TREATMENT CONSIDERATIONS IN COPD

A CLINICAL PHARMACIST'S VIEWPOINT

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DISCLOSURE STATEMENT

- I have no relevant financial or nonfinancial relationships in the products or services described, reviewed, evaluated or compared in this presentation.

- The views expressed in this presentation are my own, and I do not speak behalf of the Veterans Affairs or VA Puget Sound Health Care System.

OBJECTIVES

- Identify main purposes of treatment in COPD.
- Review GOLD treatment recommendations; compare other select guidelines.
- Discuss harms of inhaled corticosteroid (ICS).
- Understand appropriate use of ICS in COPD.
- Review medications and combinations that reduce exacerbations.
- Understand inhaled medication delivery, and the importance of technique.

GOALS OF TREATMENT FOR COPD

GOLD 2024

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REDUCING SYMPTOMS IN COPD

Short-acting bronchodilators (SABD)

- Beta-agonist (SABA)
- Muscarinic antagonist (SAMA)

SABDs preferred for rescue

Combo SABD > monotherapy

Long-acting bronchodilators (LABD)

- Beta agonist (LABA)
- Muscarinic antagonist (LAMA)

LABD > SABD for maintenance

LABD improve FEV1 and symptoms

Combo LABD > monotherapy

Inhaled steroids (ICS)

Triple therapy with ICS/LAMA/LABA improves FEV1 and symptoms, but with ↑ pneumonia

Caution: Combination SAMA + LAMA Listed as Category X drug interaction – "avoid combination"
- Increased risk of enhanced anticholinergic side-effects
- Careful with glaucoma, BPH/urinary retention

2024 GOLD REPORT - GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE - GOLD (GOLDCOPD.ORG) PAGE 72, 78

UPTODATE DRUG INFORMATION

REDUCING EXACERBATIONS IN COPD

Most are evidence A, except ǂ, which are evidence B

These reduce exacerbations better	Than this group
Long-acting bronchodilators	Short-acting bronchodilators[1]
Long-acting muscarinic antagonist (LAMA)	Long-acting beta agonist (LABA)[1] ǂ
Combination LAMA + LABA	Any monotherapy[1] ǂ
Inhaled corticosteroid (ICS) + LAMA + LABA (Triple Therapy)	Any monotherapy or any combination [2]

But increased risk of Pneumonia

These reduce exacerbations in certain populations
Roflumilast. [2]
Chronic azithromycin. [2]
N-acetyl cysteine (NAC) in certain populations. [2] ǂ

1. GOLD 2024, PAGE 72 2. GOLD 2024, PAGE 78 2024 GOLD REPORT - GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE - GOLD (GOLDCOPD.ORG)

POLL QUESTION #1

- A new patient presents to your clinic. 55 yo female patient with a significant history smoking and COPD confirmed by spirometry. She does not have any personal or family history of asthma. She is requesting a renewal for albuterol, and she reports to have shortness of breath (CAT 15, mMRC 2), using about 1 albuterol inhaler per month. She reports no COPD exacerbations in the last year.

A. Renew the albuterol, and no other changes

B. Renew the albuterol, and start a LABA/ICS inhaler

C. Start LAMA/LABA inhaler, but don't renew the albuterol

D. Start LAMA/LABA inhaler, and renew albuterol **Correct**

INITIAL MEDICATION MANAGEMENT IN STABLE COPD

Choice of medication is very important!

