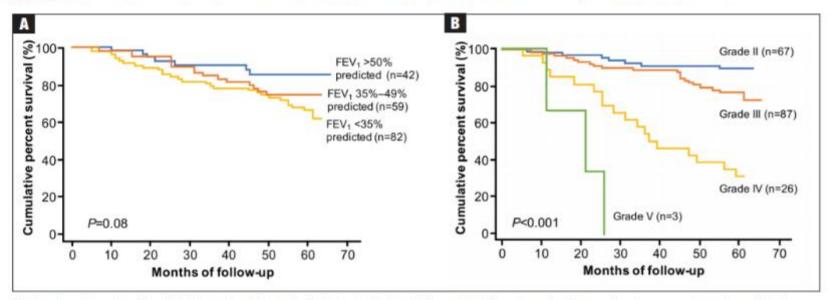
"How long can you walk at a normal pace before needing to stop to catch your breath?

| Table 2.5. Modified MRC dyspnea scale ^a | |
|--|--|
| PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY) (Grades 0-4) | |
| mMRC Grade 0. I only get breathless with strenuous exercise. | |
| mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill. | |
| mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level. | |
| mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level. | |
| mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing. | |

Fletcher CM, BMJ 1960; 2: 1662.

Why do we care about dyspnea? It's a better predictor of mortality than lung function.

FIGURE 3 Five-year survival according to (A) percentage of predicted FEV, and (B) dyspnea level²⁴



(A) Grades determined by 1995 American Thoracic Society staging guideline, which is categorized according to percentage of predicted FEV₁. (B) Grades determined by an adapted version of the Medical Research Council grading system (distinct from the modified Medical Research Council scale, which is used widely and cited in the GOLD report,⁵ in which dyspnea is classified from Grade 0 to Grade 4), developed by Fletcher et al²⁵: Grade I, I get breathless at times other than when doing strenuous exercise; Grade II, I am short of breath when hurrying on the level or walking up a slight hill; Grade III, I have to walk slower than most people on the level and I have to stop after a mile or so (or after ¹/₄ hour) on the level at my own pace; Grade IV, I have to stop for breath after walking about 100 yards (or after a few minutes) on the level; Grade V, I am too breathless to leave the house, or breathless after undressing.

Reprinted from: Chest, 121(5), Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD, 1434-1440. Copyright 2002, with permission from Elsevier.

Exacerbation risk assessment

- **COPD exacerbations** are defined as an acute worsening of respiratory symptoms that result in additional therapy.
- Classified as:
- Mild (treated with SABDs only)
- Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids)
- Severe (patient requires hospitalization or visits the emergency room).

History of exacerbation is the most important predictive factor for future exacerbations. (NOT severity of obstruction)

Asking about exacerbation history

"How many COPD exacerbations have you had?"

"Have you ever been to the ER for breathing problems?"

"How many times have you been prescribed steroid pills or antibiotics for breathing problems?"

"Low" exacerbation history

Zero to one

mod/severe exacerbations (not leading to hospital admission)

"High" exacerbation history

Two or more

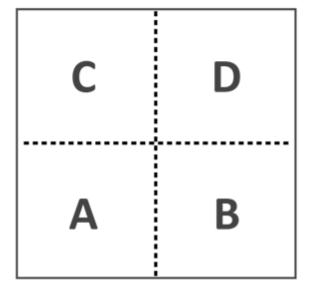
mod/severe exacerbations, <u>OR</u> any leading to hospital admission

GOLD ABCD groups

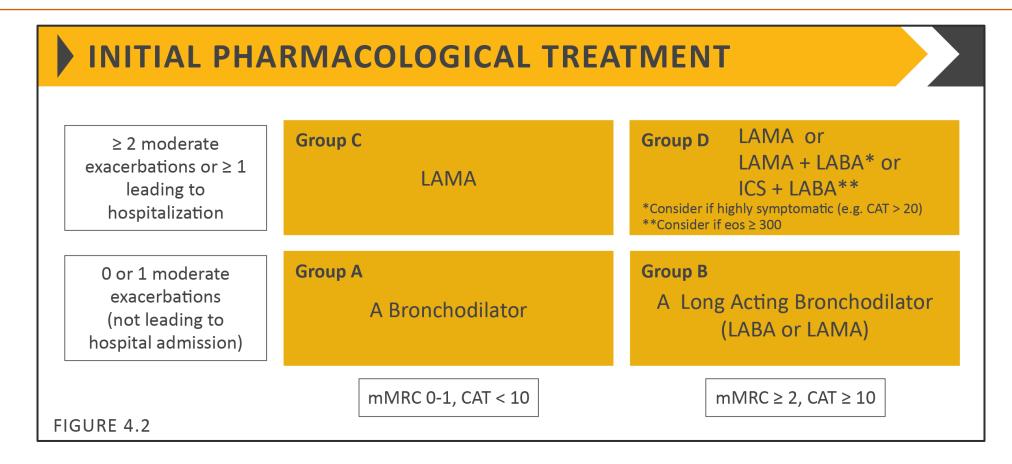
Moderate or Severe Exacerbation History

≥2 or ≥ 1 leading to hospital admission

0 or 1 (not leading to hospital admission)



Symptoms



- Consider LAMA/LAMA for highly symptomatic patients with exacerbation history
- Inhaled steroid is <u>rarely</u> a component of appropriate initial therapy.



