Apogee
CLINICAL IMMERSION
COPD Management

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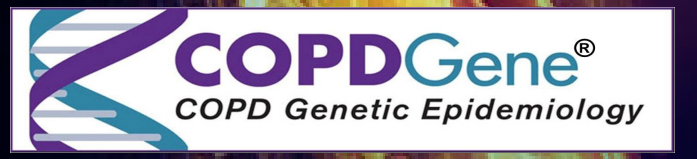


Discussion

- Goals of management
- GOLD Categorization
- Non-pharmacologic therapies
- Medications
  - Bronchodilators
  - Inhaled steroids
  - Azithromycin
  - Roflumilast
  - Biologics
  - PDE 3-4

Goals of Therapy for Stable COPD

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

→ REDUCE RISK

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

→ REDUCE SYMPTOMS

Global Initiative for Chronic Obstructive Lung Disease (GOLD).
Global Strategy for the Diagnosis, Management and Prevention of COPD-2017.

GOLD Document

Global Strategy For The Diagnosis, Management and Prevention of COPD

- "Recommendations for diagnosis, assessment and treatment of COPD"
- Reviews published literature
- Consensus driven by panel of largely academicians

Purpose and disclaimer: "Information's relevance to, and/or application to, a particular patient . . . must be carefully assessed, evaluated, and determined by a qualified health care professional treating that patient"

Global Strategy for Diagnosis, Management and Prevention of COPD, 2025. www.goldcopd.com

Clinical Practice Guideline – Institute of Medicine

- Systematically developed statements to assist practitioner and patient decisions about appropriate diagnosis and treatment.
- Rigorously developed.
- Describe recommendations.
- Not fixed protocols.
  - ***Not a substitute for advice of knowledgeable health care professional***

Other “Guidelines”

Up-to-Date®

- Universally used by clinicians
- Evidence based clinician decision support
- Deliver evidence and recommendations
- A guideline

Other national guidelines, e.g.,

- UK
- Spain
- Australia
- AAFP, USA

Global Initiative for Chronic Obstructive Lung Disease

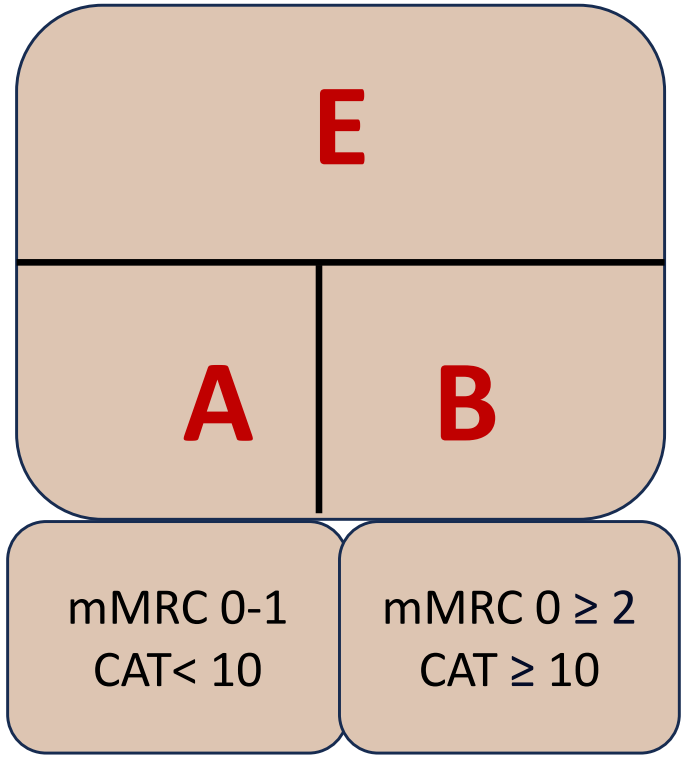
2025 REPORT

COPD Classification, GOLD

GRADE	FEV1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

≥ 2 moderate exacerbations
or
≥ 1 leading to hospitalization

0 or 1 moderate exacerbaions
(not leading to hospitalization)



RISK for Future EXACERBATIONS (Exacerbations per Year)

Current SYMPTOMS

COPD Classification, GOLD

GRADE	FEV1 (% predicted)
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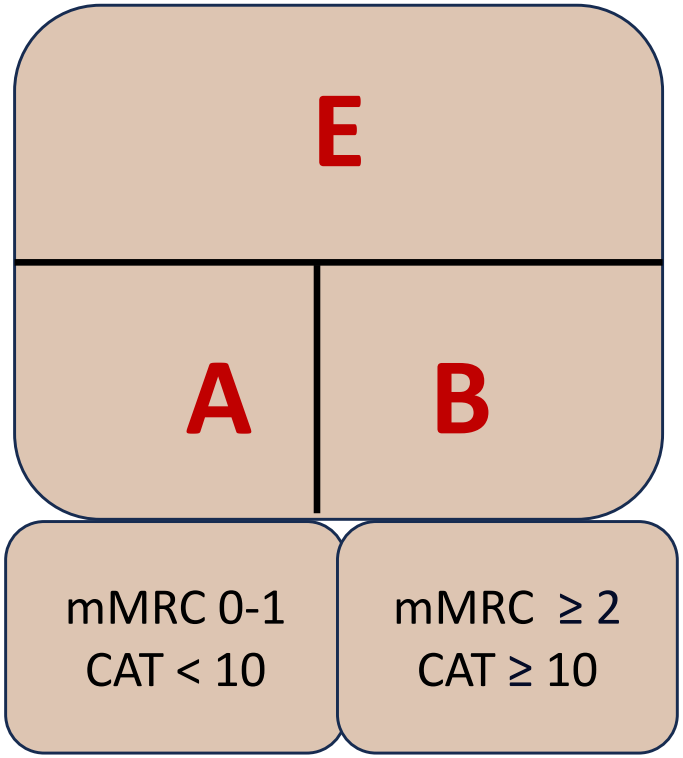


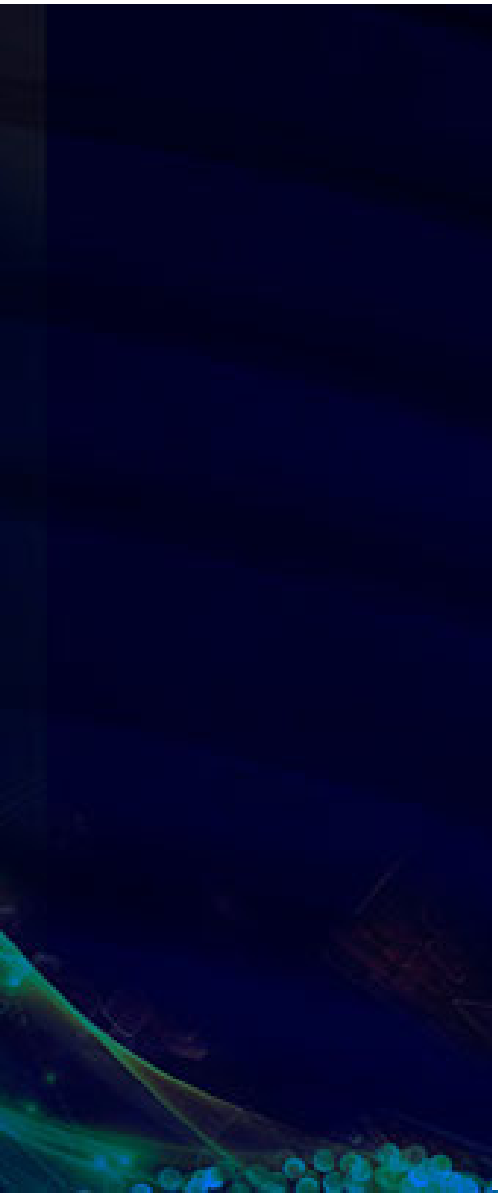
RISK for Future EXACERBATIONS (Exacerbations per year)

Current SYMPTOMS

mMRC Dyspnea Scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Global Strategy for the Diagnosis, Management and Prevention of COPD-2018. goldcopd.org/.



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

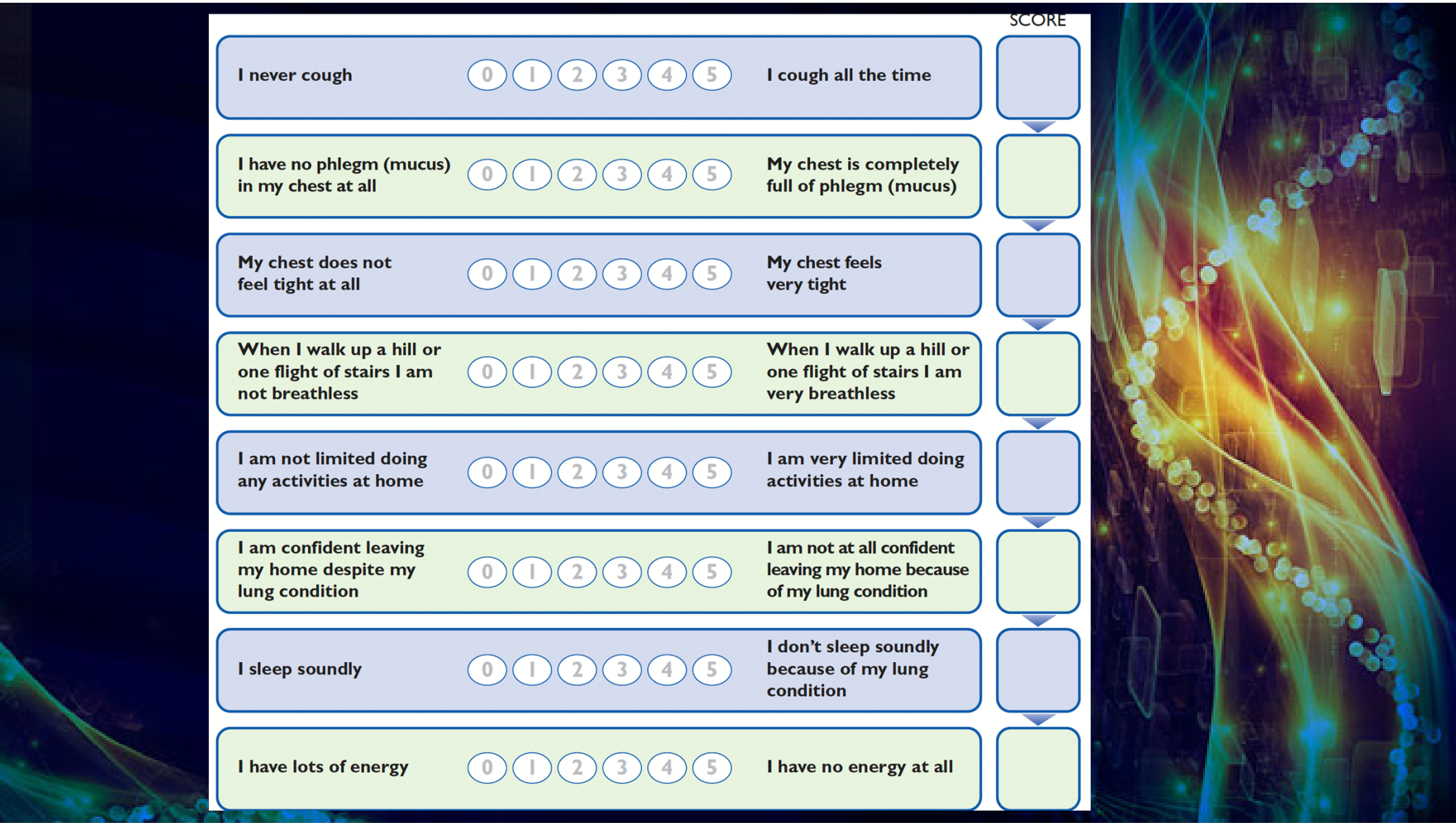
This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	

TOTAL SCORE



Exacerbation Severity – Classic Definition

1) acute worsening of respiratory symptoms beyond day-to-day variations
2) results in additional therapy

Mild exacerbation: Worsening of symptoms, often self-managed by patient, and NOT treated with systemic corticosteroids and/or antibiotics

Moderate exacerbation: Treated with systemic corticosteroids and/or antibiotics

Severe exacerbation: Results in hospitalization or ED visit > 24 hours

Unreported exacerbations

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2022 Report. www.goldcopd.org.

Rome Proposal - Updated Definition of COPD Exacerbation and Severity Classification

An event characterized by

- dyspnea and/or cough and sputum
- worsen over ≤14 days,
- *may be* accompanied by tachypnea and/or tachycardia and
- *often* associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways

Figure from Celli BR, et al. Available at: "An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations." Celli BR, et al. Am J Respir Crit Care Med 2021; 204: 1251-1258.

Severity	Criteria for judging severity
Mild (default)	**Dyspnea** VAS < 5 **RR** < 24 breaths/min **HR**< 95 bpm **SaO2** ≥ 92% on room air (or patient's usual oxygen prescription) AND change ≤ 3% (when known) **CRP** > 10mg/L (if obtained)
Moderate (meets at least 3 of 5)	**Dyspnea** VAS ≥ 5 **RR** ≥ 24 breaths/min **HR** ≥ 95 bpm **SaO2** < 92% breathing ambient air (or patient's usual oxygen prescription) AND change > 3% (when known) **CRP** ≥10mg/L **ABG** hypoxemia (PaO2 ≤ 60 mmHg) and or/ hypoxemia (PaCO2 > 45 mmHg) but no acidosis (pH >7.35)
Severe	**ABG** *may show* hypercapnia and acidosis - PaCO2 > 45 mmHg and pH <7.35

Celli BR. AJRCCM, 2021; 204(11):108.

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Global Initiative for Chronic Obstructive Lung Disease (GOLD).
Global Strategy for the Diagnosis, Management and Prevention of COPD-2017.

Non-pharmacologic therapy for COPD

- Disease-state education
  - Exacerbation recognition / management
- Smoking cessation **. Avoid other inhalant risk.
- Vaccinations
- Medication education
  - Role, expectations. Assess response. Inhaler demonstration / teach-back.
- Nutrition therapy
- Pulmonary rehabilitation
- Supplemental oxygen
- Non-invasive positive pressure ventilation
- Lung volume reduction surgery, bronchoscopic valves
- Palliative care
- Lung transplantation

Identify & Reduce Risk Factor Exposure

Figure 3.3

- Smoking cessation interventions should be actively pursued in all people with COPD **(Evidence A)**
- Efficient ventilation, non-polluting cooking stoves and similar interventions should be recommended **(Evidence B)**
- Clinicians should advise patients to avoid continued exposures to potential irritants, if possible **(Evidence D)**

Brief Strategies to Help the Patient Willing to Quit

Figure 3.4

ASK	Systematically identify all tobacco users at every visit *Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented*
ADVISE	Strongly urge all tobacco users to quit *In a clear, strong, and personalized manner, urge every tobacco user to quit*
ASSESS	Determine willingness and rationale of patient's desire to make a quit attempt. *Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days)*
ASSIST	Aid the patient in quitting *Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials*
ARRANGE	Schedule follow-up contact *Schedule follow-up contact, either in person or via telephone*

Treating Tobacco Use and Dependence

Figure 3.5

Major Findings & Recommendations from the Tobacco Use & Dependence Clinical Practice Guideline Panel:

- Tobacco dependence is a chronic condition that warrants repeated treatment until long-term or permanent abstinence is achieved
- Effective treatments for tobacco dependence exist and all tobacco users should be offered these treatments
- Clinicians and health care delivery systems must operationalize the consistent identification, documentation, and treatment of every tobacco user at every visit
- Brief smoking cessation counseling is effective and every tobacco user should be offered such advice at every contact with health care providers
- There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness
- Three types of counseling have been found to be especially effective: practical counseling, social support of family and friends as part of treatment, and social support arranged outside of treatment
- First-line pharmacotherapies for tobacco dependence — varenicline, nortriptyline, bupropion sustained release, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch— are effective and at least one of these medications should be prescribed in the absence of contraindications
- Financial incentive programs for smoking cessation may facilitate smoking cessation
- Tobacco dependence treatments are cost effective interventions

Vaccinations

- SARS-CoV-2 regularly
- Influenza yearly
- Pneumococcal pneumonia, PCV-20
- Whooping cough – Tdap
- RSV
- Herpes Zoster

Vaccination for Stable COPD

Figure 3.6

People with COPD should receive all recommended vaccinations in line with the relevant local guidelines:

- Yearly influenza vaccination **(Evidence B)**
- SARS-CoV-2 (COVID-19) vaccination based on WHO and CDC updated recommendations **(Evidence B)**
- Either one dose of 21-valent pneumococcal conjugate vaccine (PCV21) or one dose PCV20, as recommended by the CDC **(Evidence B)**. Pneumococcal vaccination has been shown to reduce the incidence of community-acquired pneumonia and exacerbations for people with COPD **(Evidence B)**
- Respiratory syncytial virus (RSV) vaccination for individuals aged ≥ 60 years and/or with chronic heart or lung disease, as recommended by the CDC **(Evidence A)**
- Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence, as recommended by the CDC **(Evidence B)**
- Zoster vaccine to protect against shingles for people with COPD aged > 50 years, as recommended by the CDC **(Evidence B)**