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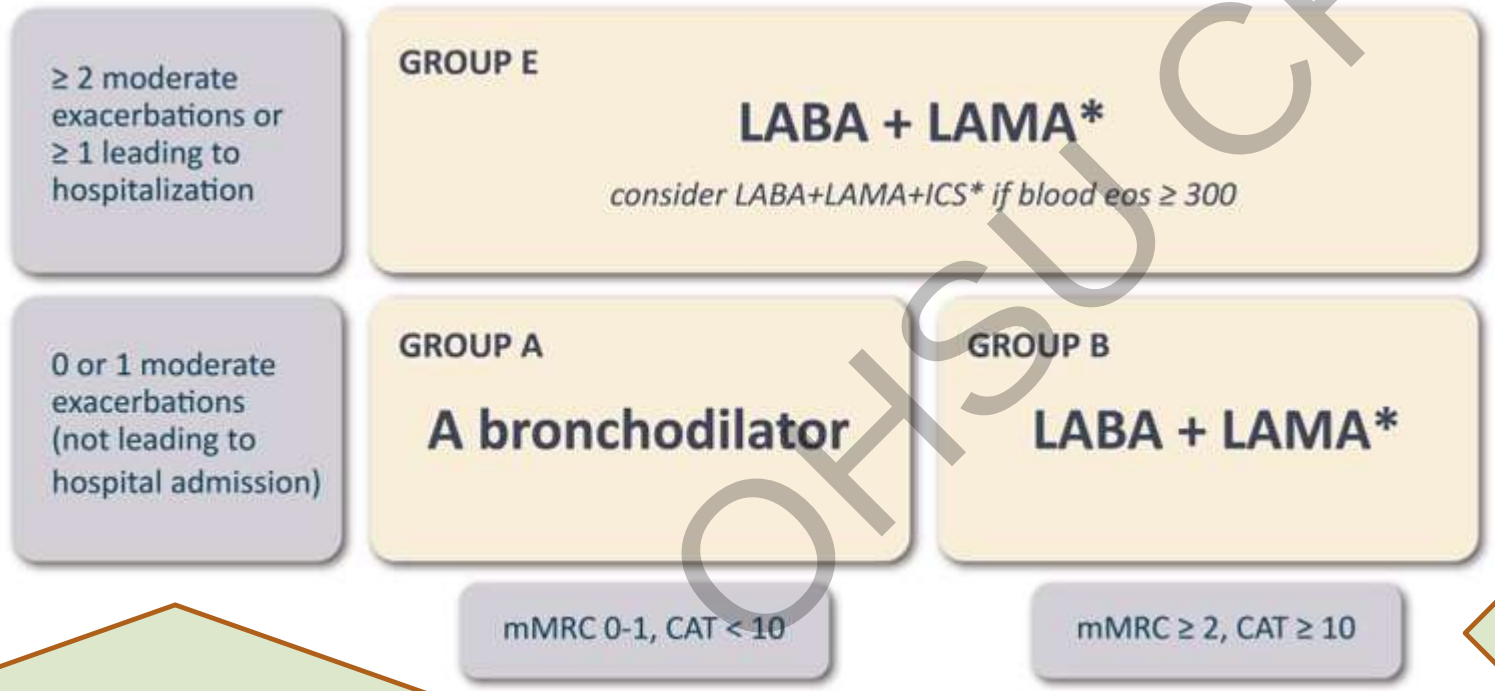


Review exacerbations

Assess symptoms

In Group A, GOLD recommends below to decrease exacerbation risk:
- **Long-acting > Short-acting**
- **LAMAs > LABAs (POET-COPD)**

Use of LABA + ICS in COPD is not encouraged. If there is an indication of ICS, then LAMA + LABA + ICS has been shown to be superior to LABA + ICS and is therefore the preferred CHOICE – GOLD 2024

2024 GOLD Report Page 48-49

WHAT DO OTHER COPD GUIDELINES SAY?

- **VA/DOD COPD Guidelines**

SABA prn then follow steps:

1. **LAMA**
2. **Add LABA for persistent symptoms**
3. **Add ICS only for continued exacerbations**
4. Pulmonology Referral

All 3 guidelines agree:
- **LAMA + LABA, before adding ICS**
- **Triple therapy with ICS if exacerbations**
- **No recommendation for LABA/ICS in COPD**

- **American Thoracic Society**
  - **Strong Recommendation**
    - **LABA/LAMA in COPD with dyspnea or exercise intolerance**
  - **Conditional Recommendations**
    - **ICS/LABA/LAMA > LAMA/LABA with dyspnea + ECOPD in last year**
    - ICS withdrawal on ICS/LABA/LAMA if no ECOPD in last year

WHY IS ICS RESERVED FOR SO FEW?

1) LAMA/LABA better combo than LABA/ICS for prevention of exacerbations **and** improvement symptoms (**FLAME 2016**) **N Engl J Med 2016; 374:2222-2234**

2) ICS carries higher risk of pneumonia

Population	Incidence w/ LABA/ICS	Difference with LAMA/LABA	Relative Odds w/ LABA/LABA
High Risk	32 per 1,000	12 fewer per 1,000	OR 0.6
Low Risk	4 per 1,000	4 fewer per 1,000	OR 0.4

Cochrane Review, 2018, PMID: 30521694 (99 studies)

3) Local effects – dysphonia, thrush

4) Systemic effects – cataracts, adrenal suppression, osteoporosis

Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD; Eur Respir Rev. 2021 Jun 23;30 (160):2100075

Slide and info courtesy of Lucas M. Donovan, MD, VA Puget Sound

WHO BENEFITS FROM TRIPLE THERAPY?

- **<u>COPD patients with recurrent exacerbations on treatment</u>**
- **IMPACT** and **ETHOS** tested triple LAMA/LABA/ICS vs. LAMA/LABA & ICS/LABA
- Among patients with:
  - COPD with prior exacerbation within the last year
  - Asthma excluded (no active asthma w/in past 5-10 years)
  - History of smoking at least 10 pack years
  - FEV1 < 50-80% pred (IMPACT) or 25%-65% pred (ETHOS)
- Triple therapy was superior to both groups in reducing exacerbation.
- Post-hoc analysis showed decreased mortality in triple therapy group.