INITIAL PHARMACOLOGICAL TREATMENT

 ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization

0 or 1 moderate exacerbations (not leading to hospital admission) **Group A**

A Bronchodilator

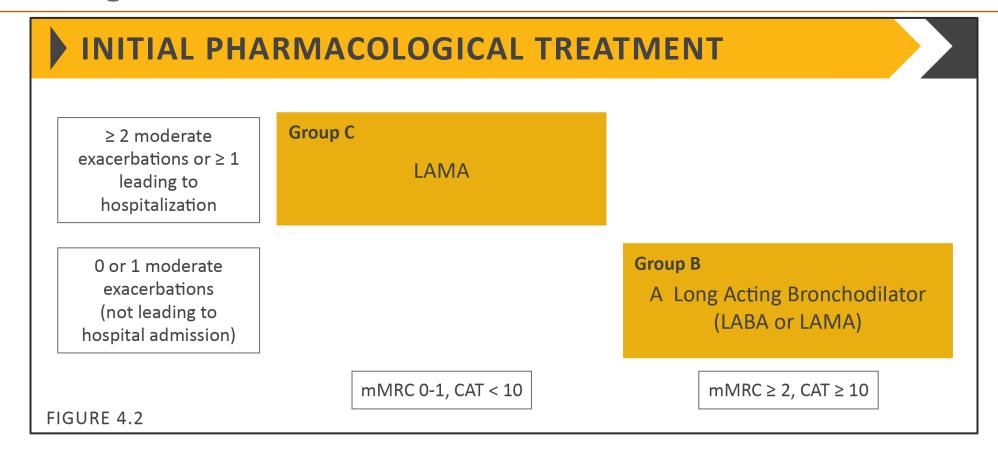
mMRC 0-1, CAT < 10

 $mMRC \ge 2$, $CAT \ge 10$

FIGURE 4.2

Group A: Low symptom burden, low exacerbation risk

- Short acting bronchodilator as needed



Group B: High symptom burden, low exacerbation risk Group C: Low symptom burden, high exacerbation risk

- LAMA: tiotropium (Spiriva), umeclidinium (Incruse), glycopyrrolate neb (Lonhala)
- LABA: formoterol (Foradil), salmeterol (Serevent), Olodaterol (Striverdi), afromoterol neb (Brovana), formoterol neb (Proformist)



INITIAL PHARMACOLOGICAL TREATMENT

 ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization

0 or 1 moderate exacerbations (not leading to hospital admission)

mMRC 0-1, CAT < 10

Group D LAMA or LAMA + LABA* or ICS + LABA**

*Consider if highly symptomatic (e.g. CAT > 20)

**Consider if eos ≥ 300

**Consider if eos ≥ 300

 $mMRC \ge 2$, $CAT \ge 10$

FIGURE 4.2

Group D: High symptom burden, high exacerbation risk

- LAMA: tiotropium (Spiriva), umeclidinium (Incruse)
- LAMA/LABA: choices reviewed on next slide
- Consider ICS/LABA as initial tx only if coexisting asthma +/- eos>300

LAMA/LABA combinations before ICS/LABA More effective at exacerbation prevention

Wedzicha et al, N Engl J Med. 2016;374(23):2222

umeclidinium/vilanterol (Anoro)

- Dry powder inhaler
- Once daily

glycopyrrolate/ indacaterol (*Utibron*)

- Capsule DPI
- Twice daily



tiotropium/olodaterol (Stiolto)

- Soft mist inhaler
- Once daily



glycopyrrolate/ formoterol (Bevespi)

- HFA MDI
- Twice daily



Little head-to-head efficacy data - consider delivery device, pt preference, cost

ICS in COPD: Known adverse drug effects

| Side-effect | Cohort studies | Population-based case- control studies | Randomized controlled trials | Systematic reviews and meta-analysis |
|--|-------------------|---|------------------------------|--------------------------------------|
| Pneumonia | + | + | + | + |
| Tuberculosis | + | + | | + |
| Non-tuberculous mycobacterial pulmonary diseases | | + | | |
| Diabetes | + | + | | + |
| Bone fracture | + | + | | + |
| Cataract | + | + | | + |
| Peptic ulcer hemorrhages | | + | | |
| Local reactions (oral candidiasis, dysphonia) | + | + | + | + |
| Skin bruising | + | | + | + |

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

ICS in COPD: In whom is BENEFIT most likely to outweigh RISK?