Oxygen therapy in stable COPD

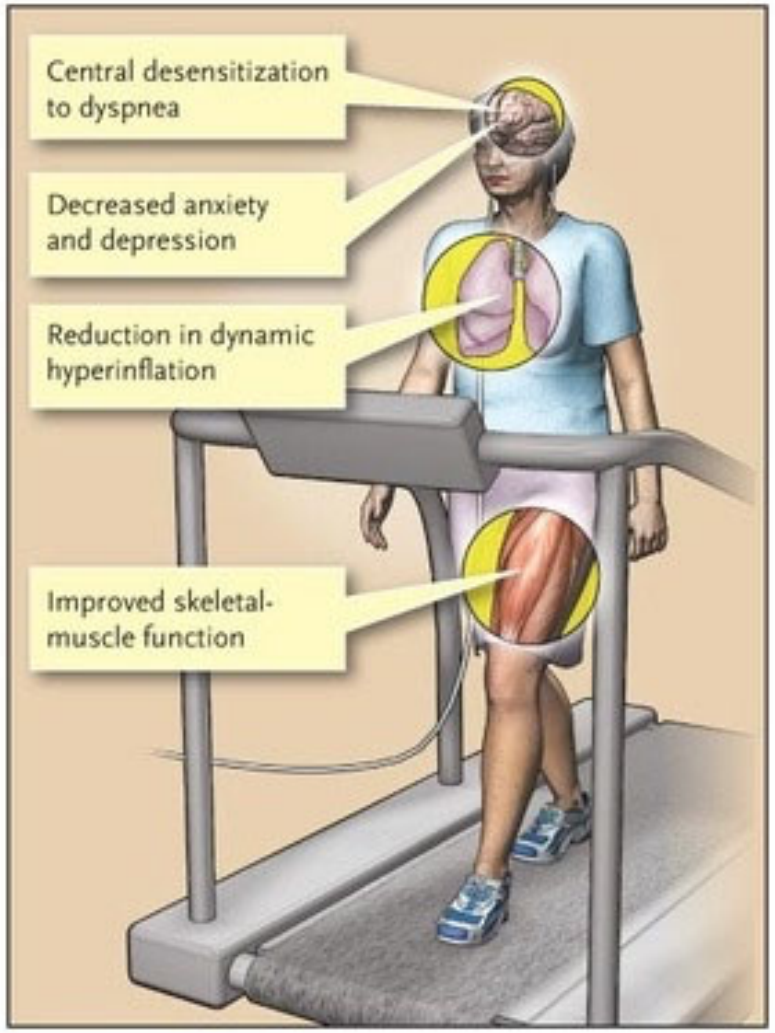
- Continuous oxygen recommended for patients with severe resting hypoxia (PaO_2 <55 mmHg) or (PaO_2 <88%).
  - With right heart strain/polycythemia (PaO_2 56-59, O_2 sat%)
  - Prolongs survival (NOTT Trial,1980)
- Moderate hypoxia - LOTT trial
  - Normal resting oxygen saturation
  - Moderate desaturation with 6-minute walk (>80% for >5 minutes and <90%)
  - Supplemental oxygen provided for half of the subjects
  - No difference in mortality, hospitalization or QOL measures

Pulmonary rehabilitation

Comprehensive program

6 - 12 weeks, longer is better

- Lower extremity aerobic exercise
- UE exercise, strengthening, flexibility
- Education
- Nutrition
- Counselling
- Disease management



Richard Casaburi, NEJM March 26, 2009

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

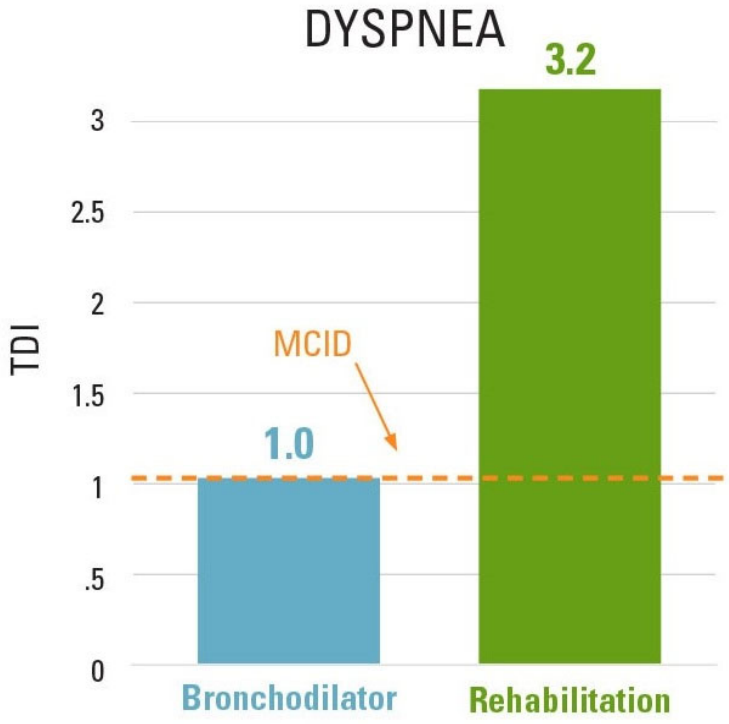
- Evidence of efficacy should be available for any model deployed
- Evidence of effectiveness should be available for any model deployed
- Health care professionals should be trained to deliver digital/technology based solutions if used within the program
- If more than one model of pulmonary rehabilitation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

Defining modern pulmonary rehabilitation; ATS report. Ann ATS 2021

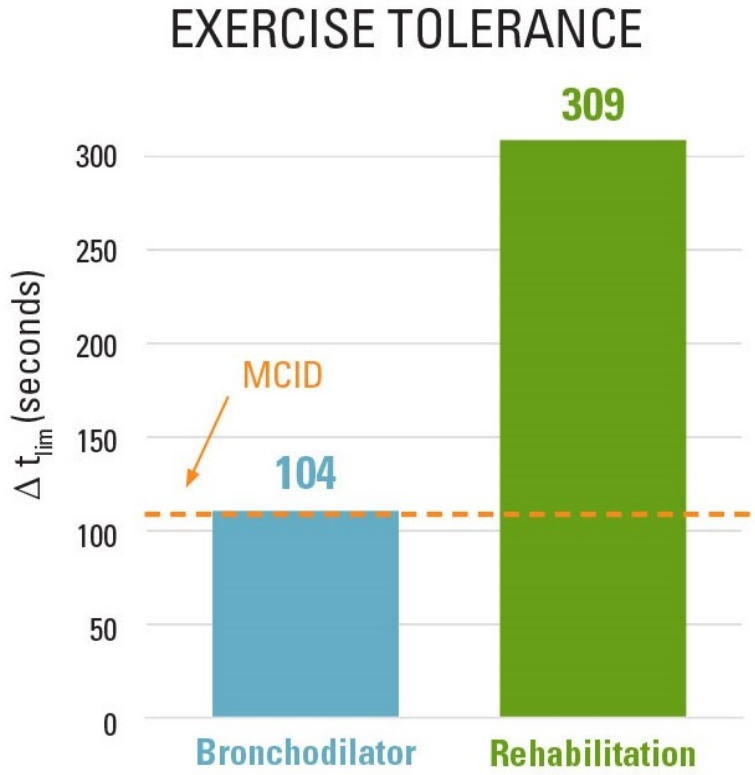
Traditional pulmonary rehabilitation improves

- Symptoms - dyspnea
- Limb muscle function - strength
- Exercise capacity – lower extremity aerobic exercise
- Emotional function – anxiety, depressive symptoms
- Respiratory related quality of life – health status
- Knowledge and behavior of collaborative self-management
- Exacerbations – health care utilization
- Self-efficacy
- Health economic benefits
- Decreased mortality, especially when started <90 days after hospitalization

Outcomes of Pulmonary Rehabilitation



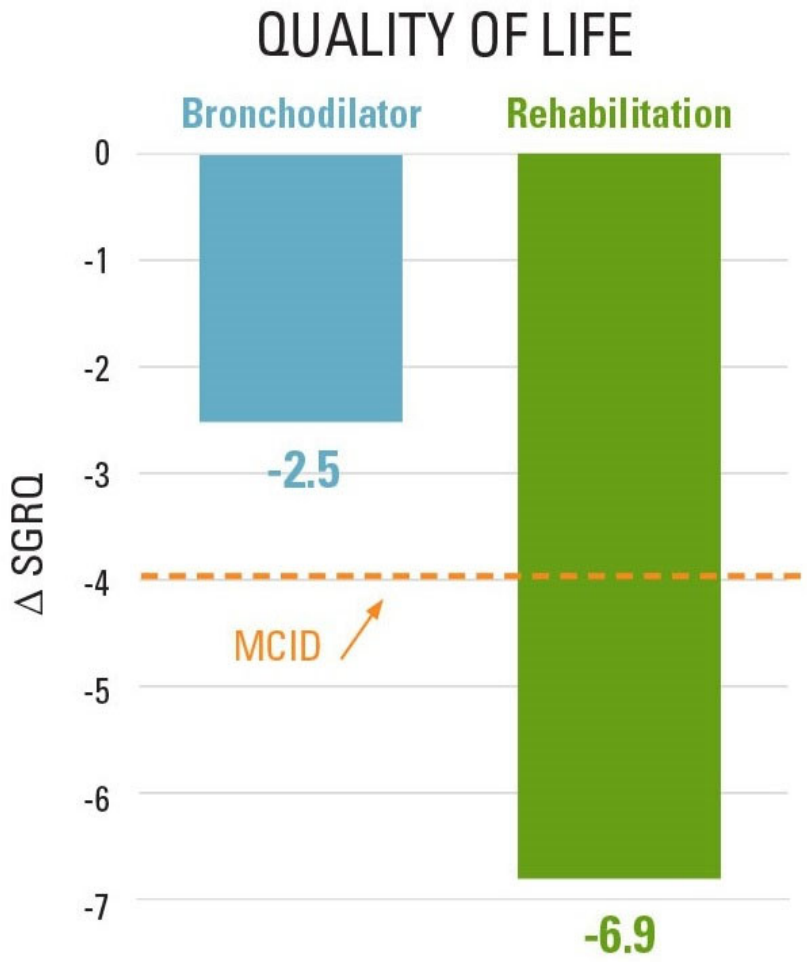
Reduction in dyspnea by the transitional dyspnea index (TDI). Bronchodilator responseA from 7 studies with 4163 individuals; rehabilitation response from 7 studies with 476 individuals (Mahler, 2005); corroboration from Ni, 2014, Zanini, 2015 and Ambrosino, 2008.



Increase in exercise duration (Δ tlim) in constant work rate exercise testing. Bronchodilator response from 19 studies with 1847 participants; rehabilitation response from 11 studies with 559 individuals (Puente, 2016)

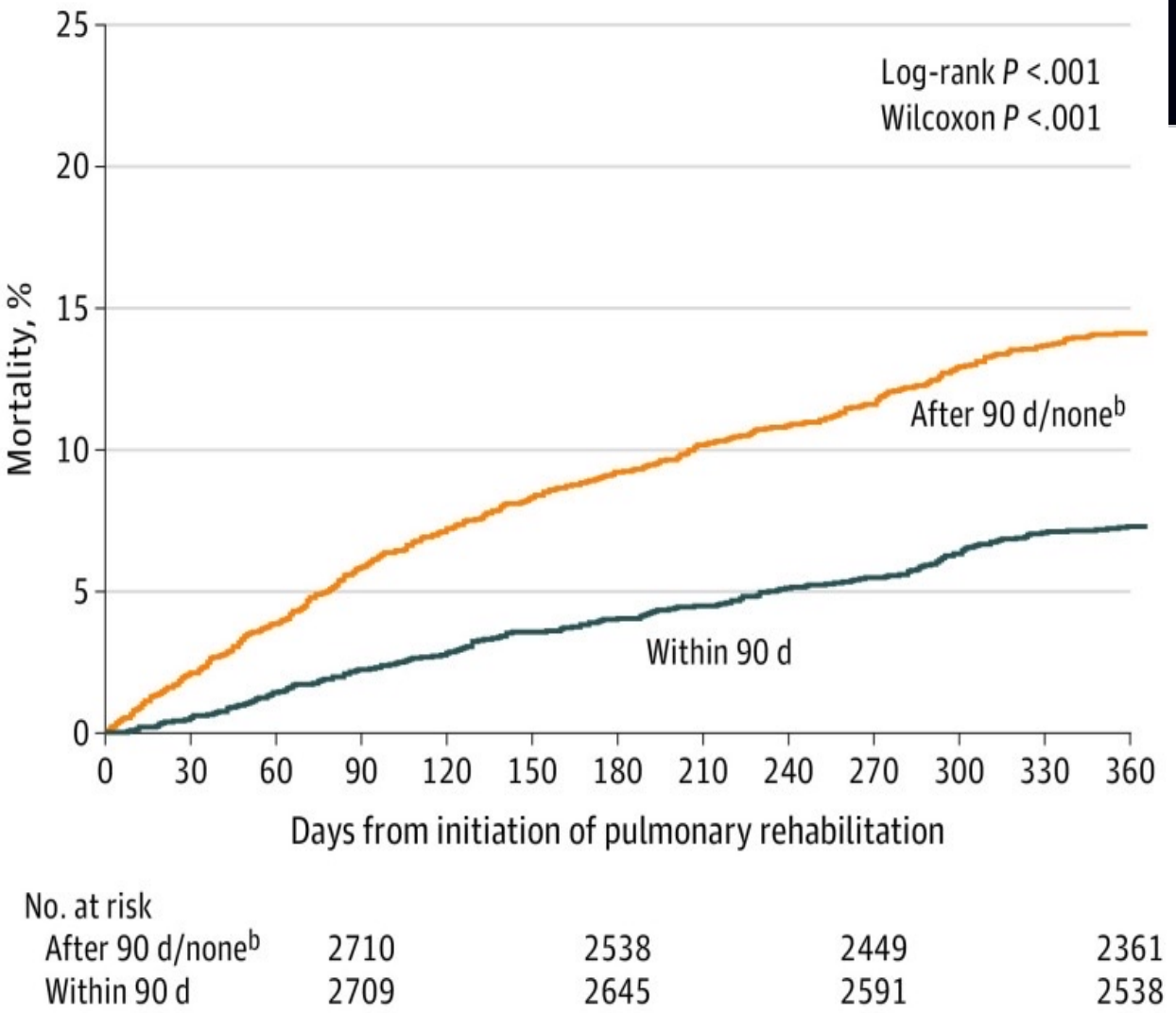
Courtesy of Richard Casaburi, MD

Outcomes of Pulmonary Rehabilitation



Improvement in health-related quality of life by St. George's Respiratory Questionnaire (ΔSGRQ, lower score indicates improvement). Bronchodilator response from 25 studies with 27,024 individuals (Kew, 2014); corroboration from Karner, 2016 and Ni, 2014. Rehabilitation responses from 19 studies with 1146 individuals (McCarthy, 2015).

Courtesy of Richard Casaburi, MD



No. at risk				
After 90 d/none[b]	2710	2538	2449	2361
Within 90 d	2709	2645	2591	2538

Pulmonary Rehabilitation

Peter Lindenauer, JAMA. 2020 May 12; 323(18): 1–11.

Non-invasive positive pressure ventilation (NIPPV)

- 2014 study with 195 patients with stable
  GOLD Stage IV COPD and hypercarbia ($PaCO_2 \geq 52$)
- NIPPV targeted to reduce CO_2 by 20% or < 48 mmHg
- 1-year mortality was 12% (12 of 102 patients) in the intervention group and 33% (31 of 93 patients) in the control group; hazard ratio 0.24 (95% CI 0.11-0.49; p=0.0004)
- NIPPV can improve survival in stable severe COPD patients with hypercarbia when added to standard treatment

Thomas Khonlein. Lancet Respir Med 2014 Sep;2(9):698-705.

Surgical Treatments

- Lung volume reduction (LVRS) *
  - Reduces hyperinflation and improves dyspnea
  - Prolongs survival compared to medical therapy in patients with severe COPD, upper lobe predominant emphysema, and low exercise capacity.
- Endobronchial valves – newer alternative

* Fishman et al. N Engl J Med 2003; 348(21): 2059-73.

