IN THE NAME OF GOD

- Recent changes in COPD management
- Masoud Nazemiyeh , MD

New changes in GOLD

- Other than Group A patients, long acting muscarinc antagonists (LAMAs) and/or long acting beta2-agonists (LABAs) were recommended as first line across all groups before considering the use of inhaled corticosteroids (ICS)/LABA combination therapy (ICS/LABA) or triple therapy (ICS/LABA/LAMA).

Recent changes in GOLD

- In 2017, the GOLD guidelines introduced significant changes to the classification and treatment

recommendations for chronic obstructive pulmonary disease (COPD) patients

Lung function was no longer incorporated in the “A, B, C, D” classification scheme and maximizing bronchodilation first and foremost was given priority.

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- LAMA).

GOLD

- The exceptions to this were patients who were deemed to be asthma/COPD overlap patients and/or demonstrated evidence of persistent sputum or peripheral blood eosinophilia regardless of any prior history of asthma

Asthma/ /COPD overlap

- For these patients, ICS/LABA combinations were proposed as an appropriate first line therapy
- This change in the treatment paradigm was largely driven by the concerns that inhaled ICSs were associated with an increased risk of pneumonia and could exacerbate other comorbidities such as cataracts, osteopenia and diabetes.

Gold 2022

KEY POINTS FOR THE USE OF BRONCHODILATORS

- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea **(Evidence A)**, and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy.

- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator treatment should be escalated to two **(Evidence A)**.

- Inhaled bronchodilators are recommended over oral bronchodilators **(Evidence A)**.

- Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable **(Evidence B)**.

Gold 2022

KEY POINTS FOR THE USE OF ANTI-INFLAMMATORY AGENTS

- Long-term monotherapy with ICS is not recommended **(Evidence A)**.
- Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators **(Evidence A)**.
- Long-term therapy with oral corticosteroids is not recommended **(Evidence A)**.
- In patients with severe to very severe airflow limitation, chronic bronchitis and exacerbations the addition of PDE4 inhibitor to a treatment with long acting bronchodilators with/without ICS can be considered **(Evidence B)**.
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered **(Evidence B)**.
- Statin therapy is not recommended for prevention of exacerbations **(Evidence A)**.
- Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**.

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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
• ≥ 2 moderate exacerbations of COPD per year#	• Blood eosinophils 100-300 cells/µL	• Blood eosinophils <100 cells/µL
• Blood eosinophils >300 cells/µL		• History of mycobacterial infection
• 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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ANTI-INFLAMMATORY THERAPY IN STABLE COPD

INHALED CORTICOSTEROIDS

- 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)**.
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**.
- Triple inhaled therapy of LABA/LAMA/ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA/ICS, LABA/LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggest a beneficial effect versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations.

ORAL GLUCOCORTICOIDS

- Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**.

PDE4 INHIBITORS

- In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:
  - » A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)**.
  - » A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations **(Evidence A)**.

ANTIBIOTICS

- Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)**.
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**.

MUCOREGULATORS AND ANTIOXIDANT AGENTS

- Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)**.

OTHER ANTI-INFLAMMATORY AGENTS

- 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)**.
- Leukotriene modifiers have not been tested adequately in COPD patients.

Phenotype / endotype targeted therapies

- There is great interest in identifying phenotypes and endotypes that allow for precise, targeted therapies based on clinical characteristics and biomarkers such as eosinophils

“Treatable traits”

- Peripheral blood eosinophil count
- Frequent moderate and severe exacerbations

New drugs

- Single triple inhaler (LABA-LAMA-ICS)
- Anti-IL-5 agents

New therapeutic approaches in COPD treatment

1 ,Single Inhaler Triple Therapy versus Inhaled Corticosteroid Plus Long-Acting B2-Agonist Therapy for Chronic Obstructive Pulmonary Disease (*TRILOGY*)

2, Single Inhaler Extrafine Triple Therapy Versus Long-Acting Muscarinic Antagonist Therapy for Chronic Obstructive Pulmonary Disease (*TRINITY*):

New therapeutic approaches in COPD treatment

- 3, A Double-Blind, Parallel Group, Randomised Controlled Trial FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease
- 4, Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

New therapeutic approaches in COPD treatment

- **TRILOGY**:Reaching therapeutic goal in the triple therapy group (42%) was higher than in the beclometasone dipropionate(BDP)/formoterol fumarate (FF) group
- **TRINITY**:Treatment with extrafine fixe triple therapy had clinical benefits compared with tiotropium in patients with symptomatic COPD, FEV1 of less than 50%, and a history of exacerbations.