FACTORS TO CONSIDER WHEN INITIATING ICS TREATMENT

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators (note the scenario is different when considering ICS withdrawal):

| · STRONG SUPPORT · | · CONSIDER USE · | · AGAINST USE · |
|--|---|---|
| History of hospitalization(s) for exacerbations of COPD# | • 1 moderate exacerbation of COPD per year# | Repeated pneumonia events Blood eosinophils <100 cells/μL |
| ≥ 2 moderate exacerbations of COPD per year# | Blood eosinophils ≥ 100 to < 300 cells/μL | History of mycobacterial infection |
| • Blood eosinophils ≥ 300 cells/μL | | |
| History of, or concomitant, asthma | | |

#despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);

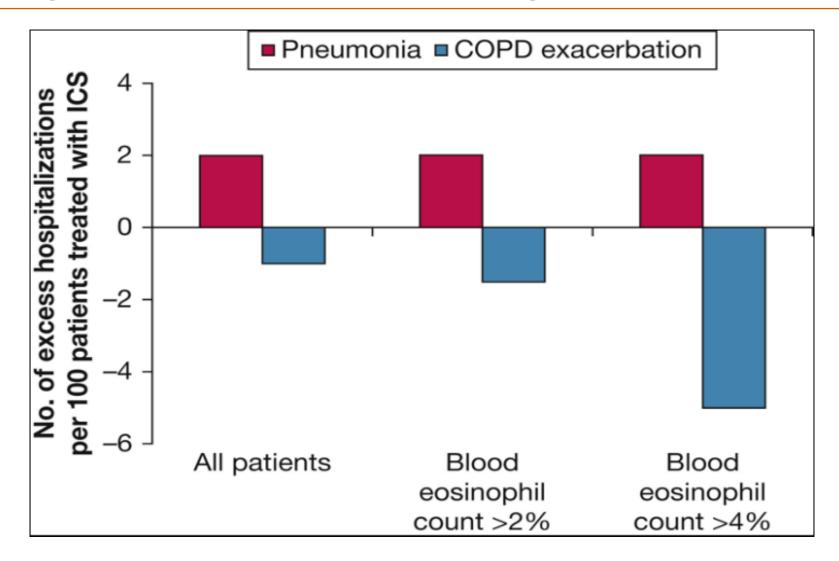
*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

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FIGURE 3.1

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Blood eosinophils as a biomarker for ICS responsiveness



ICS in COPD: Withdrawal of inappropriate ICS lowers PNA risk

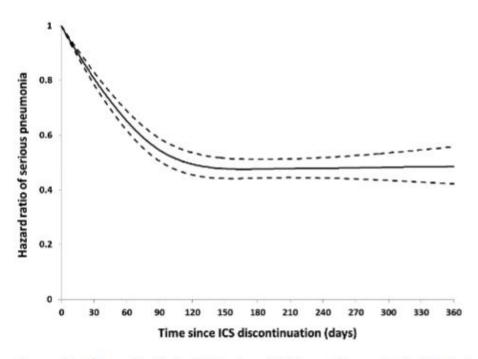


Figure 2 – Hazard ratio (solid line) and 95% confidence limits (dashed lines) of pneumonia as a function of the time since discontinuation of ICS use estimated by cubic splines models fit by conditional logistic regression, adjusted for all of the factors listed in Table 1. ICS = inhaled corticosteroid.

Case-control >100,000 Quebec COPD pts treated with ICS and discontinued (1990-2005)

Risk reduction for hospitalization/death from PNA:

- 20% at first month
- 50% at fourth month+

ICS in COPD: ICS can be withdrawn safely

| Trial | Design | N | Characteristics of the study population | Study groups | Duration of ICS therapy | Withdrawal | Main effects |
|---------------------------------|--|-------|---|---------------|---|--|--|
| COSMIC (Wouters et al, | 52-week, randomized, double-blind, parallel-group | 373 | Moderate-to-severe COPD (FEV1 30–70% predicted) | SAL/FP vs SAI | SAL/FP for 3- L month run-in period | Immediate withdrawal during randomisation | A greater FEV1 decrease in the SAL group (4.1%; 95% CI 1.6–6.6) |
| <u>2005)</u> | | | ≥2 exacerbations during preceding year | | | | |
| INSTEAD (Rossi et al, | 26-week, | | Moderate COPD (FEV1 50–80% predicted) | | SAL/FP≥3 | Immediate withdrawal during randomisation | No difference in trough FEV1 after 12 weeks (mean difference –9 mL; 95% CI –45–26) |
| 2014) | double-blind, parallel-group | 581 | No exacerbation during preceding year | SAL/FP vs IND | months | | |
| WISDOM (Magnussen et al, 2014) | 52-week, randomized, double-blind, | 2,485 | Severe-to-very severe COPD (FEV1<50% predicted) | TIO+FP+SAL | Triple therapy for 6-week | reduction every 6 | No difference between groups in time to first moderate or severe exacerbation (RR 1.06; 95% CI 0.94–1.19); a greater decrease of |
| · · · · · | parallel-group | | 1 exacerbation during preceding year | vs TIO+SAL | run-in period | | FEV1 in the withdrawal group (-38 mL) |
| SUNSET (Chapman et al, 2018) | 26-week, randomized, double-blind, parallel-group | 4.050 | COPD (FEV1 40–80% predicted), on triple therapy | TIO/SAL/FP | 1 13 | ole therapy Immediate at least 6 withdrawal during ths randomisation | No difference between groups in number of exacerbations (RR 1.08), a greater FEV1 decrease in the withdrawal group (-26 mL) |
| | | 1,053 | 0–1 exacerbation during preceding year | vs IND/GLY | months | | |