Supportive/Palliative care

- Involves symptom management, not just end of life care
- Can address need for nutritional support, psychological support and pharmacologic treatment for anxiety and breathlessness that persists despite maximal traditional management
- Nutritional supplementation can improve respiratory muscle strength and overall health
- Opiates can improve dyspnea
- Advance care planning can address questions and concerns for both patients and families

GOLD Guidelines 2025

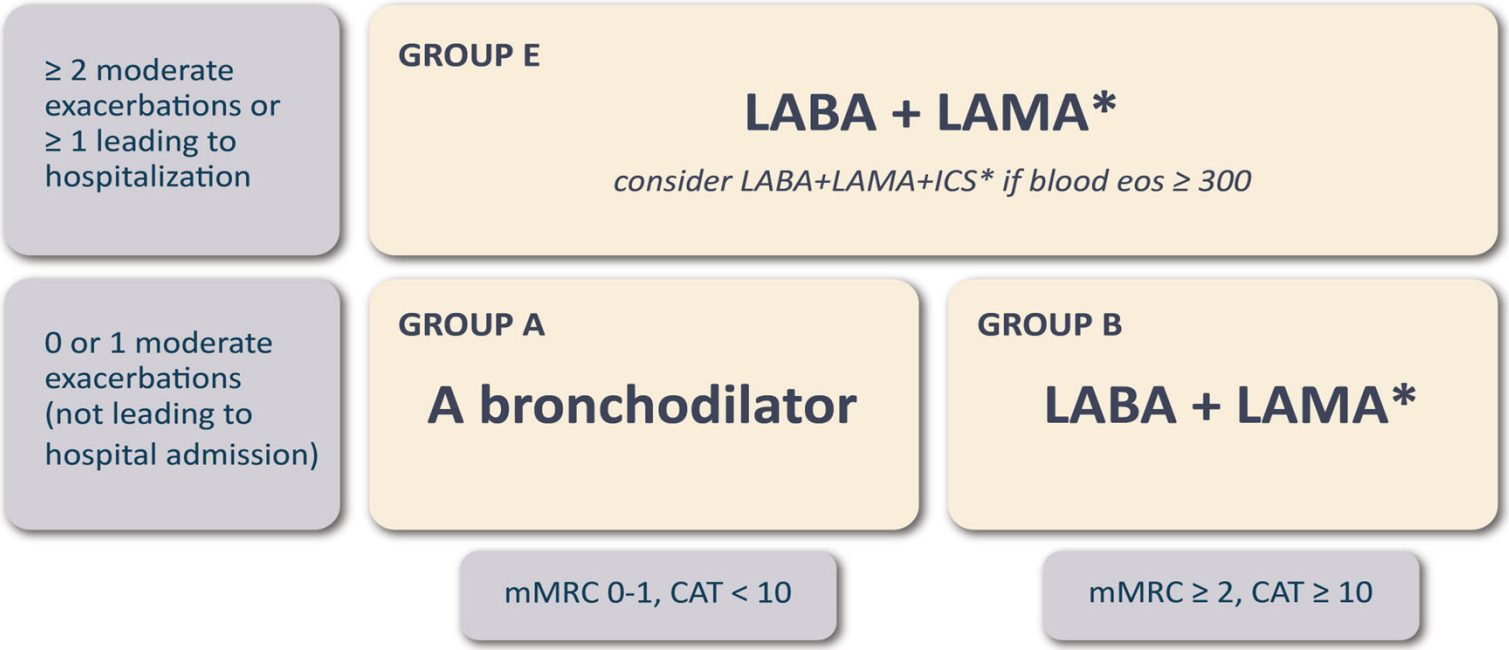
Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients

Figure 3.17

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Single inhaler triple therapy compared to dual LABD therapy relative risk reduction: IMPACT: HR 0.72 (95% CI: 0.53, 0.99)[1a] ETHOS: HR 0.51 (95% CI: 0.33, 0.80)[1b]	Symptomatic people with a history of frequent and/or severe exacerbations
Non-pharmacological Therapy			
Smoking cessation[2]	Yes	HR for usual care group compared to intervention group (smoking cessation) HR 1.18 (95% CI: 1.02, 1.37)[2]	Asymptomatic or mildly symptomatic
Pulmonary rehabilitation[3#]	Yes	Old trials: RR 0.28 (95% CI 0.10, 0.84)[3a] New trials: RR 0.68 (95% CI 0.28, 1.67)[3b]	Hospitalized for exacerbations of COPD (during or ≤ 4 weeks after discharge)
Long-term oxygen therapy[4]	Yes	NOTT: ≥ 19 hours of continuous oxygen vs ≤ 13 hours; 50% reduction[4a]	PaO_2 ≤ 55 mmHg or < 60 mmHg with *cor pulmonale* or

Initial Pharmacological Treatment

Figure 3.7

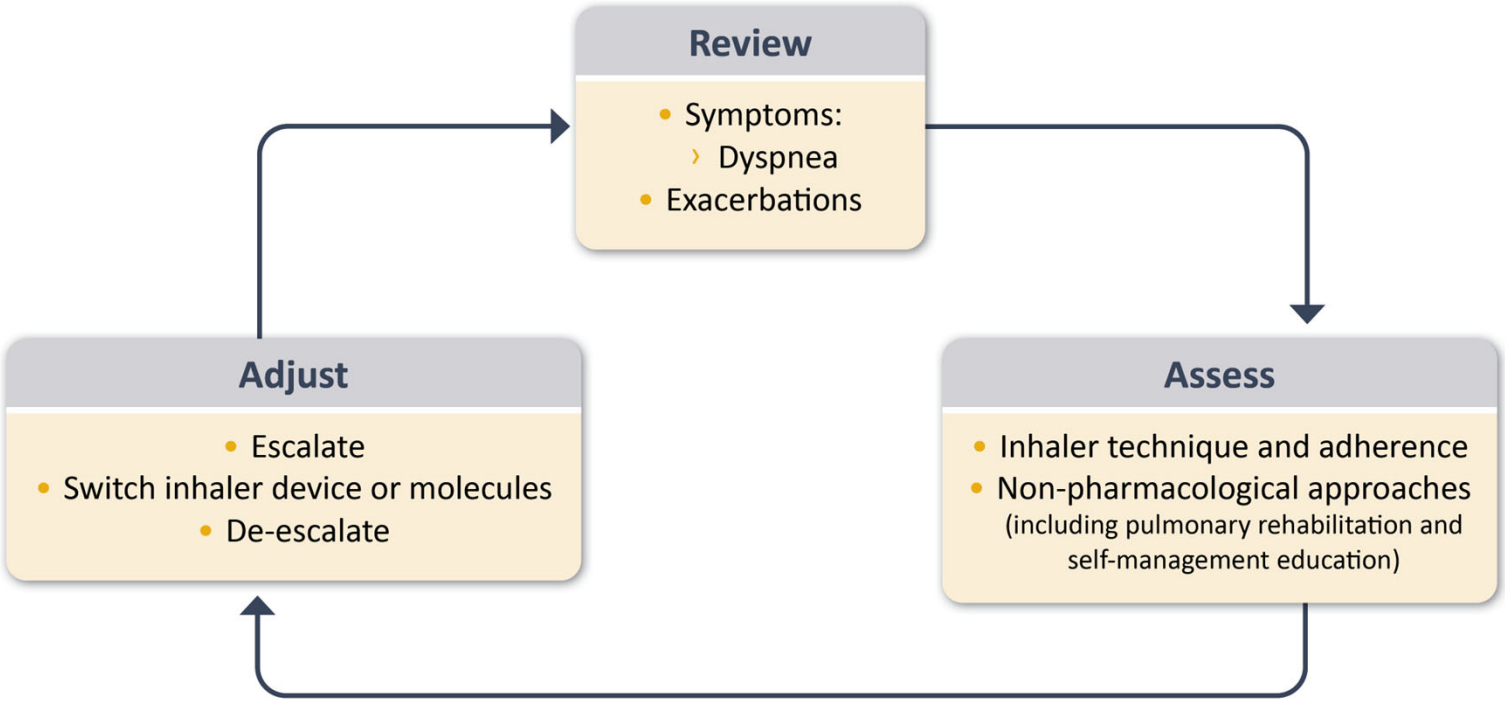


*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment

Exacerbations refers to the number of exacerbations per year; eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

Management Cycle

Figure 3.8



Frequent COPD Exacerbations: Long-term Management

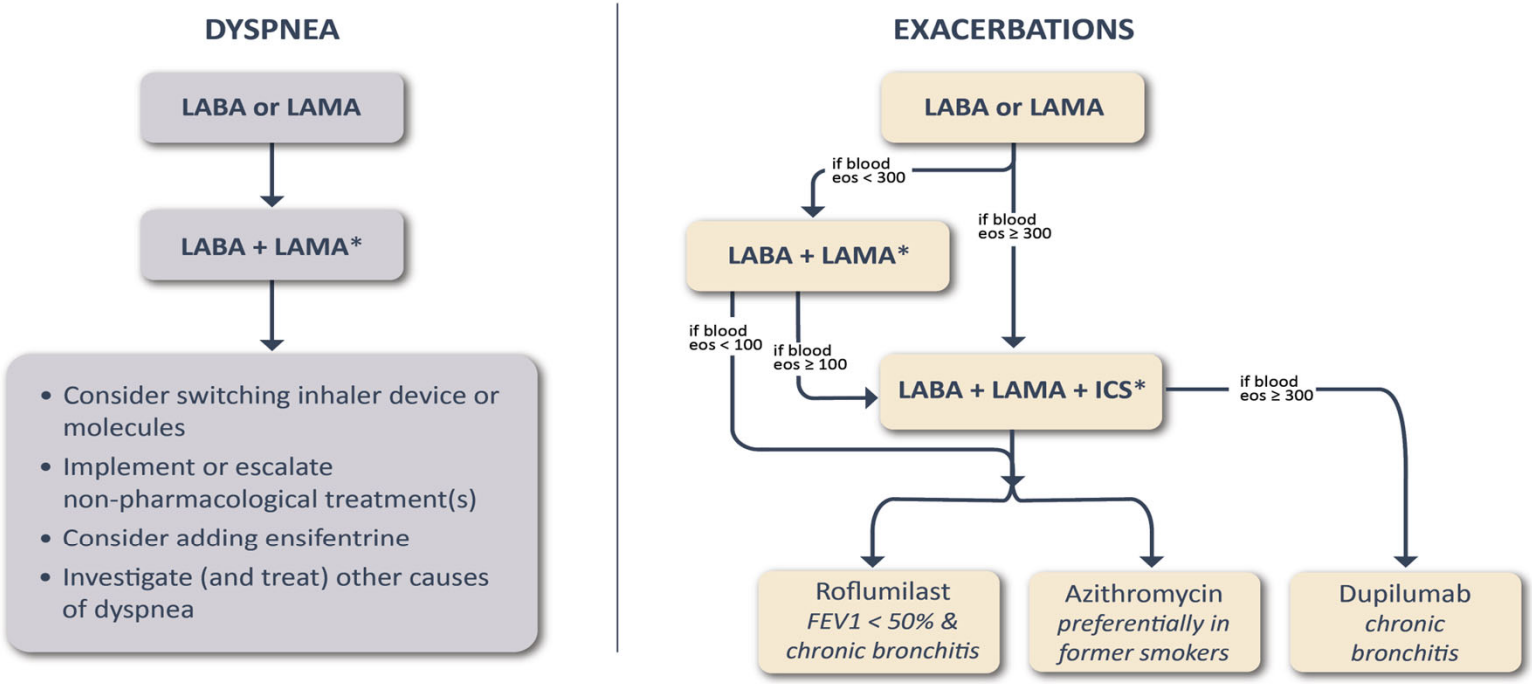
- Frequent Exacerbations:
  - 1 Hospitalization

    or
  - 2 or more uses of glucocorticoids per year

- Reassess Diagnosis
- Mitigation of environmental risk factors (smoking, dust, pollen, etc.)
- Optimize inhaled therapies
  - LAMA, LABA
  - Good inhaler technique?
- If symptoms persist, consider add-on therapy

Follow-up Pharmacological Treatment

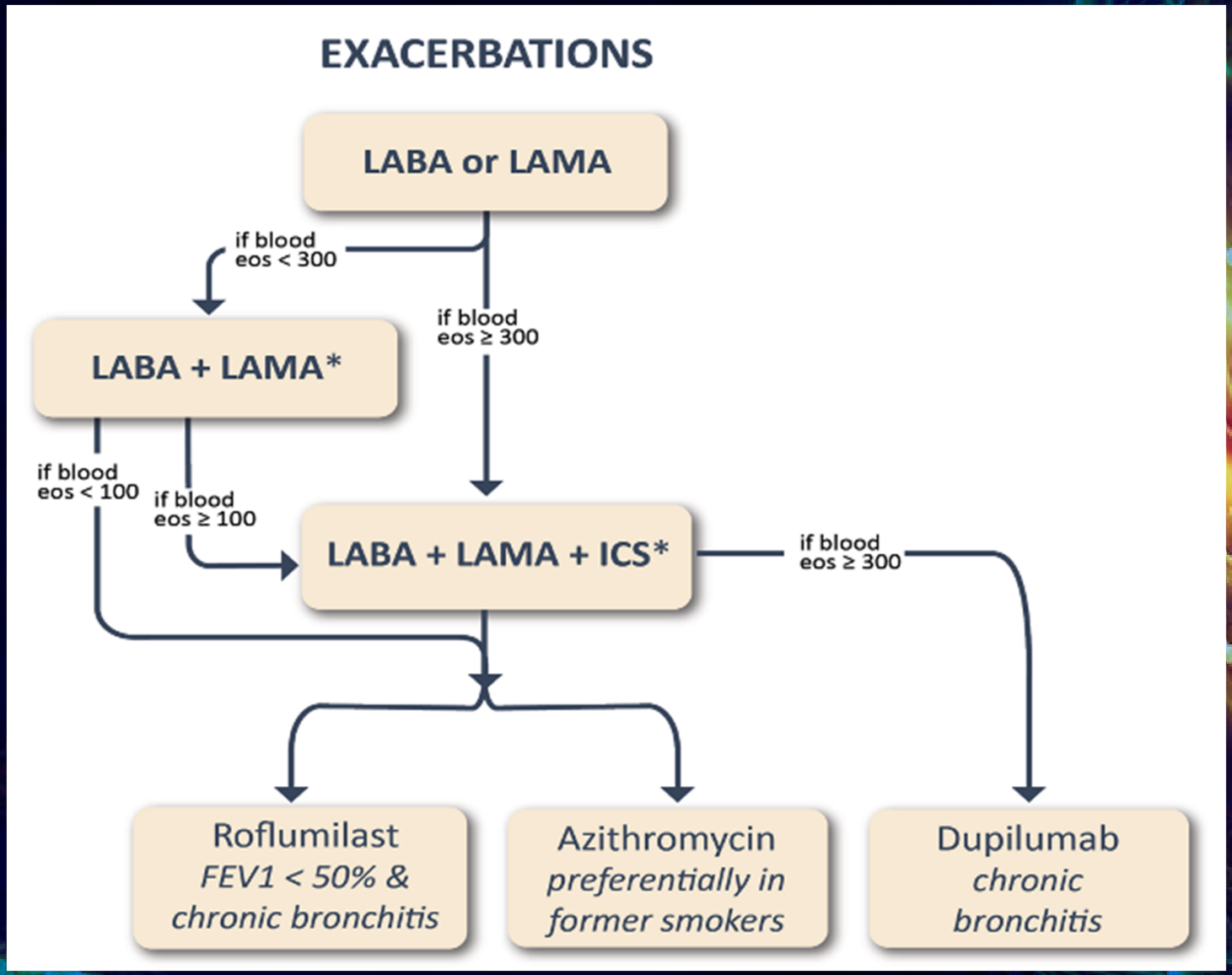
Figure 3.9



*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.

Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations.

Exacerbations refers to the number of exacerbations per year.



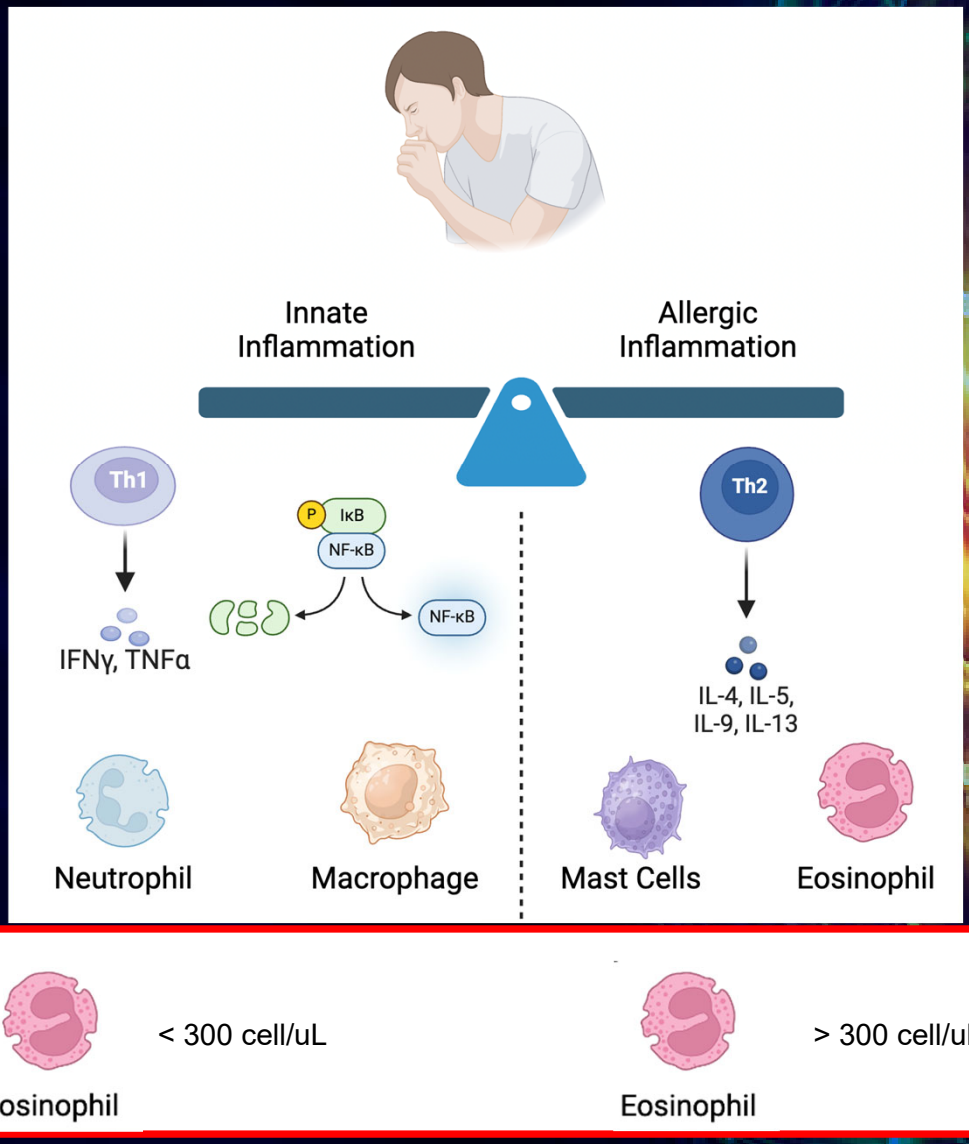
Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