New therapeutic approaches in COPD treatment

- **FULFIL** showd benefits of single-inhaler triple therapy compared with ICS/LABA therapy in patients with advanced COPD.
- A monoclonal antibody directed against interleukin-5 Mepolizumab was associated with a lower annual rate of moderate or severe exacerbations than placebo among patients with COPD and eosinophilic phenotype.

Mepolizumab

- Potential role for the anti-interleukin-5 (IL-5) agent, mepolizumab, as a treatment option for COPD patients.
- Mepolizumab has been approved for treatment of severe asthma that is refractory to standard controller therapies such as ICSs or requires high-dose ICSs and/or systemic oral corticosteroids to remain controlled

Recently developed and approved drugs

- Glycopirionium . Quarternary ammonium derivative of atropine , long lasting as Tiotropium. Less CNS and occular side effects
- Indacaterol: Ultra long acting beta agonist . Quick onset (5 min) Ultra Lasting (24 hrs)
- Vilanterol: Ultra long acting beta agonist, rapid acting , ultra long lasting
- Olodaterol:Ultra long acting beta agonist,rapid acting,ultra long lasting

New launched inhalers for asthma and COPD

Tiotropium bromide(SPIRIVA)

- Long acting muscarinic receptor antagonist
- Once daily
- 24 hrs bronchodilating activity

Tiotropium bromide(Respimat)

- Long acting muscarinic receptor antagonist
- Once daily
- 24 hrs bronchodilating activity