ICS in COPD: Barriers to guideline adherence

Unlikely to take patients off an inhaled corticosteroid prescription placed by another provider (39%)

"If someone came in on ICS or if someone see a pulmonary provider who prescribed it, I would probably be reluctant to stop it. But, most likely I would not initiate it."

Unaware that inhaled corticosteroids were associated with a higher risk of pneumonia (46%)

Unaware that LAMAs/LABAs are as effective as inhaled corticosteroids in reducing breathing exacerbations (52%)

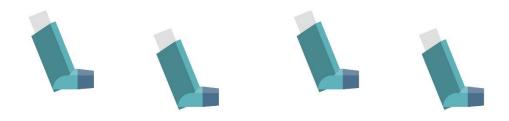
"...if things don't appear in what you normally read to stay current, then you don't get familiar with it. It's not like 'I'm going to prescribe ICS, let me go read the guidelines about that'. You just don't do that. One, you don't have time, and two, you can't necessarily go find that all out... in a busy, day-to-day practice, it's not something you'd look up."

ICS in COPD: Systemic cost of low-value care

VA study showed \$330 average increase medication cost for COPD patients receiving low-value ICS treatment

- 17.5 million Optum patients in US
- 6% with COPD (>1 million)
- 40% of these are likely treated with ICS
- 84% of these are likely low-value

(All numbers estimated!)



>350,000 Optum patients receiving low-value ICS treatment

Direct cost of >\$100 million annually

ICS in COPD:

Systemic benefit of low-value ICS discontinuation

- Difference in absolute risk for PNA in FLAME: 1.8%
- Number needed to harm (NNH): ~66
- Optum COPD patients receiving inappropriate ICS: ~350,000



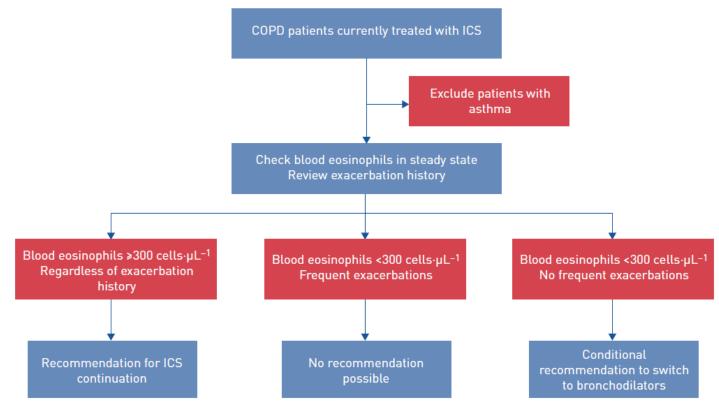




>5,000 Optum COPD patients are hospitalized for pneumonias attributable to inappropriate ICS use every year

(All numbers estimated!)

ICS in COPD: Algorithm for withdrawal



- Frequent exacerbations: ≥2 moderate or 1 severe exacerbation per year
 - Consider history of exacerbations prior to ICS
 - Assess ICS side-effects and risk of pneumonia
 - Address patient preferences

FIGURE 3 Algorithm of the European Respiratory Society guideline on inhaled corticosteroid (ICS) withdrawal in patients with chronic obstructive pulmonary disease (COPD). Note that systemic corticosteroids suppress blood eosinophil counts and so values taken during or after a recent course of oral corticosteroids should not be used.

Decoding lab report / peripheral eosinophilia

| | Test | Result |
|---|------------------------|---------------|
| | WBC | 5.8 x10E3/uL |
| | RBC | 4.35 x10E6/uL |
| | Hemoglobin | 13.1 g/dL |
| | Hematocrit | 39.1 % |
| | MCV | 90 fL |
| | Lymphs | 30 % |
| | Platelets | 224 x10E3/uL |
| | Immature Grans (Abs) | 0.0 x10E3/uL |
| 7 | Eos (Absolute) | 0.9 x10E3/uL |
| | Baso (Absolute) | 0.1 x10E3/uL |
| | MCH | 30.1 pg |
| | MCHC | 33.5 g/dL |
| | Neutrophils | 47 % |
| | Immature Granulocytes | 0 % |
| | Monocytes | 7 % |
| | Eos | 15 % |
| | Basos | 1 % |
| | Neutrophils (Absolute) | 2.7 x10E3/uL |
| | Lymphs (Absolute) | 1.8 x10E3/uL |
| | Monocytes(Absolute) | 0.4 x10E3/uL |
| | RDW | 13.9 % |

- CBC with manual diff
- Absolute eosinophil count
- Looking for >300 cells per uL.
- %Eos can be helpful but may not flag as abnormal.