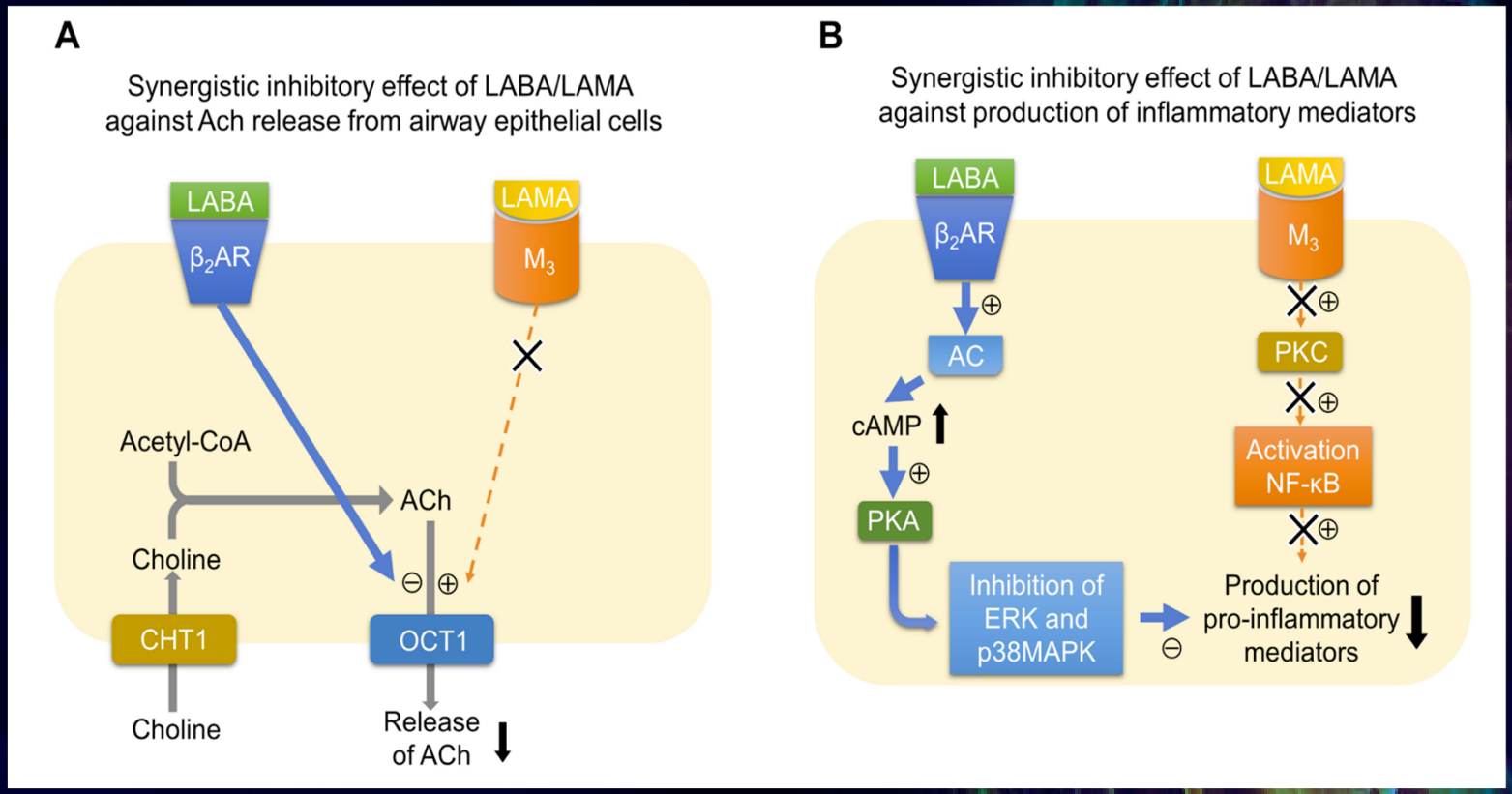
STRONGLY FAVORS USE	**History of hospitalization(s) for exacerbations of COPD[#]**
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/µL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/µL
AGAINST USE	**Repeated pneumonia events**
	Blood eosinophils < 100 cells/µL
	History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Figures 3.7 & 3.18 for recommendations); *note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Immunologic Processes in COPD



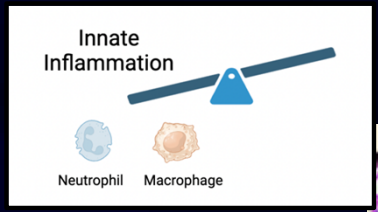
LABA / LAMA: Mechanisms



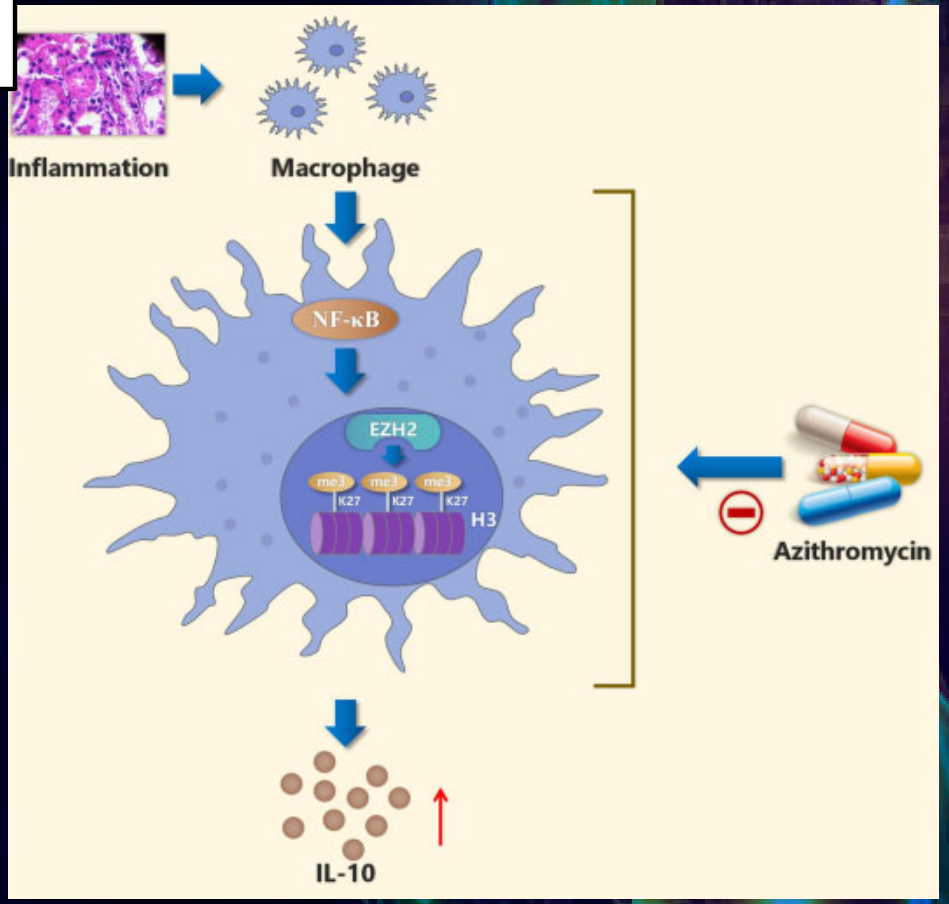
Bronchodilation **Decreased Inflammation**

Yamada, M., & Ichinose, M. (2018). The cholinergic pathways in inflammation: A potential pharmacotherapeutic target for COPD. *Frontiers in Pharmacology*, *9*(December), 1–9. https://doi.org/10.3389/fphar.2018.01426

Chronic Azithromycin



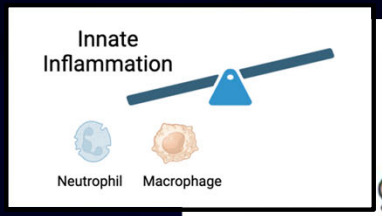
- Antibiotic, antinflammatory
- 2017 metanalysis of 4 trials:
  - Reduced risk of COPD exacerbations by 24%
  - Increased time to next exacerbation by 80 days
  - Effect observed in former, but not current, smokers
- Dose, PO: 250 mg Daily or 500 mg 3x week
- Monitor QTc and hearing

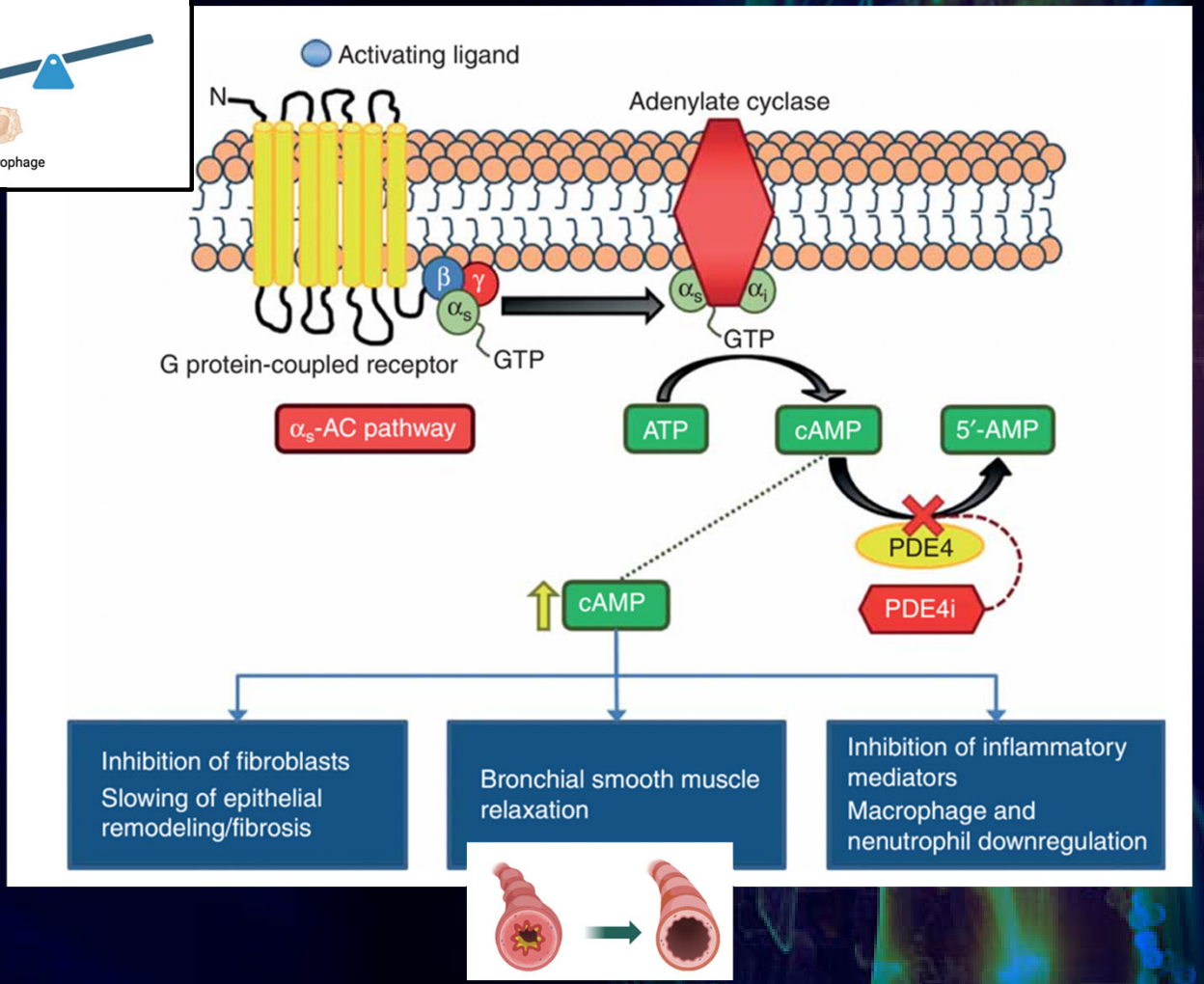


Wu, S., Tian, X., Mao, Q. *et al.* Azithromycin attenuates wheezing after pulmonary inflammation through inhibiting histone H3K27me3 hypermethylation mediated by EZH2. *Clin Epigenet* **15**, 12 (2023).
Wedzicha JA, Calverley PMA, Albert Rk *et al.*. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017 Sep 9;50(3):1602265

Roflumilast

- Phophodiesterase 4 (PDE4) Inhibitor
- 2020 Cochrane Review, 42 studies, 25,000 patients
  - 22% reduction in exacerbations
  - 50 mL improvement to FEV1
  - ONLY indicated if FEV1<50% predicted
- Dosing: 250 mcg daily x 4 weeks, then 500 mcg daily to reduce GI side effects (5%-10%)

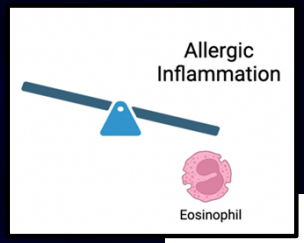


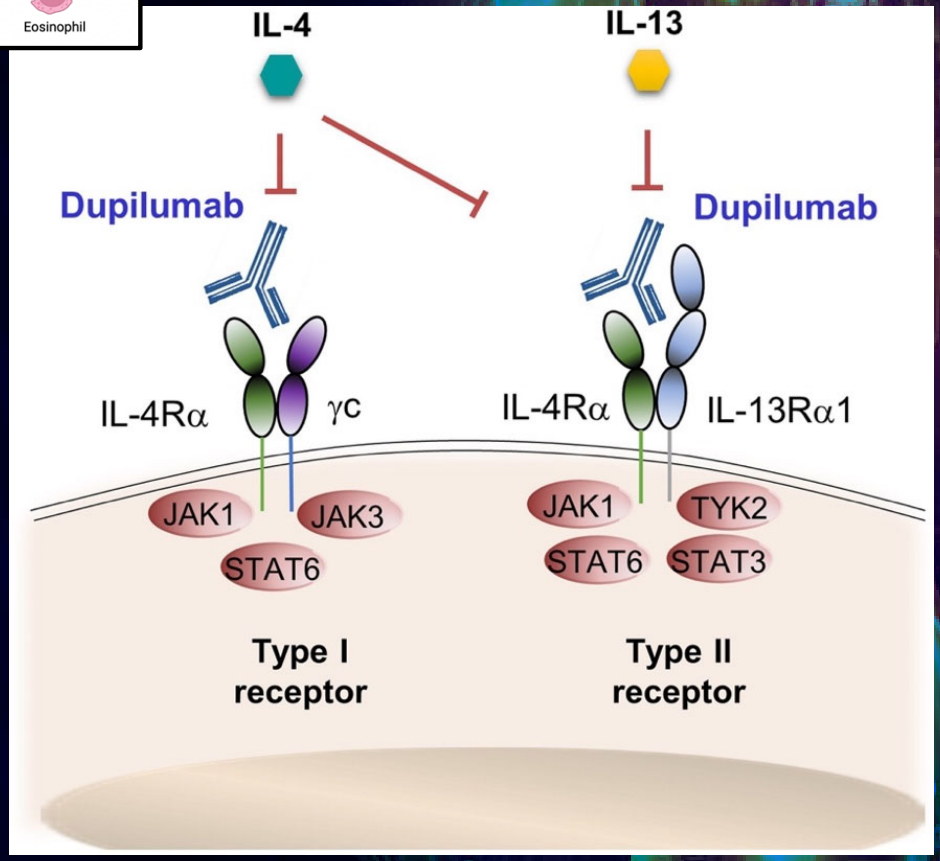


Mulhall, A. M., et al. (2015). Phosphodiesterase 4 inhibitors for the treatment of chronic obstructive pulmonary disease. *Expert Opinion on Investigational Drugs*, *24*(12),
Janjua, S., et al. (2020). Phosphodiesterase-4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, *2020*(5

Biologics: Dupilumab

- Human antibody targeting interleukin 4 (IL-4) and IL-13 receptors
  - Cytokines in allergic inflammation signaling type 2 helper T lymphocytes (Th2)
- BOREAS: 468 patients with uncontrolled COPD and eosinophils >300 cells/uL
  - Reduced mod/severe exacerbations by 33%
  - Increased FEV1 by 160 mL
- Approved for COPD Patients with uncontrolled symptoms despite therapy AND elevated eosinophils
- Dosing: 300 mg SubQ every other week