IMPACT – N Engl J Med 2018; 378:1671-1680 ETHOS – N Engl J Med 2020; 383:35-48

POLL QUESTION #2

- 72 yo male patient with stable COPD (and no asthma) presents for follow-up after their 2nd episode for pneumonia within the last year. Patient on LABA/ICS for COPD. What would be an appropriate action to take for this patient.

A. Continue LABA/ICS

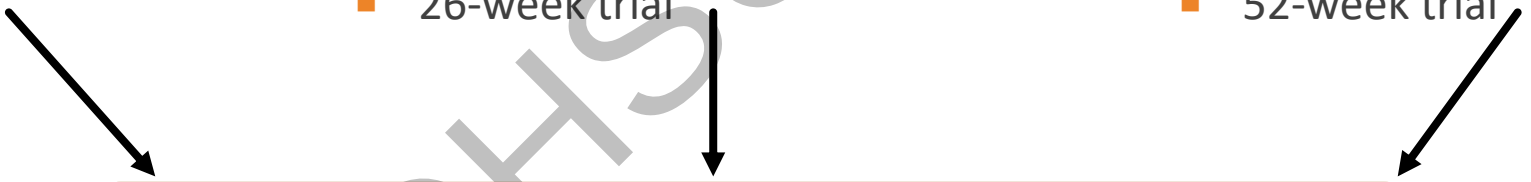
B. Continue LABA/ICS and start chronic azithromycin three times weekly

C. DC LABA/ICS and switch to LABA

D. Continue LABA/ICS and add LAMA

EVIDENCE TO DE-ESCALATE OFF AN ICS?

- **INSTEAD 2014**
  - LABA/ICS (high dose)→ LABA
  - Immediate withdrawal of ICS
  - No exacerbations last 1 year
  - 26-week trial
- **SUNSET 2018**
  - LAMA/LABA/ICS → LAMA/LABA
  - Immediate withdrawal of ICS
  - Had an exacerbation in last year
  - 26-week trial
- **WISDOM 2014**
  - LAMA/LABA/ICS → LAMA/LABA
  - Taper ICS over 12 weeks
  - Had an exacerbation in last year
  - 52-week trial



No differences in the rate of COPD exacerbations in any groups withdrawn from ICS

INSTEAD – Eur Respir J 2014 Dec;44(6):1548-56

SUNSET – AM J Respir Crit Care Med. 2018 Aug 1;198(3):329-339

WISDOM – N Engl J Med 2014; 371:1285-1294

GUIDELINES FOR ICS DE-ESCALATION

GOLD

- Consider ICS de-escalation if:
  - Pneumonia
  - other side-effects
  - \+ Eos < 300
- **LAMA/LABA/ICS →LAMA/LABA**

ATS

- Consider ICS de-escalation if:
  - No exacerbations in last year
  - No recommendations for Eos counts
- **LAMA/LABA/ICS →LAMA/LABA**

VA/DOD

- Consider ICS de-escalation if:
  - No exacerbations in 2 yrs
  - Eos < 300
- **LAMA/LABA/ICS →LAMA/LABA**
- **LABA/ICS → LAMA or LABA**

- **All agree on triple therapy ICS de-escalation but differ in which groups to address.**
- **LABA/ICS de-escalation is warranted in stable patients without exacerbations (INSTEAD & VA).**
- **Using blood eosinophil counts to guide addition or removal of ICS has not been prospectively tested***

Blood eosinophil count meta-analysis, BMC, Respiratory Research 21, Article number 3 (2020) *