0.9 x 10E3/uL = 0.9 x 0.001 Need to multiply by 1000 to get to cells per uL

(This patient's absolute eosinophil count is **900 –** likely to be an ICS responder)

ICS in COPD: Summary

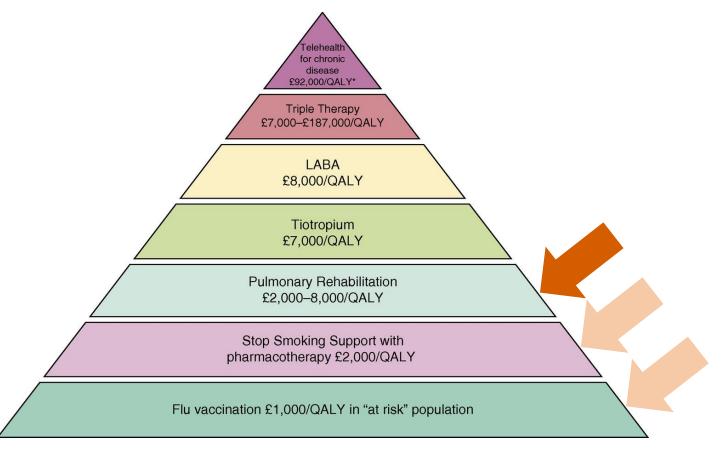
- ICS use is associated with increased risk for pneumonia.
- This risk is outweighed by benefit of decreased exacerbations in only a small subset of COPD patients:
 - Concomitant asthma
 - Peripheral eosinophils >300/uL
 - More than exacerbation annually
- ICS can be safely discontinued without taper in most pts.

Restrict ICS use in COPD to patients with eosinophilia and/or frequent exacerbations.

Stop ICS in patients that don't need it.

What non-pharmacologic treatments will benefit my COPD patients?

Cost-effectiveness of pulmonary rehabilitation relative to other treatments for COPD



Adapted from: Rochester RC et al, Am J Respir Crit Care Med. 2015 Dec 1;192(11):1373-86

Please don't forget about these other HIGH VALUE non-pharm treatments for COPD too!

What is pulmonary rehabilitation?



ESSENTIAL COMPONENTS OF PULMONARY REHABILITATION

- 1. An initial center-based assessment by a health care professional
- 2. An exercise test at the time of assessment
- 3. A field exercise test
- 4. Quality of life measure
- 5. Dyspnea assessment
- 6. Nutritional status evaluation
- 7. Occupational status evaluation
- 8. Endurance training
- 9. Resistance training
- 10. An exercise program that is individually prescribed
- 11. An exercise program that is individually progressed
- 12. Team includes a health care professional with experience in exercise prescription and progression
- 13. Health care professionals are trained to deliver the components of the model that is deployed

What is pulmonary rehabilitation?

DESIRABLE COMPONENTS OF PULMONARY REHABILITATION

PATIENT ASSESSMENT

- Anxiety and depression
- Inhaler technique
- Comorbidities

PROGRAM COMPONENTS

- Upper limb training
- ACT for bronchiectasis
- ACT for cystic fibrosis
- Structured education
- Individualized education
- Self-management training
- Goal setting
- Physical activity counselling
- Smoking cessation support
- Individualized action plan for frequent exacerbators
- Home exercise program (aerobic/ resistance) to maximize gains in exercise performance during the program
- Maintenance exercise training



METHOD OF DELIVERY

- Center-based assessment by a health care professional at discharge
- Delivery of alternative models to increase program access
- Shared decision making between patient and health care professional to choose the appropriate model
- Programs delivered in a community (non-hospital) setting
- Regular contact between health professionals and the patient
- Access to a multidisciplinary team
- Team includes a health professional with expertise in exercise prescription and progression for patients with comorbidities



QUALITY ASSURANCE

- Evidence of efficacy should be available for any model deployed
- Evidence of effectiveness should be available for any model deployed
- Health care professionals should be trained to deliver digital/technology based solutions if used within the program
- If more than one model of pulmonary rehabilitation is offered, staff should be trained in shared decision making
- Programs should document their Standard Operating Procedure for each model that is offered



Pulmonary rehabilitation: benefits

Exercise capacity and Lung function

- 43 meters longer on 6 minute walk ¹
- 7 watts higher on cycle ergometer ¹
- Slower decline in FEV1 over 3 years ²

Quality of life

• Clinically significant improvements in dyspnea, fatigue, emotional function, and mastery ³

Health care utilization

- Decreased hospital days
- Mixed studies on readmission rates ⁴

Mortality

 PR enrollment within 90 days of hospital D/C for AECOPD associated with lower 1 year mortality (19.6% vs 7.3%)

Benefits are not permanent! Exercise capacity, symptoms, and HRQoL return to pre-rehab values after ~12 months. Pulmonary rehab maintenance programs may help benefits persist 12-24 mos.