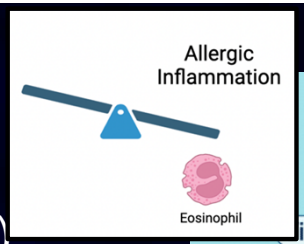


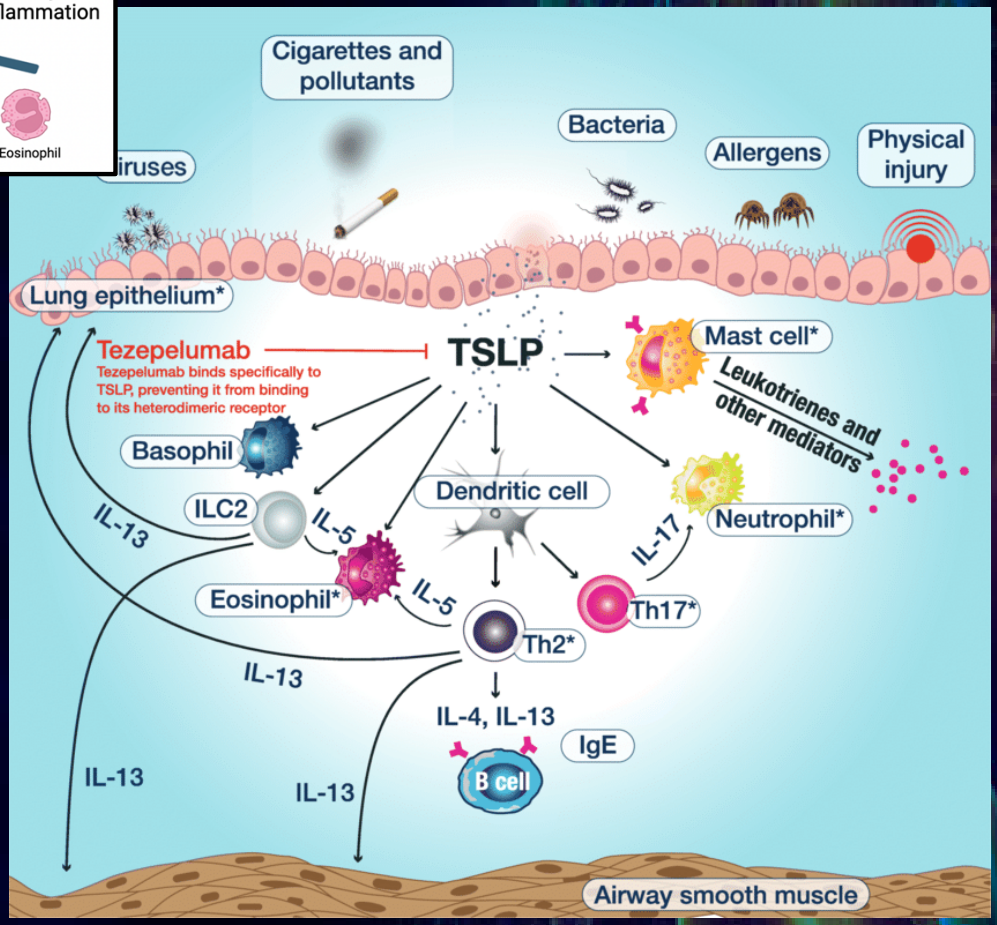


Bhatt SP, et al. Abdulai RM; BOREAS Investigators. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. ***N Engl J Med***. **2023 Jul 20;389(3):205-214. doi: 10.1056/NEJMoa2303951. Epub 2023 May 21. PMID: 37272521.**

Tezepelumab

- Human monoclonal antibody, targets Thymic Stromal Lymphopoetin (TSLP)
  - TSLP = Epithelial cell-derived cytokine
  - Antibody binding prevents TSLP from binding to receptors
- Approved for add-on maintenance therapy in severe asthma
- COURSE Study, Phase 2a:
  - 333 COPD patients > 2 mod to severe exacerbations despite therapy
  - Reduced COPD exacerbation frequency by 37% ONLY in patients with Eos > 150 cells/uL





Emson C, et al. CE. CASCADE: a phase 2, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the effect of tezepelumab on airway inflammation in patients with uncontrolled asthma. ***Respir Res. 2020 Oct 13;21(1):265. doi: 10.1186/s12931-020-01513-x. PMID: 33050900; PMCID: PMC7550845.***

G1#Wlqjk/hwdc#rq#ehkdc#ri#kh#FRXUVH#vwxg|#qyhvwjdwruv1#Wh}hshoxp de#q#Dgxow#Z lk#P rghudwh#wr#Yhu|#Vhyhuh#Fkurqlf#Revwuxfwlyh#Sxqp rqdu|#Glvhdvh#FRSG,#Hiilfdf|#dqg#Vdihw|#Eurp #kh#Skdvh#5d#FRXUVH#Vwxg|#devwudfw,1Dp #MJhvsl#Fulw#Fduh#P hg 5357>53<=D5:;51

New Medications: Reduce COPD Exacerbations

Dupilimab (Dupixent)
Ensifentrine (Ohtuvayre)

Ensifentrine For Inhalation

Dosage and Administration

- 3 mg (one ampule)
- twice daily by inhalation using a nebulizer

Average nebulization time: 7 minutes

PDE 3/4 Inhibition

Airway smooth muscle[1-4] Cells[1,5,6]

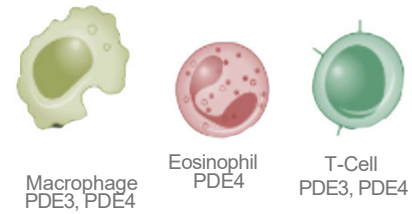
PDE3, PDE4

↑ cAMP
Bronchial relaxation

↓

Bronchodilation

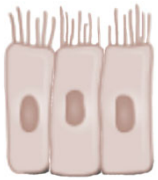
Inflammatory



↑ cAMP ↓ ↓ Cell activation, recruitment

Anti-Inflammatory

Epithelial cells[1,7,8]



PDE3, PDE4

↑ cAMP
↑ CFTR activation
↑ Ciliary function

↓

Mucociliary Clearance

cAMP=cyclic adenosine monophosphate; CFTR=cystic fibrosis transmembrane regulator; PDE=phosphodiesterase.

[1]Zuo H, et al. *Pharmacol Ther*. 2019;197:225-242.; [2]Calzetta L, et al. *J Pharmacol Exp Ther*. 2013;346(3):414-423.; [3]Calzetta L, et al. *Pulm Pharmacol Ther*. 2015;32:15-23.; [4]Venkatasamy R, et al. *Br J Pharmacol*. 2016;173(15):2335-2351.; [5]Boswell-Smith V, et al. *J Pharmacol Exp Ther.* 2006;318(2):840-848.; [6]Franciosi LG, et al. *Lancet Respir Med.* 2013;1(9):714-727.; [7]Turner MJ, et al. *Am J Physiol Lung Cell Mol Physiol*. 2016;310(1):L59-L70.; [8]Turner MJ, et al. *Am J Physiol Lung Cell Mol Physiol*. 2020;318(5):L908-L920.

Inclusion/Exclusion Criteria

ENHANCE 1 & 2

- Efficacy / safety randomized, controlled trials
- 24 – 48 week duration
- N=1549

Key Exclusion Criteria:

- History of asthma
- Hospitalizations for COPD, pneumonia, or COVID-19 in the 12 weeks prior to screening
- COPD exacerbation requiring oral or IV steroids within 3 months of screening

Key Inclusion Criteria

- Age 40-80 years
- Current or former smoker, ≥10 pack years
- Symptomatic COPD
  - ≥2 on mMRC Dyspnea Scale
- Lung function:
  - FEV1/FVC < 0.70
  - Post bronchodilator FEV1 ≥30% and ≤70%
- Allowed concomitant maintenance therapy
  - None
  - Stable LABA or LAMA +/- ICS

Anzueto A, et al. *Am J Respir Crit Care Med.* 2023;208(4):406-416.

Key Endpoints

Primary Endpoint:

- Average FEV_1 AUC over 12 hours at Week 12

Secondary Endpoints:

- Peak FEV_1 over 4 hours at Week 12
- St. George's Respiratory Questionnaire (SGRQ) Total Score and Responder Rate at Week 24
- Morning trough FEV_1 at Week 12

Additional endpoints:

- Moderate/Severe COPD Exacerbation Rate Frequency and Time to First at Week 24

Anzueto A, et al. *Am J Respir Crit Care Med.* 2023;208(4):406-416

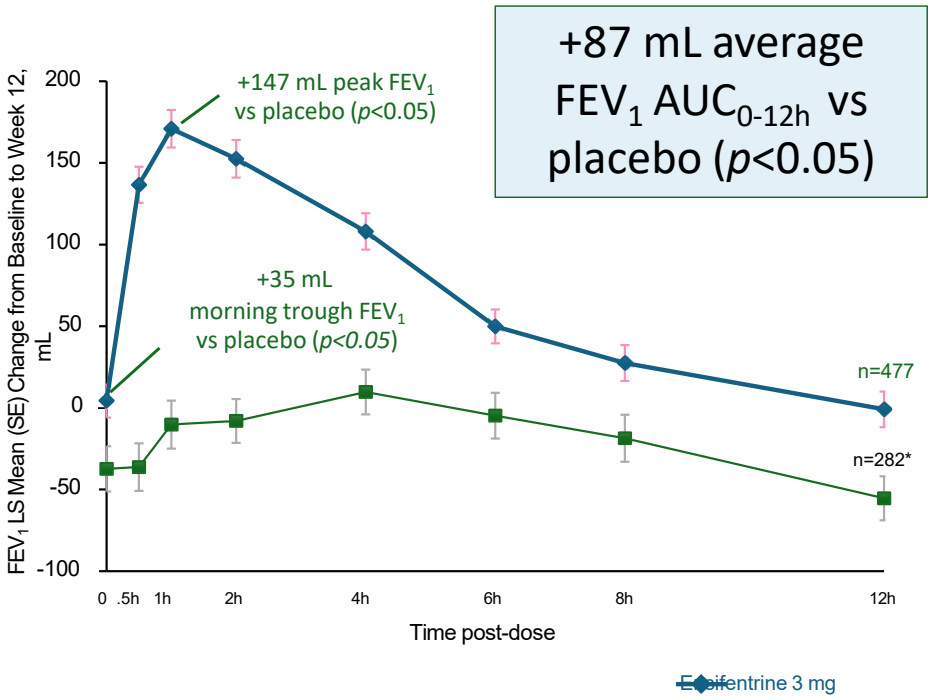
	ENHANCE-1		ENHANCE-2	
Characteristic	***Ensifentrine n=477***	***Placebo n=283***	***Ensifentrine =498***	***Placebo n=291***
Age, mean	65	65	65	65
Gender, Male, n (%)	274 (57)	167 (59)	244 (49)	138 (47)
North America Region, n (%)	87 (18)	58 (21)	287 (58)	180 (62)
White Race, n (%)	435 (91)	250 (88)	471 (95)	276 (95)
% Current Smokers, n (%)	268 (56)	163 (58)	276 (55)	160 (55)
Background Meds:				
Yes, n (%)	**331 (69)**	**192 (68)**	**275 (55)**	**160 (55)**
LAMA	**151 (32)**	**76 (27)**	**168 (34)**	**90 (31)**
LAMA/	**4 (0.8)**	**5 (2)**	**1 (0.2)**	**0**
ICS	**89 (19)**	**45 (16)**	**34 (7)**	**23 (8)**
LABA	**87 (18)**	**66 (23)**	**72 (15)**	**47 (16)**
LABA/ ICS				

Anzueto A, et al. *Am J Respir Crit Care Med*. 2023;208(4):406-416.

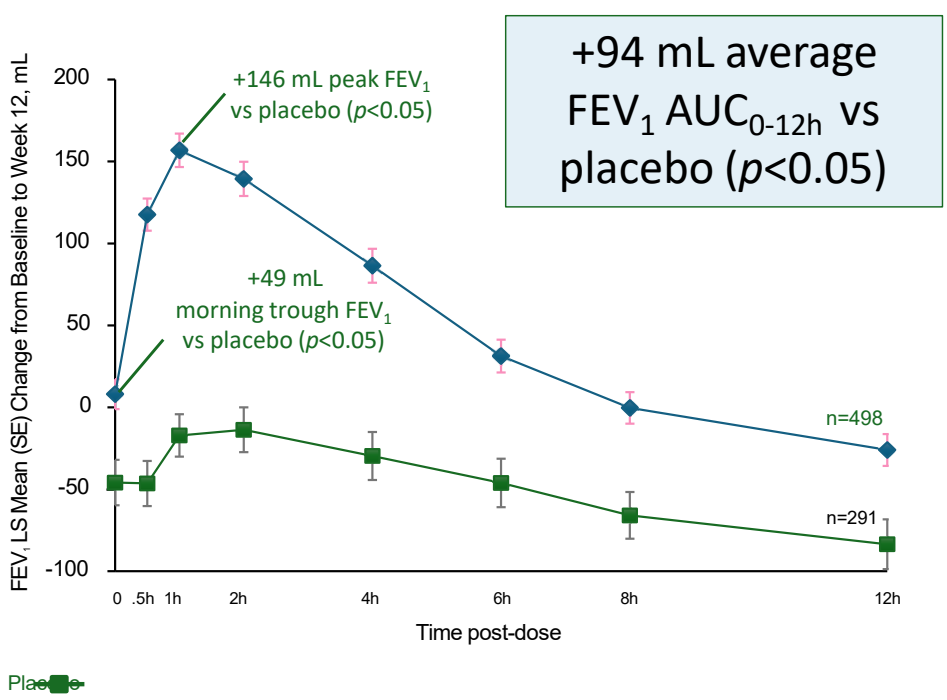
Primary Endpoint

Week 12 Average Change from Baseline: FEV_1 $AUC_{0\text{-}12h}$

ENHANCE-1 Trial

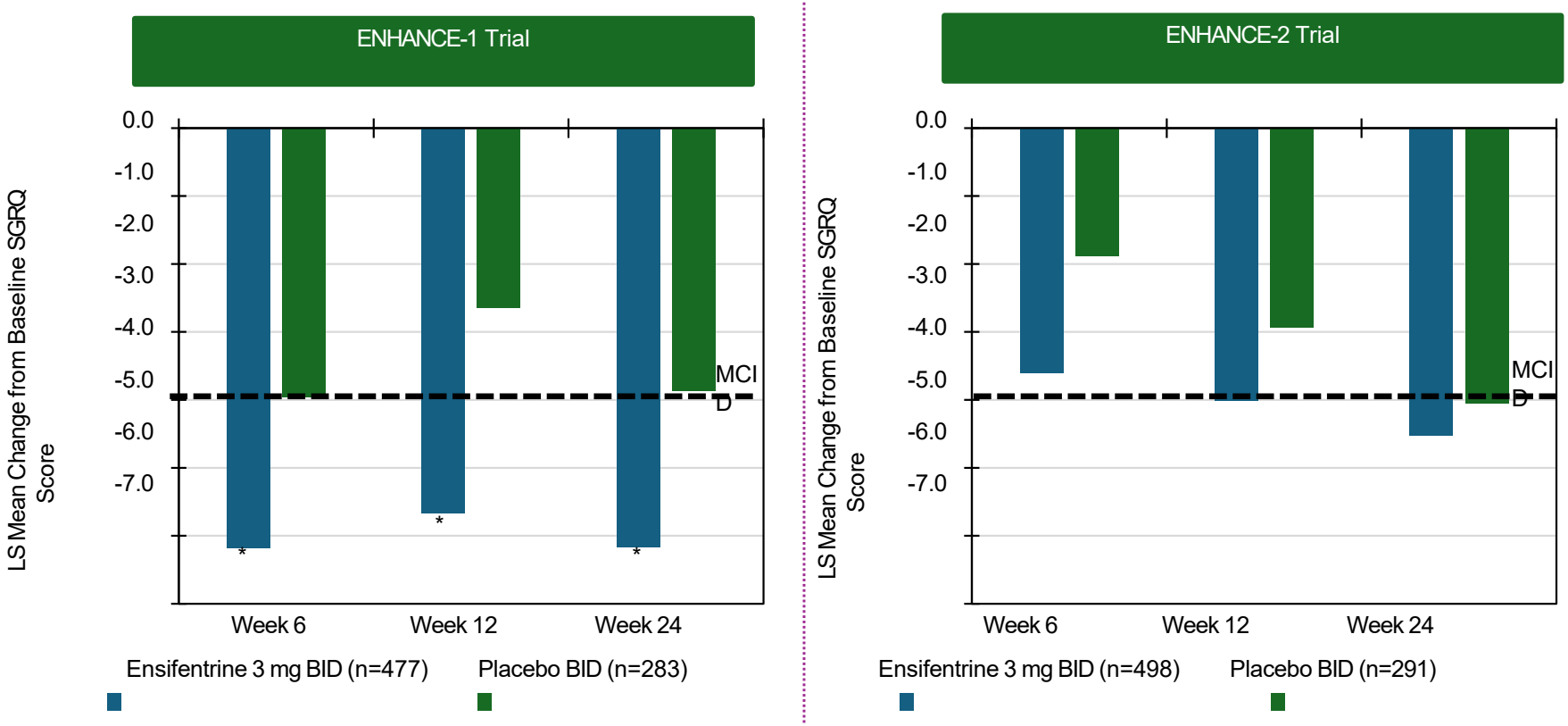


ENHANCE-2 Trial



Anzueto A, et al. *Am J Respir Crit Care Med.* 2023;208(4):406-416.

SGRQ Total Score



SGRQ Total Score at Week 24 was evaluated as a secondary endpoint in the ENHANCE-1 and ENHANCE-2 study protocols.