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ATS COPD PAGE 1039-1047

VADODCOPDCPGFINAL508.PDF PAGE 19

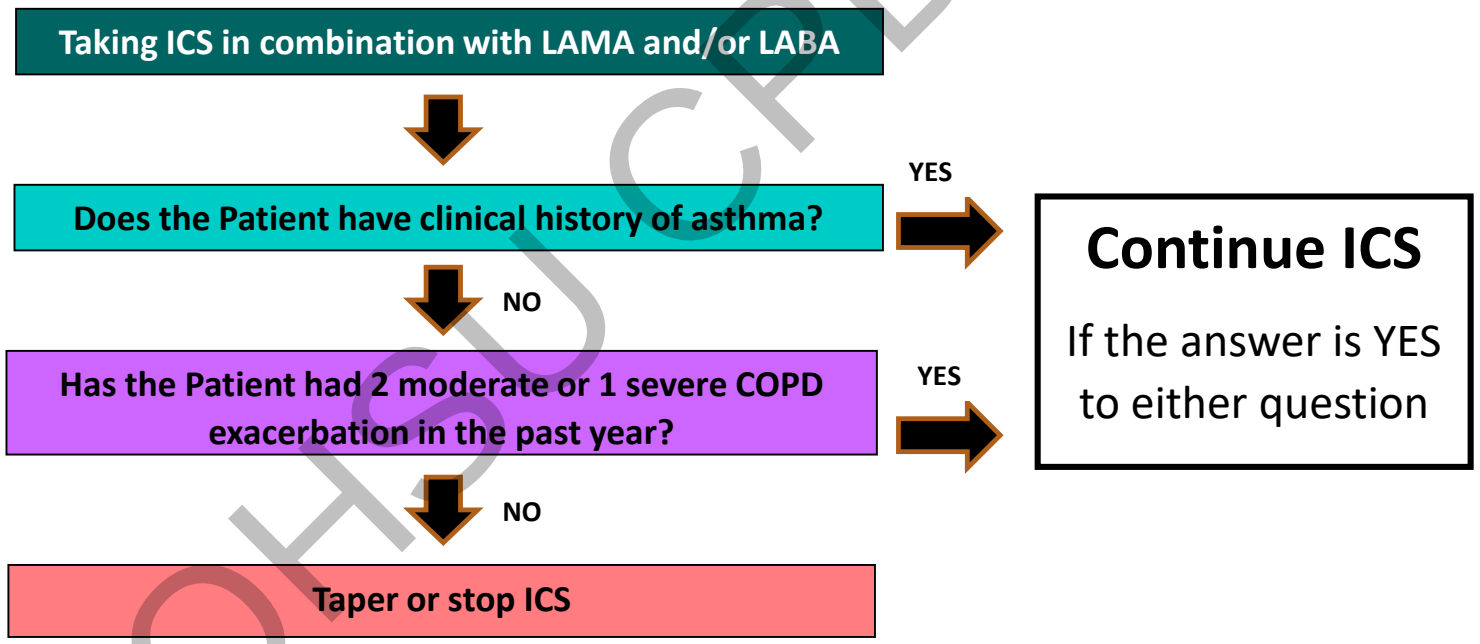
POLL QUESTION #3

- A 60 yo male COPD patient transfers to you on ICS/LAMA/LABA. Patient reports he was started on this after his first COPD exacerbation (previously on no inhaled medications). Your intake reveals no personal or family history of allergies or asthma. He has no complaints and reports no flares of COPD in over 1 year. He uses his albuterol inhaler occasionally. You assess benefit/risk of ICS and decide to de-escalate off the ICS, by doing the following:

A. Stop triple therapy, start LABA, continue albuterol prn
B. Stop triple therapy, start LAMA, continue albuterol prn
C. Stop triple therapy, start LAMA /LABA, continue albuterol prn **Correct**
D. Stop triple therapy, , continue albuterol prn

CONSIDERATIONS FOR DE-ESCALATING ICS IN COPD*

*Note that this pathway is not validated or intended to replace clinical judgment, but simply what the presenter uses in clinical practice, based on available evidence and guideline documents