Pulmonary rehab is PROFOUNDLY UNDERUTILIZED

Patients aren't aware

Most COPD patients have never heard of pulmonary rehab (ATS 2018)

Doctors don't refer

Only 3-16% of eligible patients referred, across multiple countries

<3% of Medicare patients referred to a pulmonary rehabilitation program within 12 months of hospitalization for COPD exacerbation

Non-Hispanic white patient referral double that of black patients

Barriers: low knowledge of PR, low knowledge of referral process

Patients don't complete

Many patients do not complete prescribed PR (attrition rates ~60%)
Strong predictors of attrition: White race, current smoking, low functional capacity, low neighborhood SDI

Pulmonary rehab in COPD: Summary

- Pulmonary rehab programs are:
 - Highly effective at improving health-related quality of life and health care utilization in COPD patients
 - Highly cost-effective
 - Profoundly underutilized
- PCPs have a role as advocates and educators for PR

Learn about pulmonary rehab resources in your area

Refer symptomatic COPD patients for pulmonary rehab and encourage participation

Borderline hypoxemia



OXYGEN THERAPY AND VENTILATORY SUPPORT IN STABLE COPD

OXYGEN THERAPY

- The long-term administration of oxygen increases survival in patients with severe chronic resting arterial hypoxemia (Evidence A). [Severe: Resting SpO2 </= 88%]
- In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance (Evidence A).

Long-Term Oxygen Treatment Trial (LOTT)

2016 RCT, 738 pts with stable COPD and:

- Moderate resting hypoxemia (Resting SpO2 89-93%), OR
- Exercise-induced desaturation (SpO2< 90% for ≥10 s and ≥ 80% for ≥5 min)

Supplemental oxygen had **no effect** on:

- Mortality and time to first hospitalization
- COPD exacerbation
- Dyspnea and well-being questionnaires

Resting sat >88% or desats into 80's with exercise are NOT indications for O2 in stable COPD.

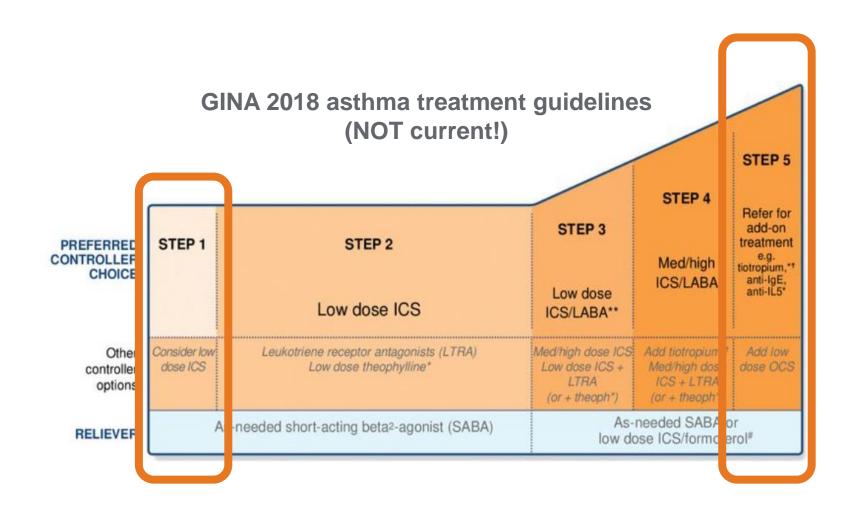
Key messages: COPD

- We use WAY too much ICS in COPD.
 - Evaluate your patients for d/c of ICS
 - Use LAMA or LAMA/LABA as better initial tx choices
- We use WAY too little pulmonary rehab in COPD.
 - Familiarize yourself with local resources
 - Refer and educate
- There is <u>no</u> proven benefit of O2 in stable COPD patients with exertional O2 desaturation only.
 - Limit chronic O2 use to SpO2 <89% at rest

Asthma: Clinical questions to be answered today

- What are my options for treatment of intermittent asthma?
- What's the role of biologic therapy in asthma?

Big changes in management for both mild and severe asthma in the last few years







EDITORIAL GINA 2019

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel ¹, J. Mark FitzGerald², Eric D. Bateman³, Leonard B. Bacharier⁴, Allan Becker⁵, Guy Brusselle⁶, Roland Buhl⁷, Alvaro A. Cruz⁸, Louise Fleming ⁹, Hiromasa Inoue¹⁰, Fanny Wai-san Ko ¹¹, Jerry A. Krishnan¹², Mark L. Levy ¹³, Jiangtao Lin¹⁴, Søren E. Pedersen¹⁵, Aziz Sheikh¹⁶, Arzu Yorgancioglu¹⁷ and Louis-Philippe Boulet¹⁸

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New understanding of mild asthma

Patients with apparently mild asthma are still at risk for serious adverse events!