Anoro elipta

Umeclidinium bromide/vilanterol

Trelegy

Fluticasone furoat 100 and 200 mcg
Umeclidinium 62.5 mcg
Vilanterol 25 mcg

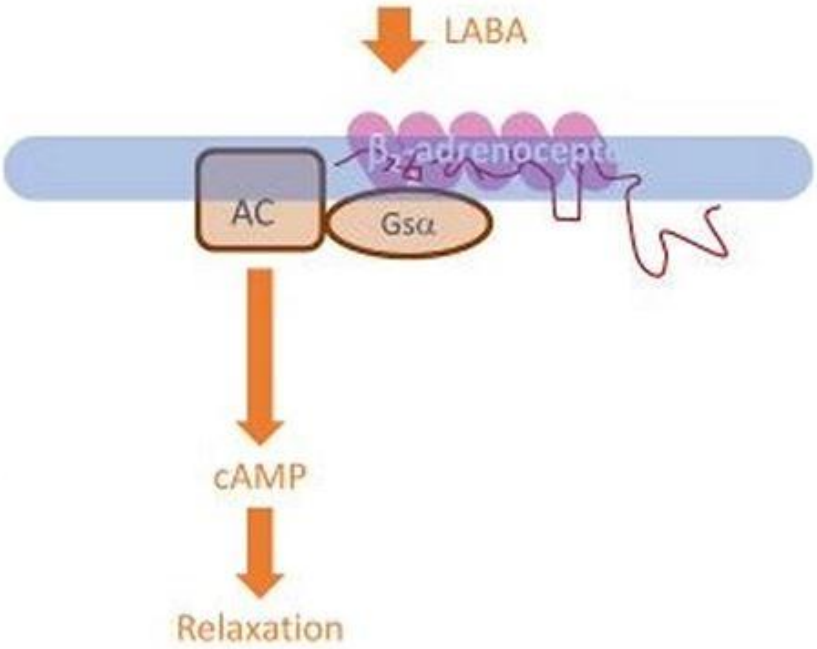
100/62.5/25 mcg
For COPD

100/62.5/25 mcg &
200/62.5/25 mcg
For ASTHMA

Beta2 Agonists

- **Characteristics and Classification**
  - **Receptor Selectivity**

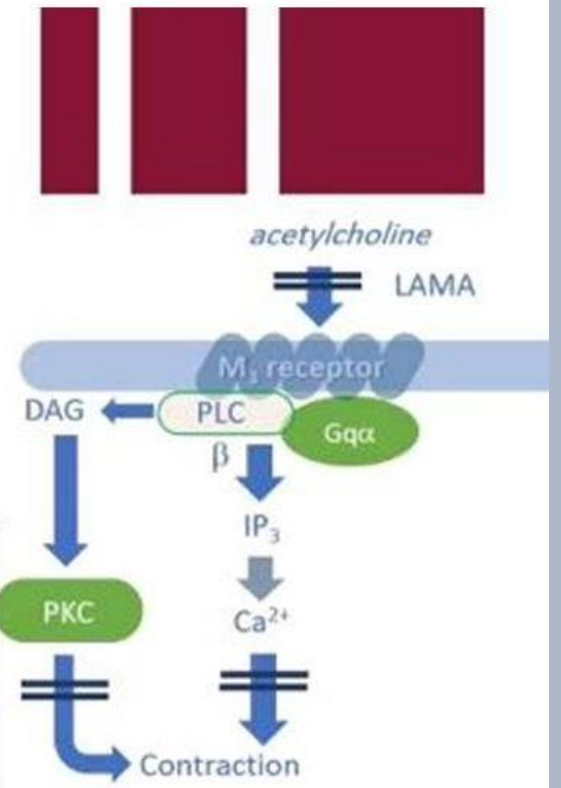
Beta 2 Agonists	Beta 2 Selectivity Ratio
Salbutamol	27
Vilanterol	2400
Formoterol	150
Salmeterol	3000
Indacaterol	16



Anticholinergics

Anticholinergics block muscarinic receptors on airway smooth muscles

Anticholinergic agents can reduce airway hyper-responsiveness



	Potency	Onset of action		Offset of action	
	pIC_{50}	$T_{1/2}$ (min)	Tmax	$T_{1/2}$ (min)	% inhibition at 9h
Tiotropium	9.75 ± 0.05	12 ± 3	34 ± 5	> 540	70 ± 8
Umeclidinium	8.88 ± 0.09	9 ± 2	55 ± 3	> 540	75 ± 3
Glycopyyrronium	9.37 ± 0.12	14 ± 3	36 ± 6	129 ± 40	26 ± 4
Ipratropium	9.00 ± 0.09	7 ± 1	30 ± 7	59 ± 27	33 ± 13
Aclidinium	8.61 ± 0.11	10 ± 3	47 ± 3	(200, > 540)	47 ± 7

Anticholinergics

Metabolism

LAMA	Metabolism Rout
Tiotropium	Renal
Glycopyrronium	Partly Renal
Aclidinium	Non P450 Involved Esterases
Umeclidinium	CYP2D6

"Renal Impairment"

Side effects of Anoro Trelegy

- Hypokalemia
- Prostate/ urinary retention
- Constipation
- Increased pneumonia with trelegy
- oral candidsiasis with trelegy

Contraindication to Anoro and trelegy

- Severe hypersensitivity to milk proteins
- Caution with drugs increase QTC interval
- Formotrol, vilantrol increase QTC but salmetrol usually not increase
- Coadministration with other anticholinergics
- such as tiotropium (Spiriva)

Phosphodiesterase-4 (PDE4) inhibitors (Roflumilast)

- The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.
- Roflumilast is a once daily oral medication with no direct bronchodilator activity.
- Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis,
- severe to very severe COPD, and a history of exacerbations.
- .

Phosphodiesterase-4 (PDE4) inhibitors (Roflumilast)