Pathway favors ATS recommendations

GUIDANCE FOR ESCALATING TREATMENT IN COPD

GOLD 2024

Am Thoracic Society 2020

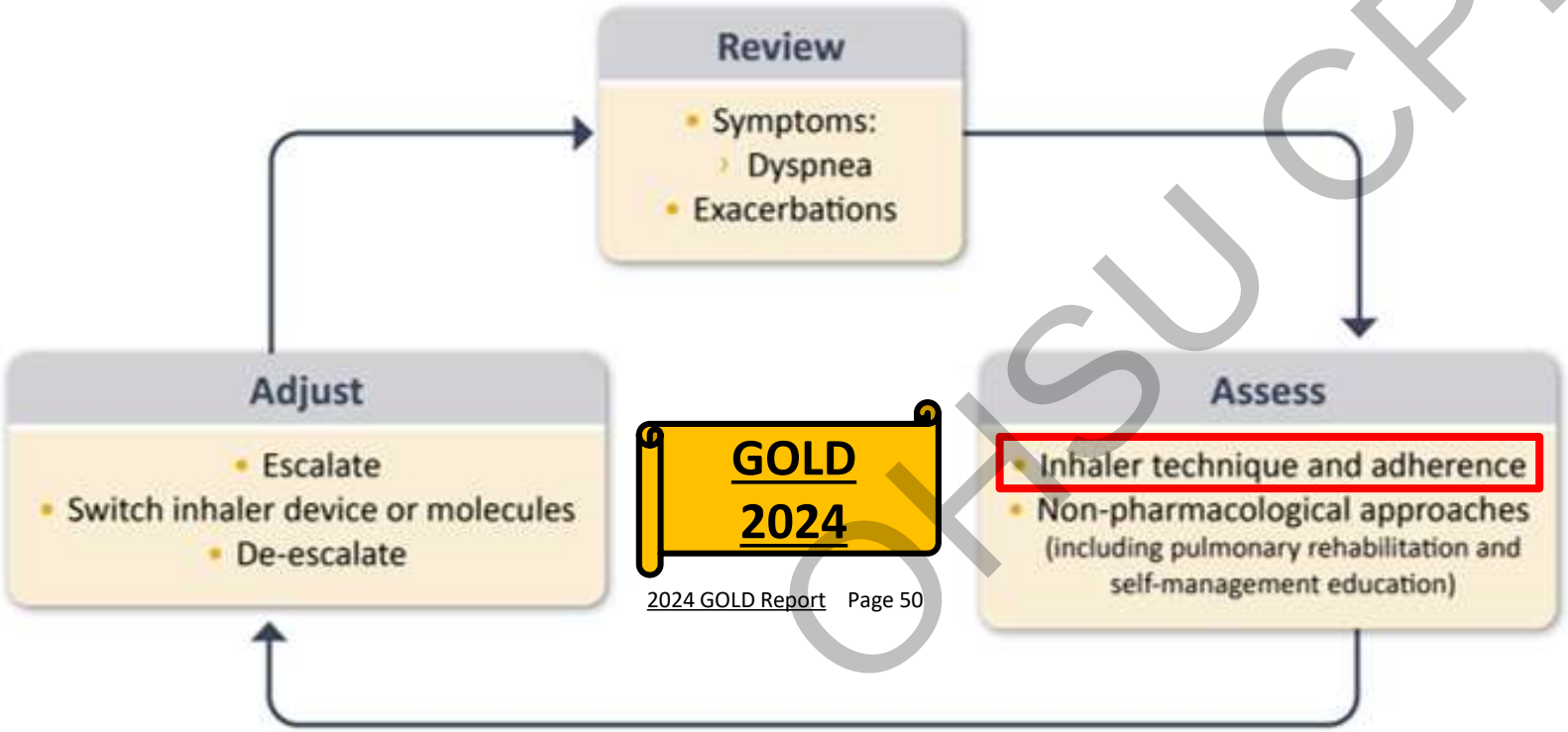
VA/DOD 2021

Where the guidelines agree:

- **Start with LAMA (+ LABA per ATS)**
- **LAMA/LABA for next step**
- **Add ICS <u>if still having exacerbations</u>**
- **No one recommends ICS/LABA for COPD**

REFER TO SLIDES 8 & 9 FOR TREATMENT PATHWAYS/STATEMENTS

FACTORS TO CONSIDER AT FOLLOW-UP'S



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79% have 1 potential impediment for optimal inhaler technique[1]

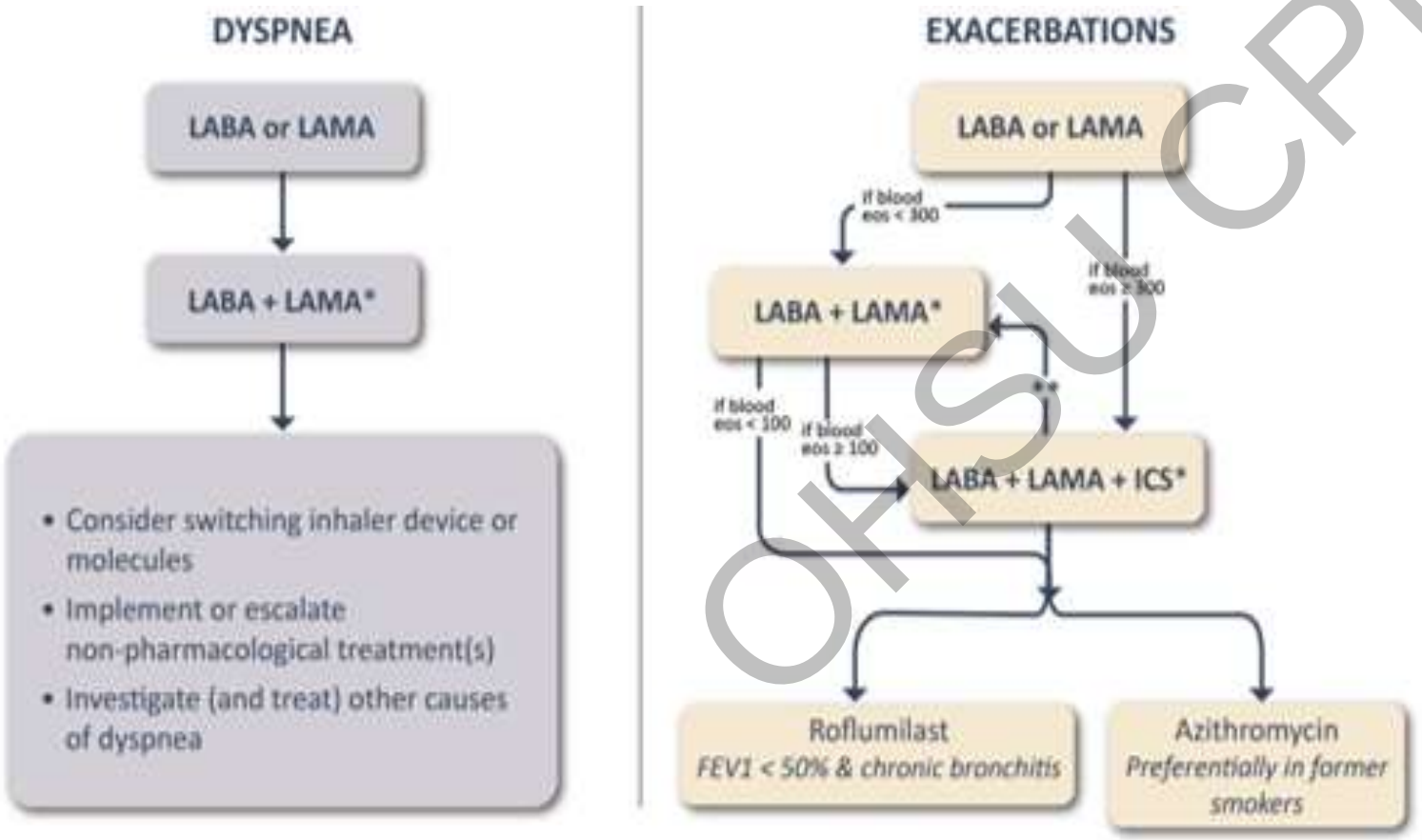
Inhaler technique should be evaluated every 2 months[2]