37% of adults with acute asthma

16% of patients with near-fatal asthma

20% of adults dying of asthma

(Dusser, Allergy 2007)

Mild asthma accounts for 50-75% of all asthma, and 40% of severe exacerbations

DO NOT treat ANY asthmatic with prn albuterol only!

SYGMA trials (2018): PRN ICS/LABA for mild asthma

Patients: Age 12+ with dx of asthma

- Uncontrolled on as-needed short acting bronchodilator (SABA) only, OR
- Controlled on low-dose inhaled corticosteroid (ICS)

SYGMA 1 DB-RCT

SYGMA 2 Open-label

- ICS/LABA prn had similar exacerbation rate to daily ICS
- Total ICS exposure >75% less with prn regimen
- However, daily sx control slightly better with daily ICS

As-needed ICS-LABA is the *preferred* treatment approach for mild asthma

Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review for individual patient needs





CONTROLLER and PREFERRED RELIEVER

(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1-2

As-needed low dose ICS-formoterol

STEP 3

Low dose maintenance ICS-formoterol

STEP 4 Add

STEP 4

Medium dose
maintenance
ICS-formoterol

Add-on LAMA
Refer for phenotypic
assessment ± anti-IgE,
anti-IL5/5R, anti-IL4R
Consider high dose

RELIEVER: As-needed low-dose ICS-formoterol

CONTROLLER and ALTERNATIVE RELIEVER

(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1

Take ICS whenever SABA taken

STEP 2

Low dose maintenance ICS

STEP 3

Low dose maintenance ICS-LABA

STEP 4

Medium/high dose maintenance ICS-LABA

STEP 5

ICS-formoterol

Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA

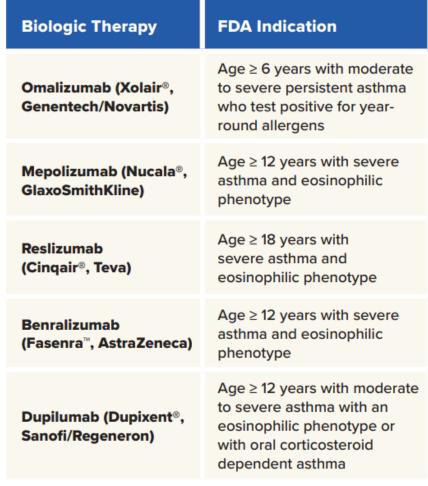
RELIEVER: As-needed short-acting β2-agonist

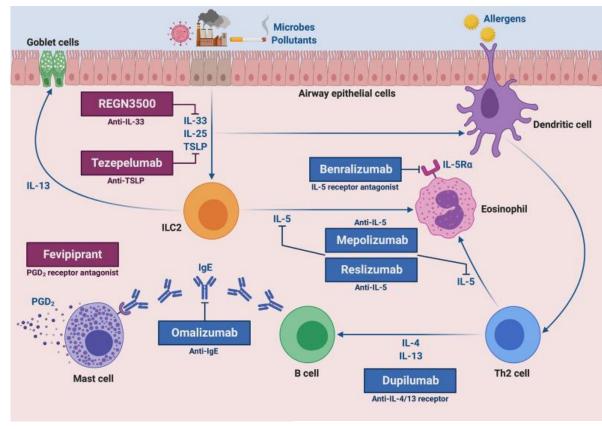
GINA, 2021

Mild asthma: How to put EBM into practice?

- RCTs used Symbicort Turbohaler (DPI)
 - This specific device/drug combo not available in US
 - Symbicort MDI available but costly (list price >\$350)
 - Off-label not FDA approved for relief
 - Generic fluticasone-formoterol approved by FDA 3/14/2022
- US guidelines (NHLBI EPR-4 targeted update, 2020) suggest prn ICS immediately followed by SABA
- Other ICS/LABA for this off-label indication?
 - Mometasone/formoterol (Dulera) → same LABA as the RCT
 - Fluticasone/salmeterol (Advair/generic) → salmeterol is slow-acting
 - Fluticasone/vilanterol (Breo) → vilanterol faster, ultra-long acting

Biologics in Asthma - overview





Pelaia C. Front Immunol. 2020;11:603312.



Biologics provide modest benefit at very high cost

How effective are these treatments compared to standard of care?

Asthma Exacerbations

Asthma control

Quality of life

Oral Corticosteroid Use*

Modest benefit

Did not reach minimally important difference

Modest benefit

Did not reach minimally important difference

Oral Corticosteroid Use*

Reduced

Reduced

Do the biologics meet established thresholds for long-term cost-effectiveness?