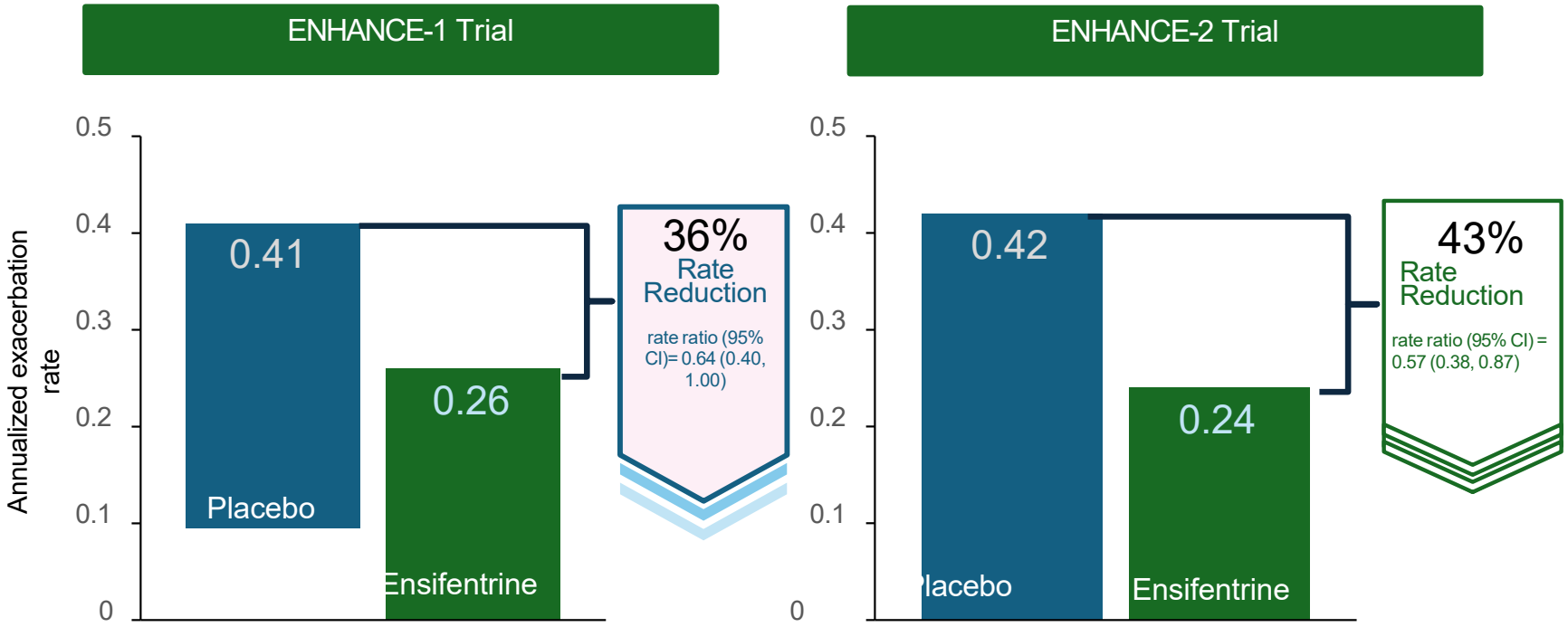
SGRQ Responder Rate

- SGRQ response was defined as an improvement in score ≥ 4

SGRQ Responder Rate at Week 24	Ensifentrine	Placebo	Odds Ratio [95% Confidence Interval]
ENHANCE-1	58.2%	45.9%	1.49 [1.07-2.07]
ENHANCE-2	45.4%	50.3%	0.92 [0.66-1.29]

Sciurba F, et al. Presented at ATS, May 19-24, 2023; Washington, DC.

Moderate/Severe Exacerbation Rate at 24 Weeks



The time to first moderate or severe COPD exacerbation and the annual rate of moderate or severe COPD exacerbations were evaluated for ensifentrine compared with placebo in ENHANCE-1 and ENHANCE-2 as prespecified exploratory analyses to support the primary endpoint. These observations were not statistically significant as the exacerbation endpoints were not included in the analysis hierarchy and thus were not controlled for multiplicity.

Exacerbations defined as worsening of symptoms requiring a minimum of 3 days of treatment with oral/systemic steroids and/or antibiotics (moderate) OR hospitalization (severe).

Anzueto A, et al. *Am J Respir Crit Care Med.* 2023;208(4):406-416.

Adverse events over 24 weeks: Pooled Datax

Safety population

TEAEs, n (%)	ENHANCE-1		ENHANCE-2	
	Ensifentrine (N=477)	Placebo (N=283)	Ensifentrine (N=498)	Placebo (N=291)
Nasopharyngitis	13 (2.7)	16 (5.7)	9 (1.8)	3 (1.0)
Hypertension	12 (2.5)	4 (1.4)	5 (1.0)	1 (0.3)
Back Pain	10 (2.1)	1 (0.4)	8 (1.6)	5 (1.7)
COPD	7 (1.5)	6 (2.1)	11 (2.2)	5 (1.7)
Toothache	6 (1.3)	2 (0.7)	0 (0)	1 (0.3)
Pneumonia	6 (1.3)	2 (0.7)	4 (0.8)	5 (1.7)
Urinary Tract Infection	5 (1.0)	1 (0.4)	8 (1.6)	5 (1.7)
Diarrhea	2 (0.4)	2 (0.7)	8 (1.6)	2 (0.7)
Sinusitis	1 (0.2)	1 (0.4)	6 (1.2)	0 (0)

ICER Evidence Report, July 16, 2024

Based on your knowledge of Ensifentrine, how would you use it in your patients?

A. To reduce COPD exacerbations
B. To improve dyspnea and lung function
C. To reduce COPD exacerbations and improve dyspnea / lung function

Based on your knowledge of Ensifentrine, how would you use it in your patients?

A. As an alternative to dual bronchodilators
B. As an add-on to dual bronchodilators
C. As an alternative to triple therapy (LAMA, LABA, ICS)
D. As an add-on to triple therapy
E. All the above
F. In another way

Ensifentrine and GOLD, 2025

“ significantly improved lung function and dyspnea, inconsistent quality of life effects. Reduction in exacerbation rate suggested but populations not enriched for exacerbation risk. Not designed to assess impact on top of LABA/LAMA, LABA/LAMA/ICS so can not position it in our algorithm.”

Ensifentrine and GOLD

"GOLD medication recommendations are based on best available evidence from published literature and not on labeling directives from government regulators. Does not make recommendations for therapies that have not been approved by at least one major regulatory agency."

Up To Date, July 2024

- As an alternative bronchodilator in COPD patients requiring dual bronchodilator therapy but unable to tolerate one of the other inhaled agents.
- As an add-on agent in those with persistent dyspnea or exacerbations despite LAMA, LABA, and inhaled glucocorticoids.
- As an add-on to LAMA-LABA therapy in those with dyspnea who are less likely to benefit from inhaled glucocorticoids.

Dupilumab BOREAS Trial

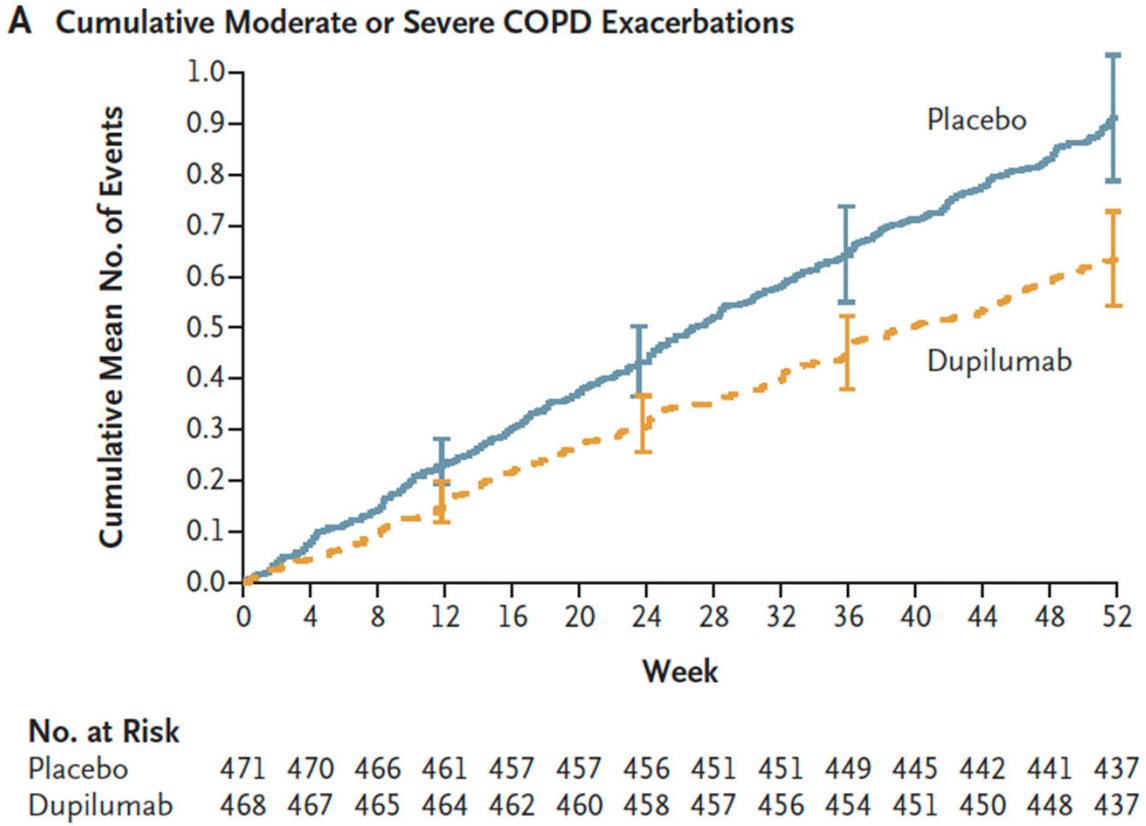
Double-blind, randomized, placebo controlled, n=942.

Inclusion criteria:

- COPD diagnosis ≥ 12 months
- Chronic bronchitis
- Exacerbations: ≥ 2 moderate or ≥ 1 severe in past year
  - ≥ 1 treated w/ systemic steroids
  - ≥ 1 while on triple therapy
- Triple therapy for ≥ 3 months
- Eosinophil count ≥ 300 cells/ul at screening
- Cigarette smoking history ≥ 10 pack-years
- Symptomatic: ≥ 2 on mMRC Dyspnea Scale
- Airflow obstruction: FEV1/FVC < 0.70
  - Post bronchodilator FEV1 ≥ 30% and ≤ 70%
- 40 – 80 years old

Bhatt SP et al. Dupilumab for COPD. New Engl J Med 2023; 389:205-14.

Dupilumab BOREAS Trial

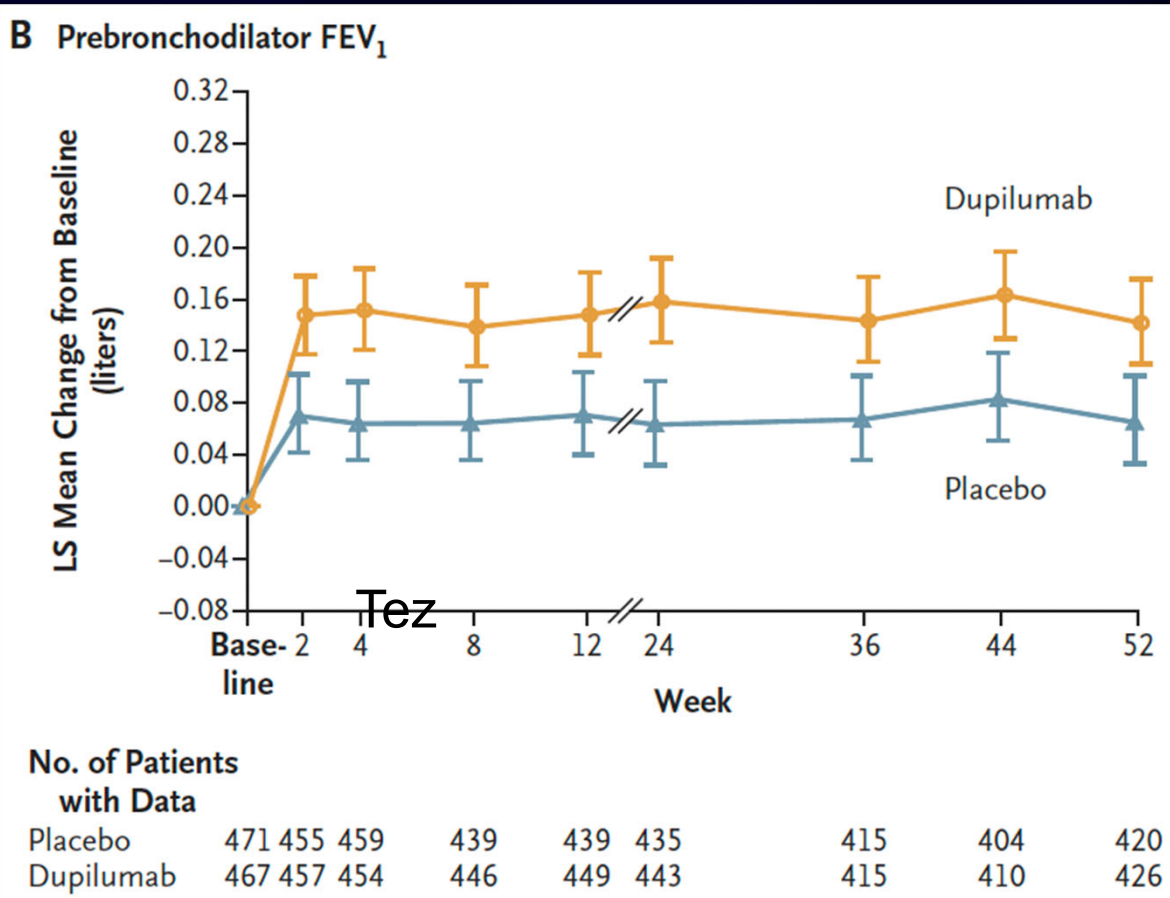


Exacerbation rate
Dupilumab 0.78
Placebo 1.10

Rate ratio - 0.70
(95% CI 0.58-0.86)
(p<0.0001)

Bhatt SP et al. Dupilumab for COPD. New Engl J Med 2023; 389:205-14.

Dupilumab BOREAS Trial



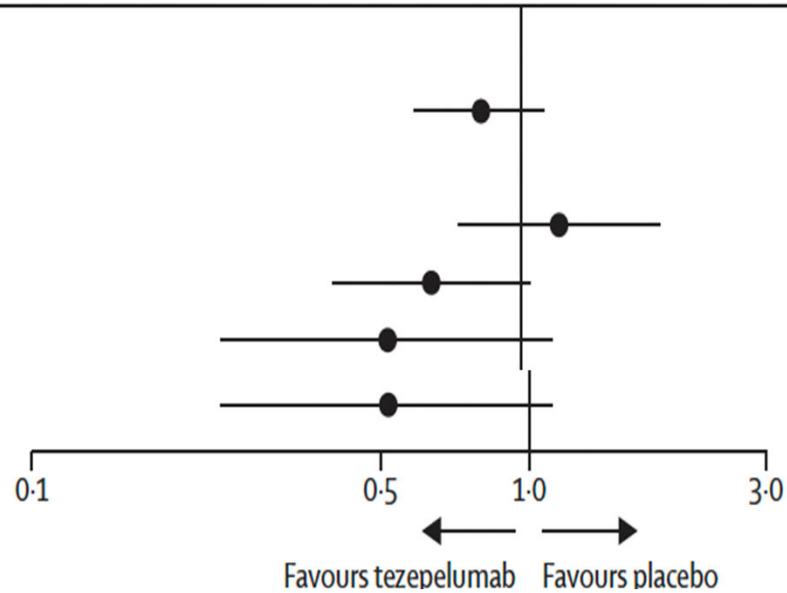
FEV1 pre-BD
Dupilumab 0.78
Placebo 1.10

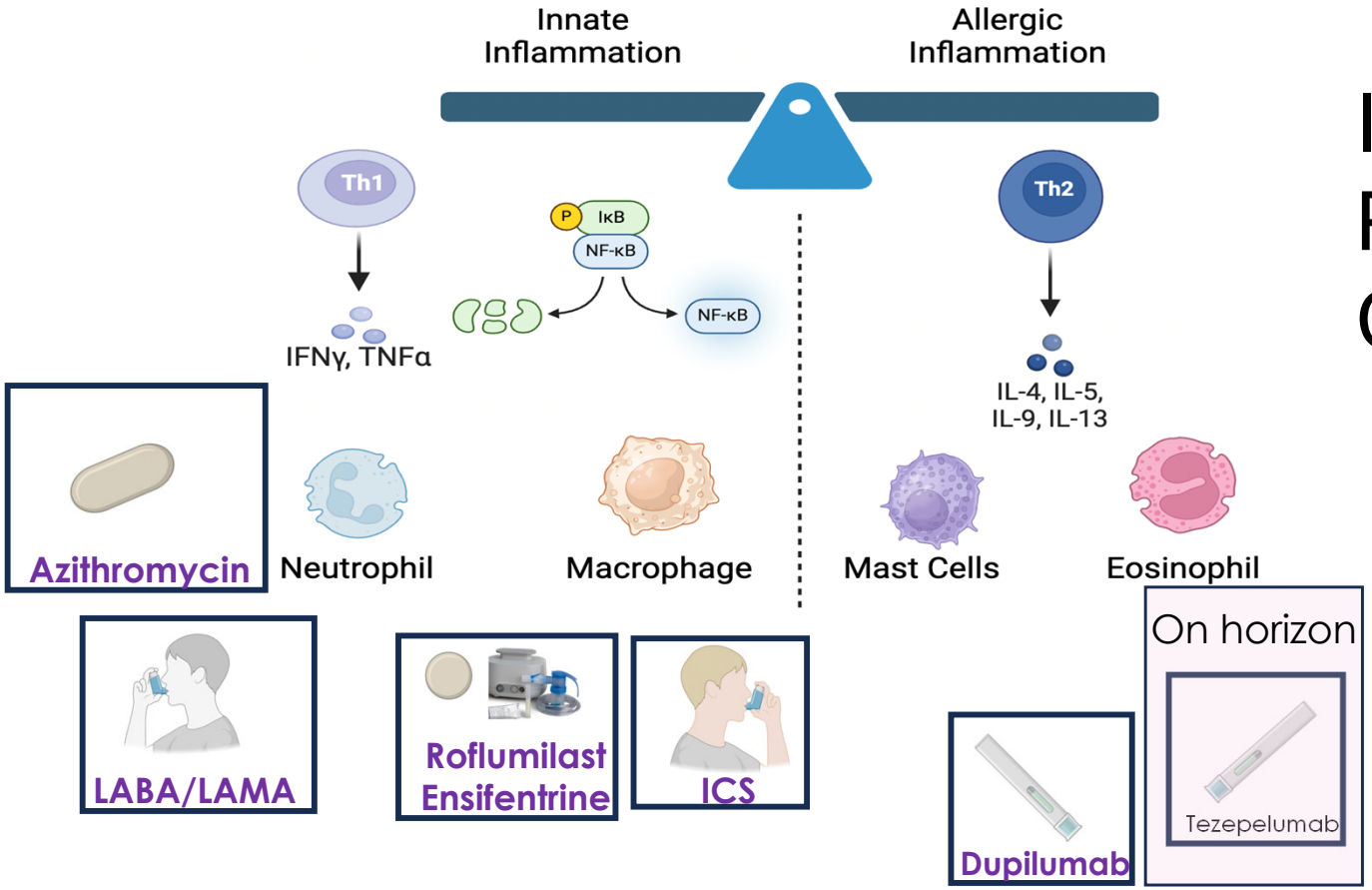
Rate ratio - 0.70
(95% CI 0.58-0.86)
($p<0.0001$)

Bhatt SP et al. Dupilumab for COPD. New Engl J Med 2023; 389:205-14.