15% of HCPs are able to demonstrate inhaler proficiency[1,2]

Adherence is significant, if not adherent, don't escalate to ICS

1. HANANIA ET AL., THE ROLE OF INHALATION DELIVERY DEVICES IN COPD: PERSPECTIVES OF PATIENTS AND HEALTH CARE PROVIDERS > JOURNAL OF THE COPD FOUNDATION
2. COPD FOUNDATION

FOLLOW-UP PHARMACOLOGIC TREATMENT



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No ICS on dyspnea Pathway

No ICS/LABA anywhere

GOLD recommends Eos counts to guide escalation, but ATS and VA/DOD do not

POLL QUESTION #4

- Your 65 yo female patient with confirmed COPD (former smoker) was on LAMA/LABA therapy as guidelines would suggest. She presents to your clinic for a post-hospitalization appointment after she was admitted with a severe COPD exacerbation. She was given prescriptions at discharge to finish 5-day courses of antibiotics and corticosteroids, but no changes were made to her inhaler regimen. What would be the best course of action for her maintenance inhaler regimen, at this time?

A. Change to a different LAMA/LABA combination

B. Add ICS so now on triple therapy with ICS/LAMA/LABA **Correct**

C. Add short-acting nebulizers around the clock

D. Refer patient to pulmonology for consideration of advanced therapies

POLL QUESTION #5

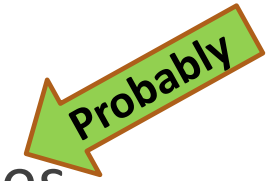
- This same patient was lost to follow-up x 1 year (COPD/former smoker), but she reports good adherence with once daily triple therapy ICS/LAMA/LABA. She states that had 3 exacerbations in the last year (once hospitalized). What would be the best course of action for her treatment at this time?

A. Change ICS/LAMA/LABA to different triple therapy inhaler

B. Start patient on Roflumilast 250mcg daily x 4 weeks, then 500mcg daily

C. Start patient on Azithromycin 250mg once daily

D. Refer patient to pulmonology for consideration of advance therapies



CONSIDERING ADVANCED THERAPIES IN COPD

Roflumilast

Metabolized by CYP3A4
Inc. risk for interactions

- FEV1 < 50% & Chronic Bronchitis
- Frequent exacerbations (≥ 1 hospitalization)
- On optimal dual LABD +/- ICS
- Adverse effects:
  - ●Diarrhea ●Nausea ●Dec. appetite
  - ●Wt. loss ●Abd. Pain ●Sleep disturbance
  - ●Headaches ●Depression/Anxiety/Suic. Ideation

Azithromycin

- Best evidence in former smokers
- On optimal dual LABD +/- ICS
- 250-500mg TIW or 250mg daily
- Adverse effects
  - ●QT prolongation ●Ototoxicity
  - ●Nausea/Diarrhea ●Fungal infxn
  - ●Increased risk for ABX resistance

- UpToDate drug information
- 2024 GOLD Report Page 52
- VA criteria for use - Roflumilast (DALIRESP))

Most guidance documents recommend above medications to be started by pulmonology

POLL QUESTION #6

- Your patient with confirmed COPD returns to your clinic, with the complaint that the LAMA/LABA inhaler you prescribed, does not help their COPD symptoms. You choose to do the following, to help with their symptoms.