At their current prices, all five treatments **exceed commonly accepted thresholds for cost-effectiveness** of \$50,000–\$150,000 per quality-adjusted life years (QALY) gained, when compared to standard of care.

| | Omalizumab | Mepolizumab | Reslizumab | Benralizumab | Dupilumab |
|-------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Cost per QALY gained | \$325,000/ QALY | \$344,000/ QALY | \$391,000/ QALY | \$371,000/ QALY | \$351,000/ QALY |
| Annual net price* | \$28,900 | \$29,500 | \$28,900 | \$27,800 | \$31,000 |

*Average annual price of each treatment, net of discounts and rebates, as reported to ICER by each manufacturer.

ICER, 2018

Biologic therapies for asthma need to get a lot cheaper before they can be considered a reasonable value in the US

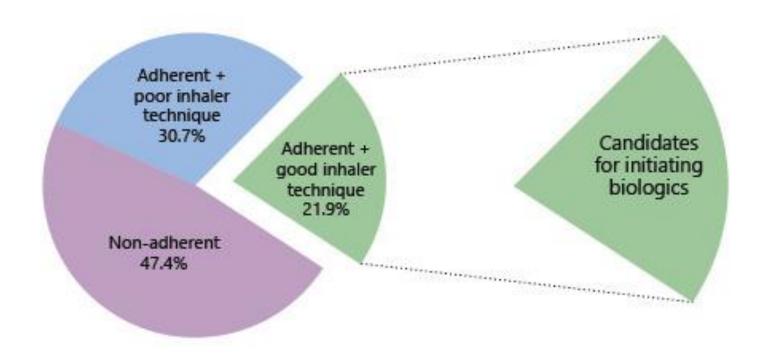
VALUE-BASED PRICE BENCHMARKS

What is a fair price for the biologics based on their value to patients and the health care system?

| Intervention | Current Annual List Price* | Annual Price at \$100,000 per QALY Threshold | Annual Price at \$150,000 per QALY Threshold | Discount from List Price Required to Achieve Threshold Prices | Is Current Net Price Within Value-Based Range? |
|--------------|----------------------------------|--|--|--|---|
| Omalizumab | \$39,048 | \$9,000 | \$13,300 | 66% to 77% | NO |
| Mepolizumab | \$37,293 | \$9,200 | \$13,400 | 64% to 75% | NO |
| Reslizumab | \$31,637 | \$6,500 | \$10,400 | 67% to 80% | NO |
| Benralizumab | \$30,889 | \$8,300 | \$11,900 | 62% to 73% | NO |
| Dupilumab | \$38,110 | \$10,100 | \$14,300 | 62% to 73% | NO |

^{*}Annual wholesale acquisition cost (WAC), prior to any discounts or rebates

ICS non-adherence and/or poor inhaler technique is common in poorly controlled asthmatics



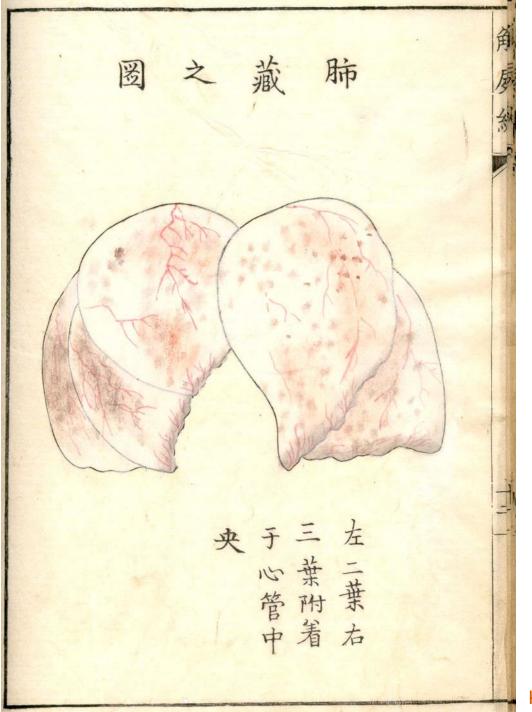
Biologic therapy for asthma should not prescribed to patients with high OCS use without thorough verification that inhaled ICS therapy is being used in an adequate and appropriate manner!

Online resources for inhaler technique

- https://www.cdc.gov/asthma/inhaler_video/default.htm
- https://www.nationaljewish.org/conditions/medications/inhaled-medication-asthma-inhaler-copd-inhaler/instructional-videos
- https://www.thoracic.org/professionals/clinical-resources/video-lectureseries/obstructive-lung-disease/asthma/inhaler-device-selection-and-technique.php

Key messages: Asthma

- Mild/intermittent asthma still results in poor outcomes.
 - Do <u>not</u> treat any asthmatic with albuterol only.
- ICS/LABA prn is a good approach to mild asthma.
 - Step up to daily ICS if inadequate sx control.
- Biologic therapies are modestly effective and very expensive.
 - Med adherence/technique is worthy of a lot of attention.



Questions?

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