Tezepelumab Exacerbation Effects

	Patients/rate		Rate ratio (95% CI)
	Tezepelumab group (n=165)	Placebo group (n=168)	
Moderate or severe COPD exacerbations			
Overall	165/1·75	168/2·11	0·83 (0·61–1·11)
BEC, cells per µL			
<150	73/2·04	64/1·71	1·19 (0·75–1·90)
150 to <300	68/1·64	72/2·47	0·66 (0·42–1·04)
≥300	24/1·20	32/2·24	0·54 (0·25–1·15)
Overall	165/0·13	168/0·25	0·52 (0·24–1·11)





Immunologic Processes in COPD

Frequent COPD Exacerbations: Add-on Therapy

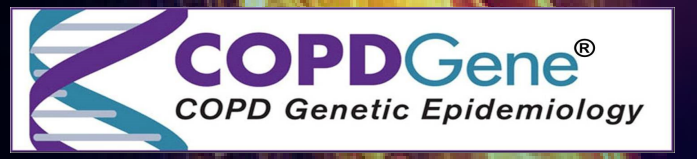
Inset 2: Choosing between azithromycin, roflumilast, and dupilumab for frequent exacerbations in patients with refractory COPD

Intervention	Factors that favor	Factors against	Important side effects
Chronic azithromycin	Established recurrent bacterial infection; bronchiectasis	Active smoking; cardiac dysrhythmia; multiple QT prolonging medications; poor baseline hearing; concern for atypical mycobacterial infection	Prolonged QTc; hearing loss
Roflumilast	Chronic bronchitis¶ and FEV1 <50% (**required**); Inability to tolerate one class of inhaled bronchodilator (either LABA or LAMA)	Comorbid gastrointestinal conditions (eg, IBS, IBD, dyspepsia) Comorbid depression or insomnia	Diarrhea, nausea/vomiting, weight loss, dyspepsia, insomnia, adverse psychiatric reactions
Dupilumab	Peripheral eosinophilia (>300 cells/microl) **required**; increased bronchodilator reversibility; concomitant atopic dermatitis or nasal polyposis; history of asthma	Needle phobia, logistical barriers to biweekly injections	Injection site reactions, hypereosinophilia (typically transient), which may occasionally lead to rash, arthralgias, and fevers.

UPTODATE.COM, 2025

Apogee
CLINICAL IMMERSION
COPD Management

Barry Make, MD
Professor
Chair, Faculty Promotions Committee
National Jewish Health
Clinical Site Director
COPDGene



What is a COPD Phenotype (Subtype)?

- "a single or combination of **disease attribute(s)** that describe differences between individuals with COPD as they **relate to clinically meaningful outcomes** (symptoms, exacerbations, response to therapy, the rate of disease progression, or death)"

Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010; 182(5):598–604.

Endotype vs. Subtype

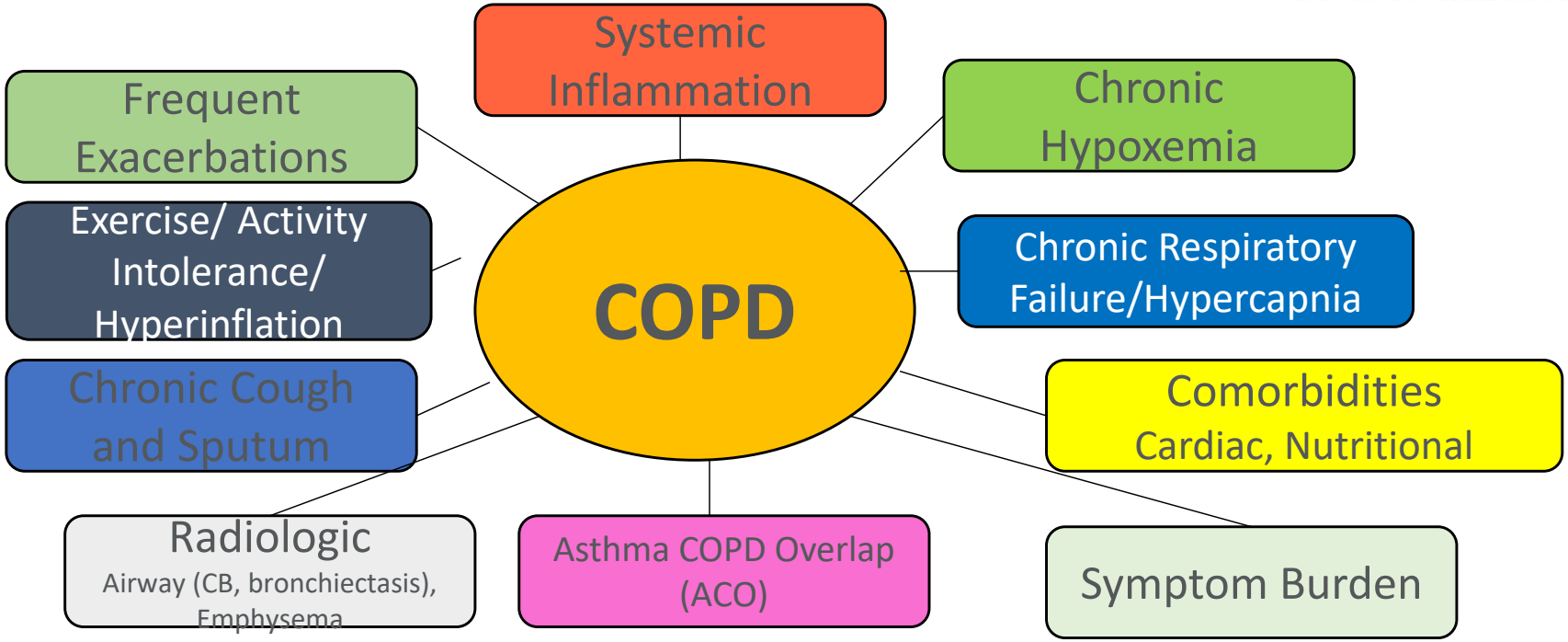
Endotypes:

- Alpha-1 Antitrypsin Deficiency
- Eosinophilic (+/- Th2 high inflammation) airway inflammation
- Neutrophilic airway inflammation

Subtypes:

Endotype:
A subtype defined functionally and pathologically by a distinct molecular mechanism or distinct treatment responses

Multiple Identified and Novel COPD Subtypes



Preserved ratio impaired spirometry (PRISm)

Smokers with Preserved Lung Function and symptoms

Chen X et al. Front. Med. 2013;7(4):425-432. Oga T et al. Chest. 2005;128:62-69. Westwood M et al. Respir Res. 2011;12:40.

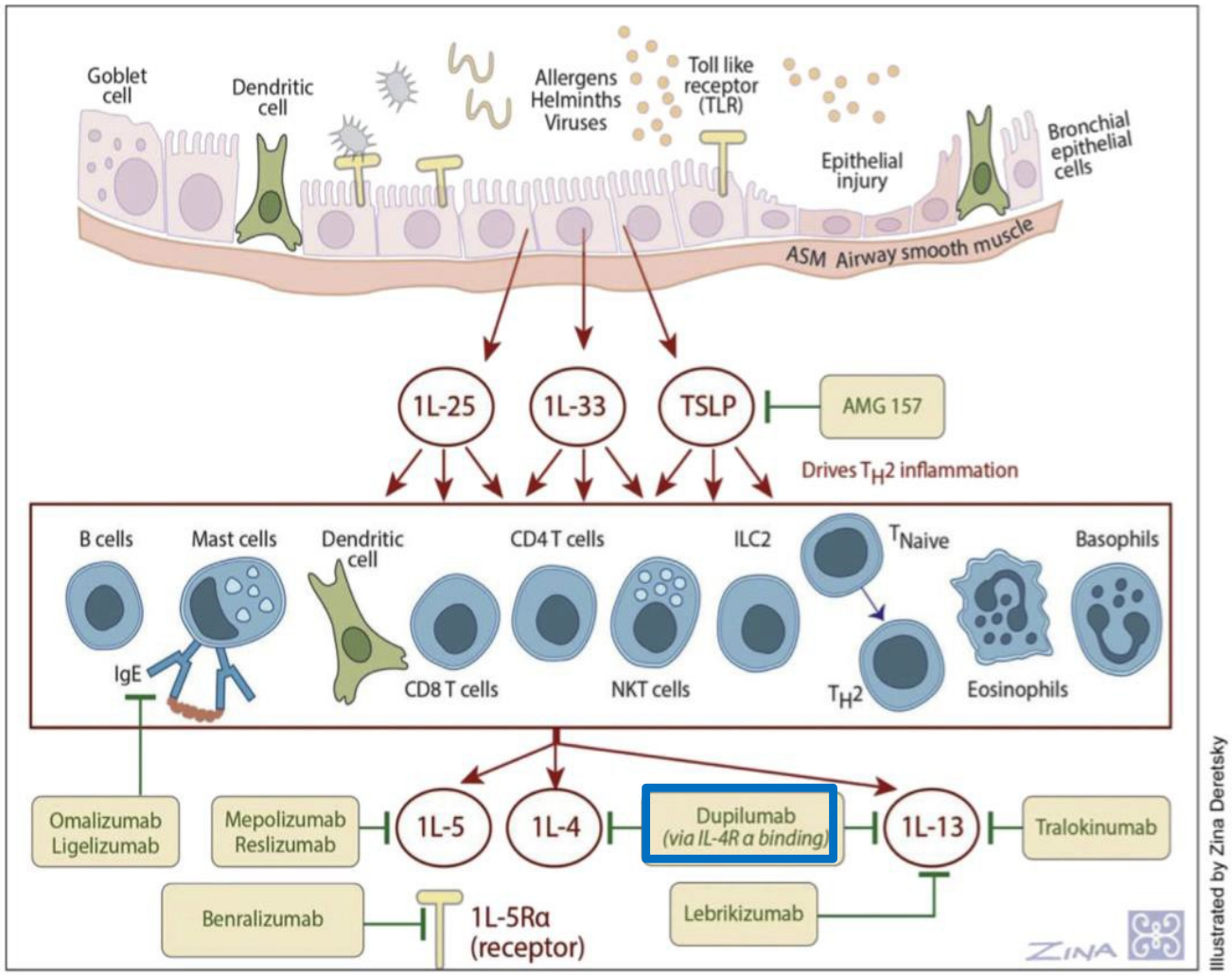
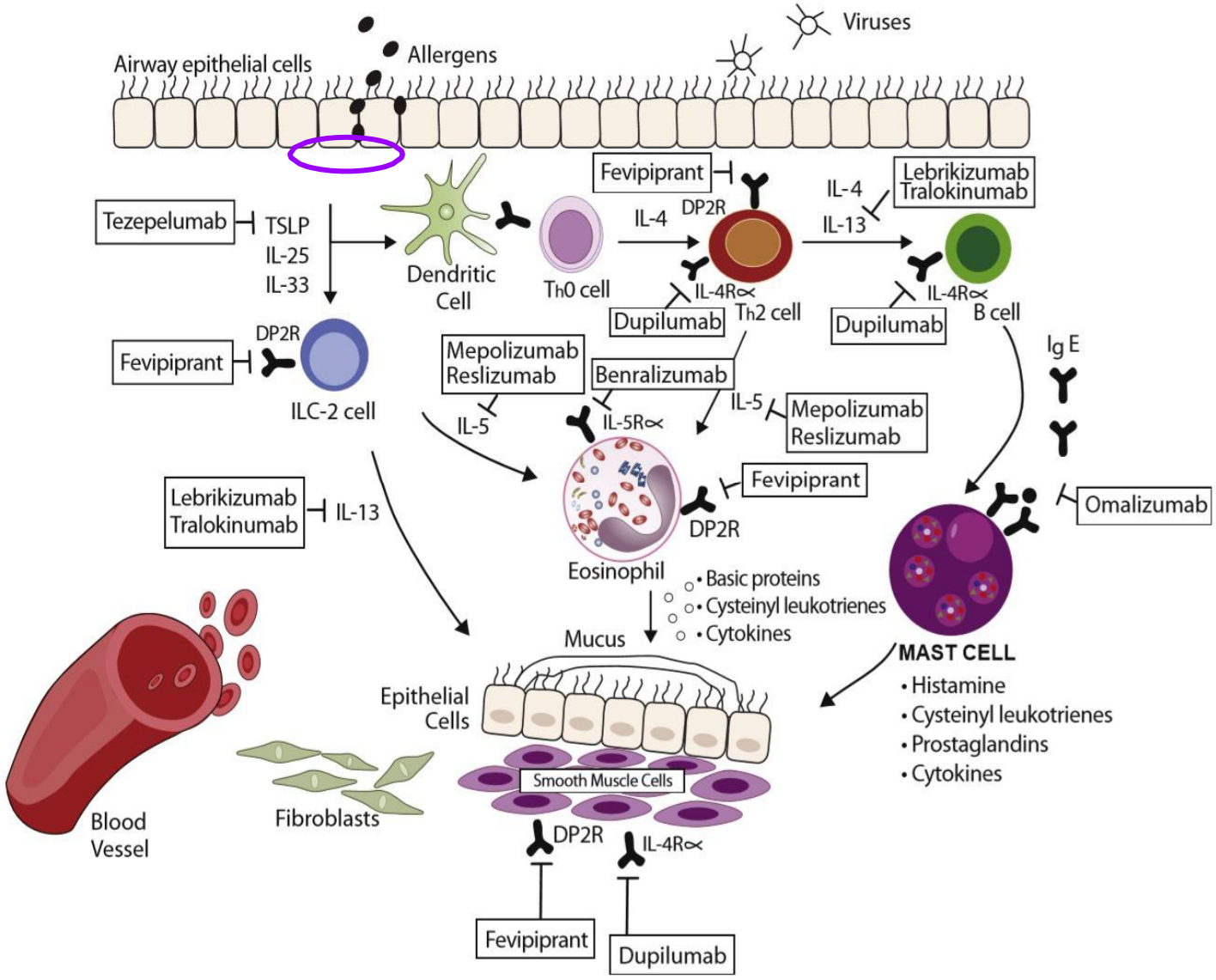
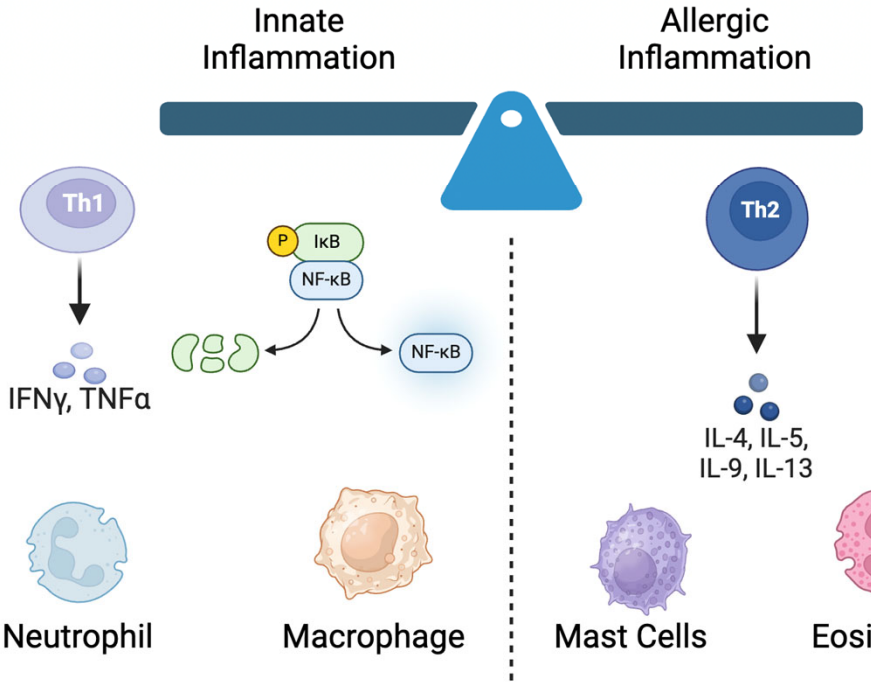