A. Escalate inhaled treatment to triple therapy ICS/LAMA/LABA

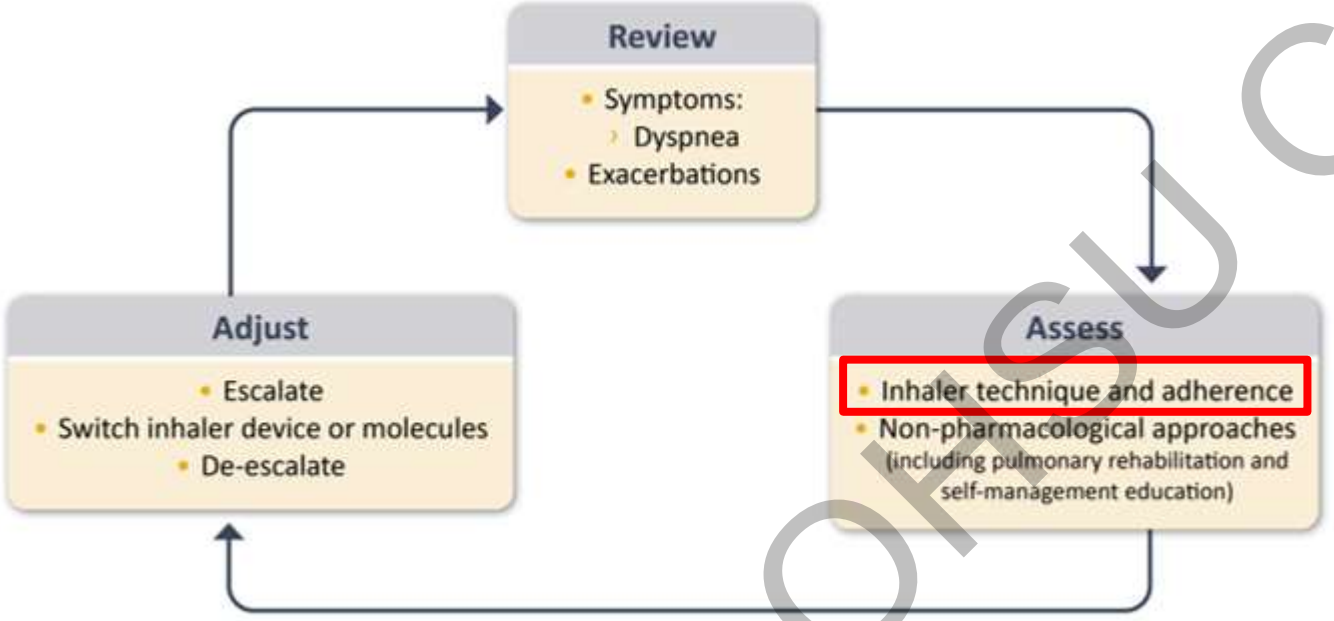
B. Try a different LAMA/LABA inhaler

C. Consider switching LAMA & LABA meds to nebulized solutions

D. Assess/Educate regarding inhaler technique

Correct

IMPORTANCE OF INHALER TECHNIQUE



GOLD – Review regularly
COPD Foundation – Review Q 2 months

Placebo devices could be helpful for demo

YouTube videos can assist with teaching

COPD Foundation app has resources for providers and patients, including videos all inhaler devices

Understand the differences between devices (MDI, DPI, and Soft Mist Inhaler)

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American Lung Association.

Asthma and COPD Medicines

REVIEW OF INHALER TYPES

Metered Dose Inhaler (HFA)

- Must be “primed” first time
- Remove cap & and shake
- Place MDI into spacer device
- Exhale your air, away from MDI
- Place mouthpiece, between teeth, and seal lips around it
- Take a slow deep breath, while pressing down on cannister
- Hold breath x 10 seconds
- Exhale and replace cap, or repeat steps for another dose