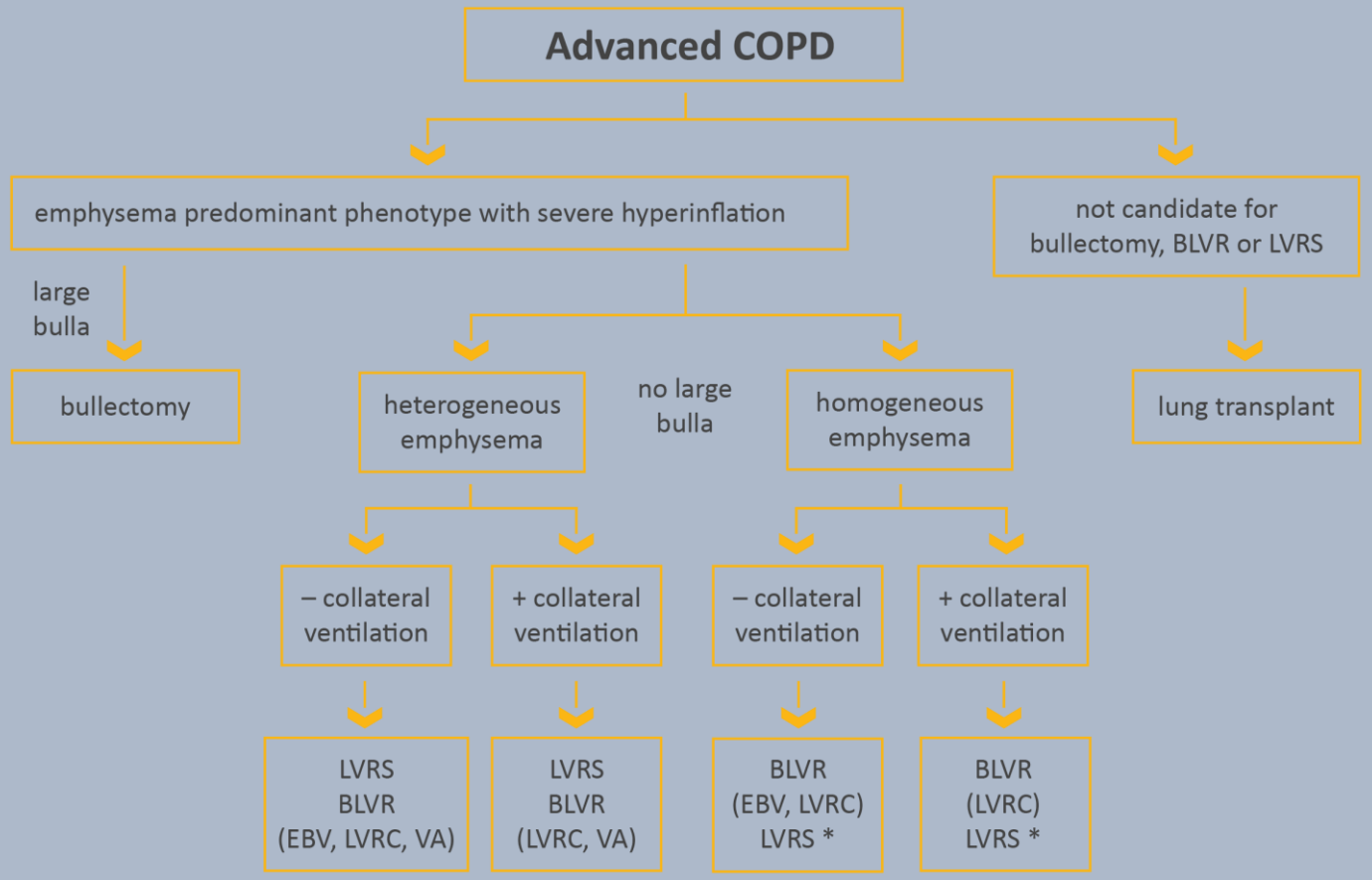
- The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation.
- It decreases exacerbations

PDE4) inhibitors (Roflumilast)

- The most common side effect is diarrhea
- Others nausea, reduced appetite,
- weight loss,
- abdominal pain,
- sleep disturbance,
- and headache

INTERVENTIONAL BRONCHOSCOPIC AND SURGICAL TREATMENTS FOR COPD

Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. Additionally, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown.



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

*at some but not all centers

KEY POINTS FOR THE MANAGEMENT OF PATIENTS WITH COPD AND SUSPECTED OR PROVEN COVID-19

SARS-CoV-2 TESTING

- Swab/Saliva PCR if new or worsening respiratory symptoms, fever, and/or any other symptoms that could be COVID related

OTHER INVESTIGATIONS

- Avoid spirometry unless essential
- Consider CT for COVID pneumonia and to exclude other diagnoses e.g. PE
- Avoid bronchoscopy unless essential
- Assess for co-infection

COPD PHARMACOTHERAPY

- Ensure adequate supplies of medication
- Continue maintenance therapy unchanged including ICS
- Use antibiotics and oral steroids in line with recommendations for exacerbations
- Avoid nebulization when possible