FIGURE 2. Important type 2-inflammation targets for biologic therapies. *TSLP,* Thymic stromal lymphopoietin. Adapted with permission from Mitchell et al.[57]

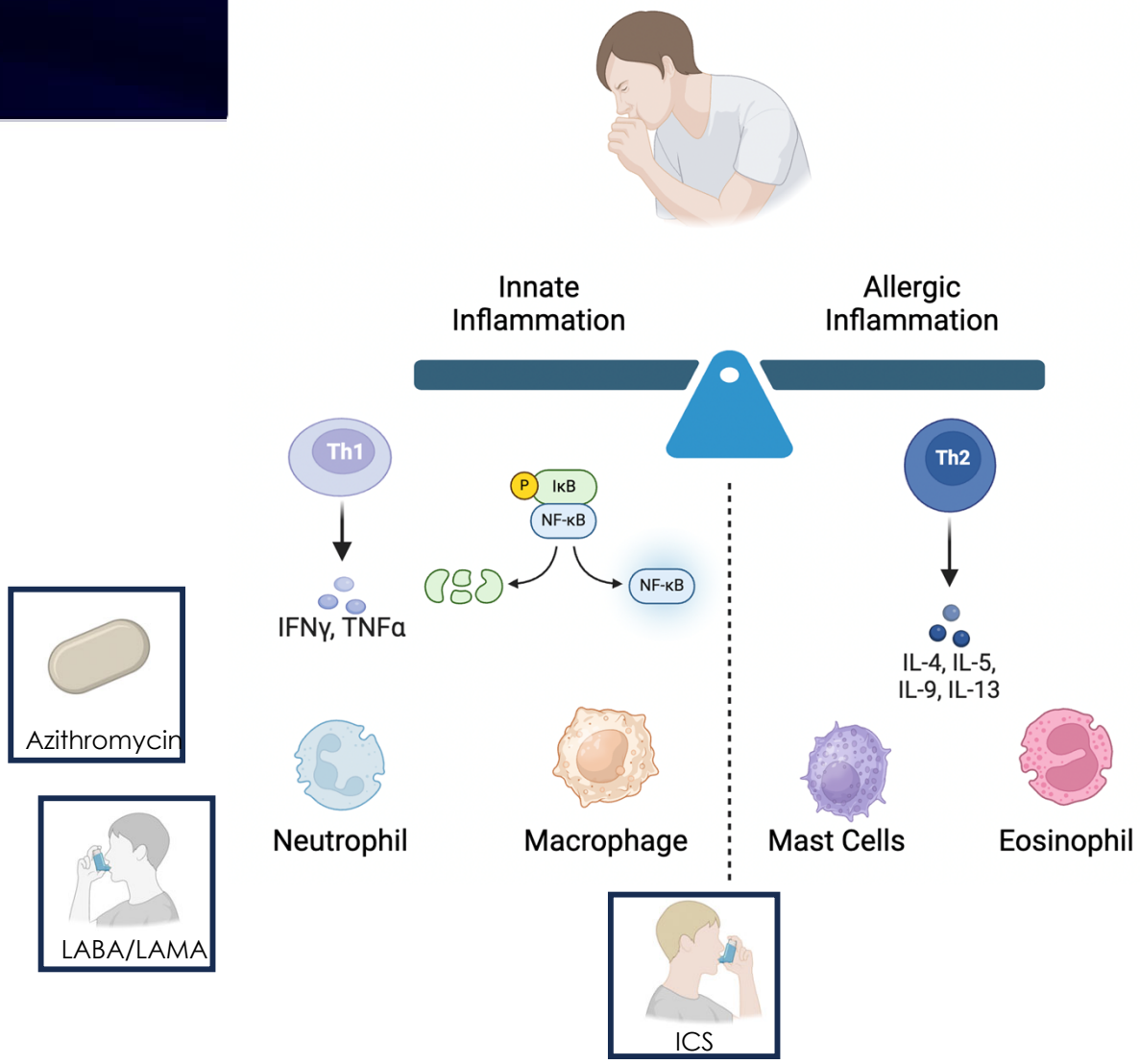
Katial et al. JACI: In Practice 2017. 5(2): S1-S14.



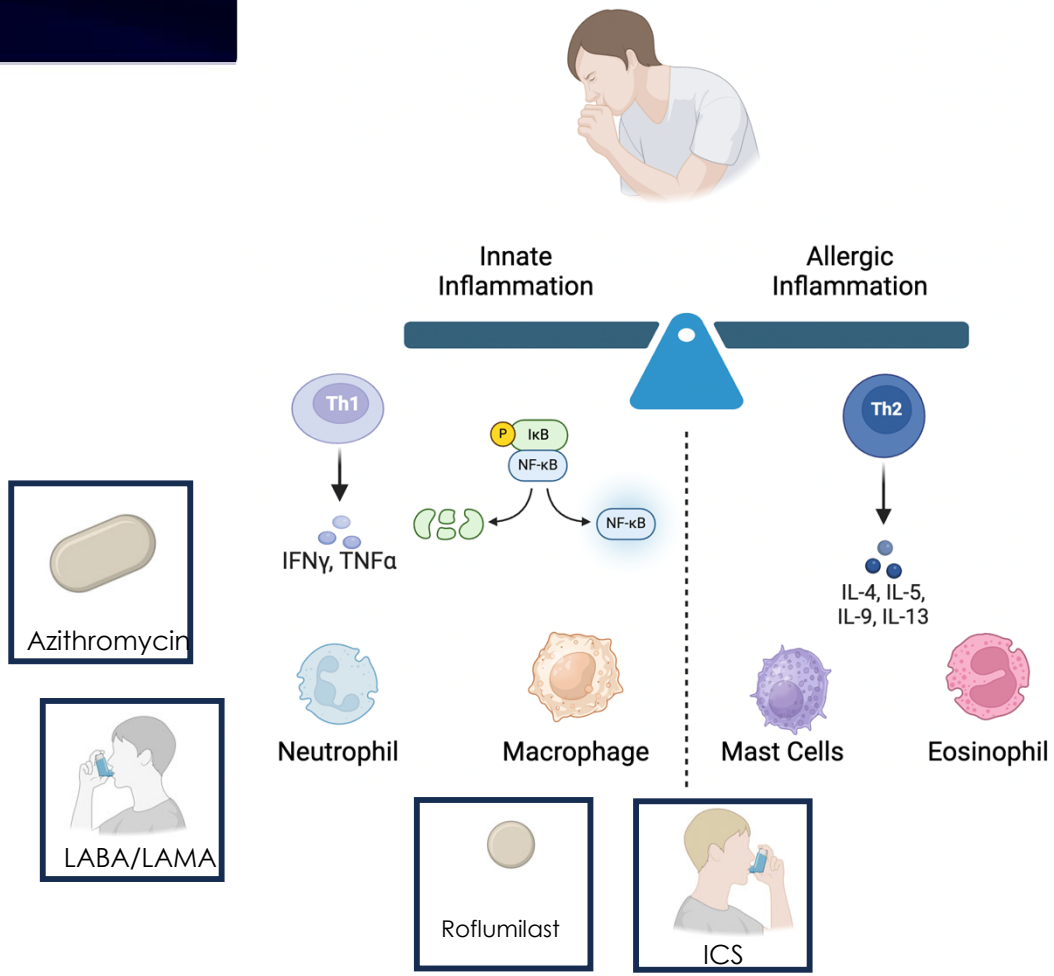


Immunologic Processes in COPD

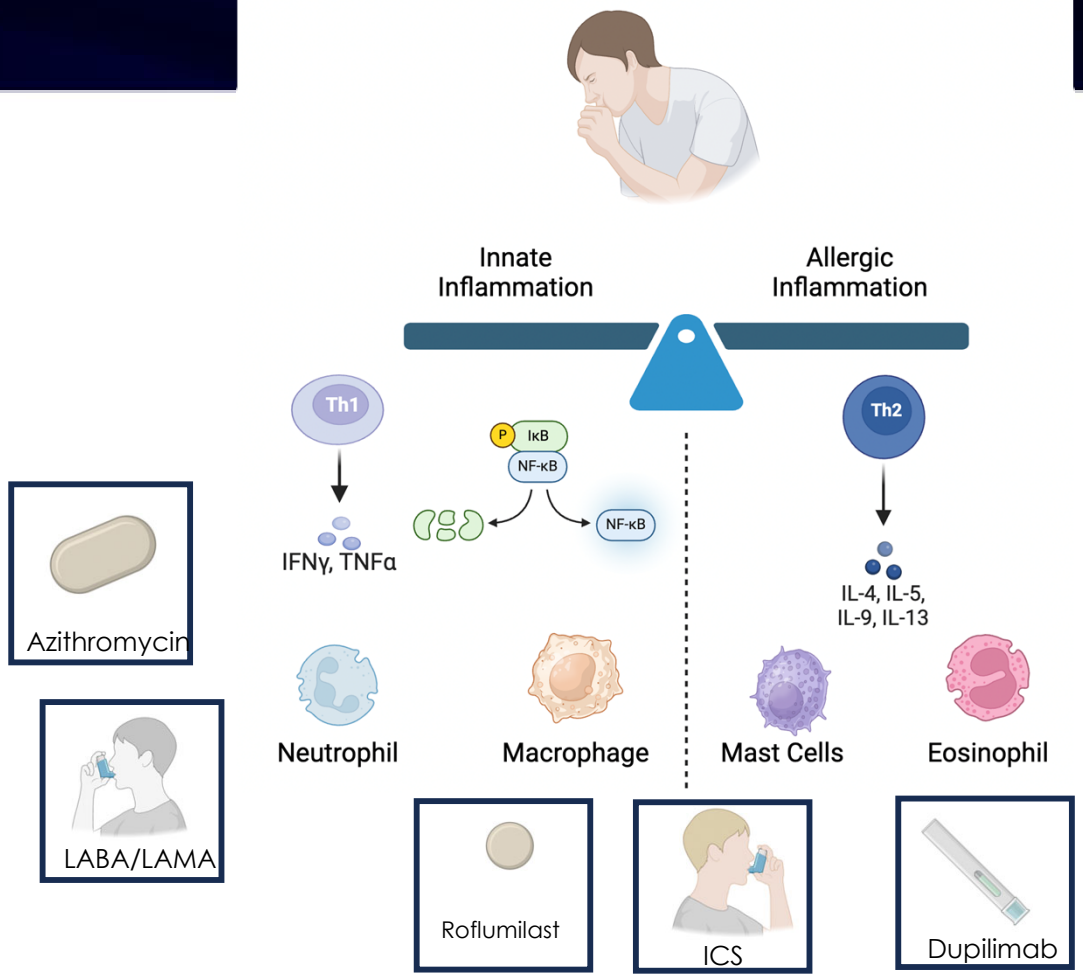
Immunologic Processes in COPD



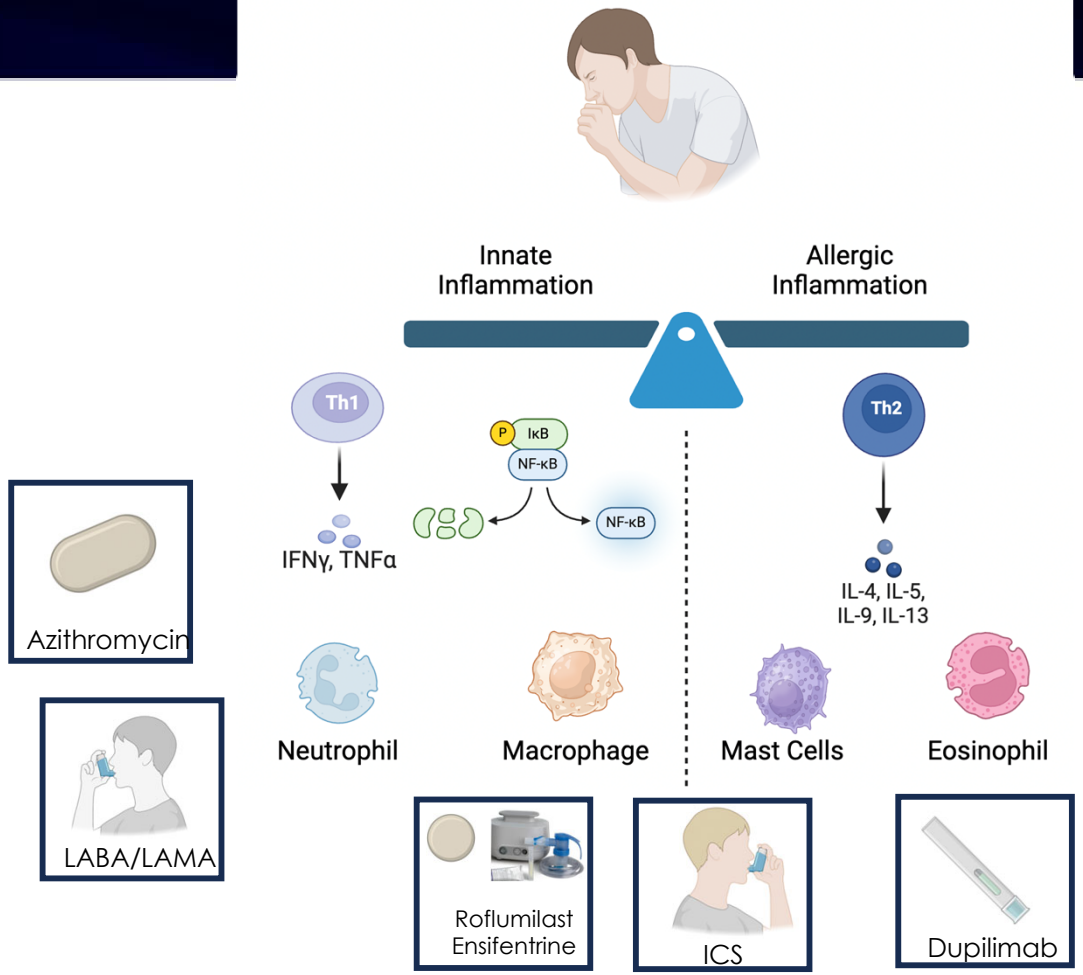
Immunologic Processes in COPD



Immunologic Processes in COPD

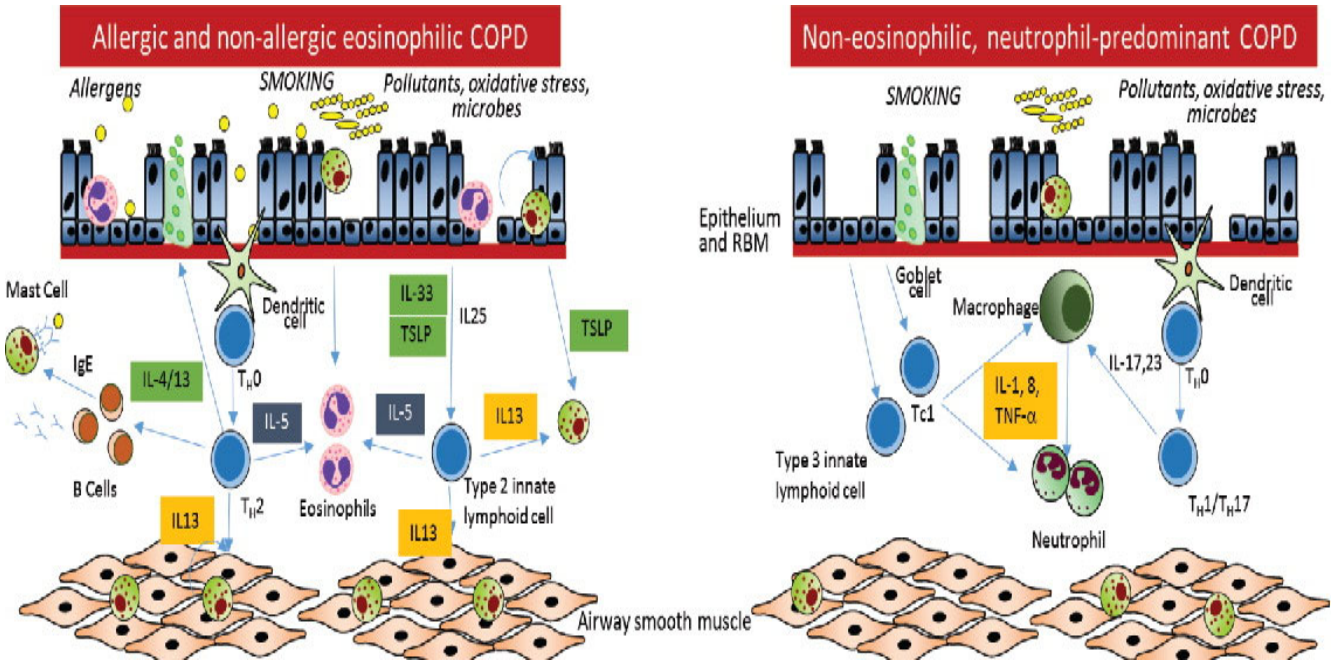


Immunologic Processes in COPD



Biologic Drugs: A new Target Therapy in COPD

Yousef A et al JCOPD:2018;15(2)99-107



T2 high COPD vs Non T2 COPD