COPD NON-PHARMACOLOGICAL THERAPY

- Maintain physical activity as able

PROTECTIVE STRATEGIES

- Follow basic infection control measures
- Maintain physical distancing
- Wear a face covering

COVID-19 THERAPY

- Use systemic steroids and remdesivir as recommended for patients with COVID-19
- Use HFNT or NIV for respiratory failure if possible
- Use invasive mechanical ventilation if HFNT or NIV fails
- Post COVID-19 rehabilitation
- Ensure appropriate post COVID-19 follow-up

KEY POINTS FOR THE MANAGEMENT OF STABLE COPD DURING COVID-19 PANDEMIC

PROTECTIVE STRATEGIES

- Follow basic infection control measures
- Wear a face covering
- Consider shielding/sheltering-in-place

INVESTIGATIONS

- Only essential spirometry

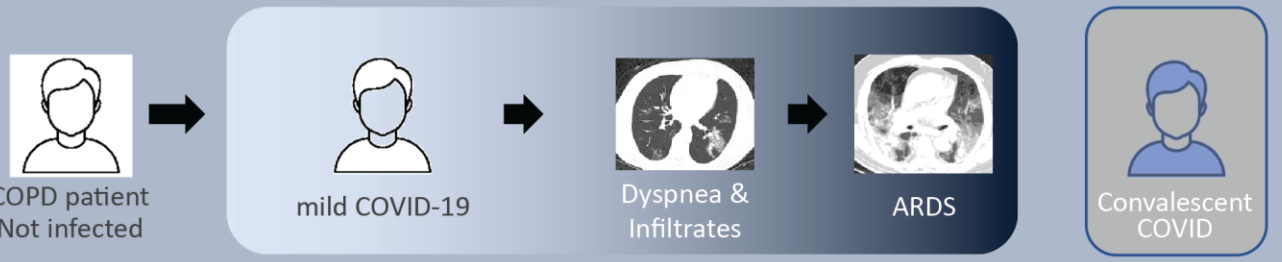
PHARMACOTHERAPY

- Ensure adequate supplies of medications
- Continue unchanged including ICS

NON-PHARMACOLOGICAL THERAPY

- Ensure annual influenza vaccination
- Maintain physical activity

COVID-19 & COPD



Clinical Features	**COPD:** Cough, SOB	Mild constitutional symptoms Fever > 37.5 °C, ↑ SOB Dry Cough, Fatigue, Diarrhea	↑↑ SOB ± hypoxia $PaO_2/FiO_2 \leq 300$ mmHg	ARDS SIRS/Shock Cardiac Failure VTE	Fatigue SOB Cough
Abnormal Investigations		SARS-CoV-2 PCR CXR/CT, SpO_2 Lymphopenia Thrombocytopenia CRP, D-dimer	CXR/CT, SpO_2 Lymphopenia Thrombocytopenia Transaminases D-dimer, PCT	SpO_2 CRP, LDH, IL-6 D-dimer, ferritin troponin, BNP	PFT CT Chest
	Continue Usual COPD Maintenance Therapy				
Possible Interventions	Home Exercise Protective Strategies	Protective Strategies, COPD Exacerbation Therapy Low intensity exercise *Therapeutic Trials*	Controlled Oxygen Systemic Steroids Remdesivir Anticoagulation *Therapeutic Trials*	NIV, HFNT IMV Prone positioning Anticoagulation *Therapeutic Trials*	Home exercise PR

(ARDS, Adult respiratory distress syndrome; BNP, brain natriuretic peptide; CRP, C reactive protein; CT, computed tomography; CXR, chest radiograph; HFNT, high flow nasal therapy; IL-6, interleukin 6; IMV, invasive mechanical ventilation; LDH, lactate dehydrogenase; NIV, non-invasive ventilation; PCT, procalcitonin; PFT, pulmonary function tests; PR, pulmonary rehabilitation; SOB, Shortness of breath; SpO_2 , peripheral oxygen saturation; VTE, venous thromboembolism)

Halpin et al. 2020. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The 2020 GOLD Science Committee Report on COVID-19 & COPD. Published Ahead of Print: https://www.atsjournals.org/doi/abs/10.1164/rccm.202009-3533SO

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Thank you for your attention