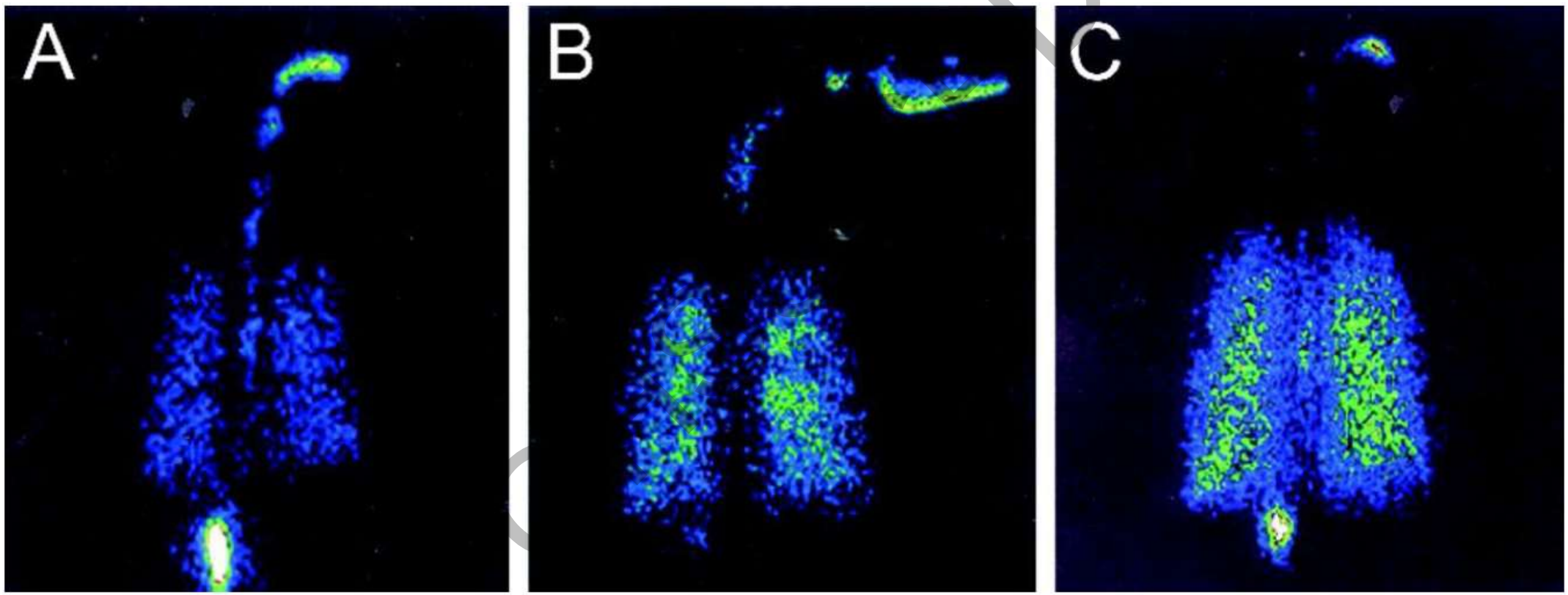
Soft Mist Inhaler (Respimat)

- Must be “primed” first time
- Assemble your SMI device according to instructions
- Using the acronym **T.O.P.**
- **T**urn the base ½ turn; cap on
- **O**pen the cap from mouthpiece
- Place mouthpiece, between teeth, and seal lips around it
- **P**ress dose-release button
- Take a slow deep breath
- Hold breath x 10 seconds
- Exhale and replace cap, or repeat steps for another dose

Dry Powder Inhaler (DPI)

- Some are “pre-loaded” while others you need to load dose
- Load dose when you are ready
- Exhale your air, away from DPI
- Place mouthpiece, between teeth, and seal lips around it
- Breathe in quickly and forcefully through the mouthpiece.
- Be sure not to block any vent holes
- Hold breath x 10 seconds
- Exhale and replace cap, or repeat steps for another dose

EXAMPLES OF MEDICATION DEPOSITION



Pressurized metered dose inhaler

Pressurized metered dose inhaler with spacer

Early Respimat design

J Pharm Sci 1996;85(9);960-964

Some images/info on slides 27-31 courtesy of Ashley McKnight, Pharm.D., Durham VA

POLL QUESTION #7

- Your patient with severe COPD presents to your clinic complaining that the rescue puffer works, but the other one doesn't. He is prescribed albuterol MDI prn and LAMA/LABA dry powder inhaler (DPI). The patient was able to show adequate technique with the MDI but is unable to generate enough inspiratory force use the DPI after multiple attempts. You decide to make the following change:

A. Change to a different DPI in the same classes
B. Change LAMA/LABA meds to nebulizers
C. Change to triple therapy, since he has severe COPD
D. Change LAMA/LAMA to MDI or soft mist inhaler (SMI) **Correct**

WHEN SHOULD PATIENTS GET NEBULIZERS

- **When needed for prn use** (SABA and/or SAMA)

- **When needed for maintenance medications** (LAMA, LABA, & ICS available)
  - Low peak inspiratory flow rate (short duration of inspiration, shallow depth)
  - Elderly and/or with cognitive or visual impairment
  - Diminished manual dexterity
  - Poor coordination/unable to use other inhaler types

A REVIEW OF NEBULIZED DRUG DELIVERY IN COPD. INTJ CHRON OBSTRUC PULMON DIS 2016; 11; 2585-2596

PROS AND CONS WITH NEBULIZERS

- Pros
  - No hand-breath coordination
  - No extra effort during inhalation
  - Patients seem to like it
- Cons
  - Time consuming
  - Expensive
  - Storage requirements
  - Easy to confuse ampules
  - Infection risk (nebulizers not changed/cleaned properly)

A REVIEW OF NEBULIZED DRUG DELIVERY IN COPD. INTJ CHRON OBSTRUC PULMON DIS 2016; 11; 2585-2596

Ngim K, et al. Int J Pharm Compd, 2020; 24(3):242-245

NEBULIZER SOLUTION COMPATIBILITY

Compatibility of Common Aerosolized Medications

	Albuterol	Formoterol	Arformoterol	Levalbuterol	Budesonide	Ipratropium	Revefenacin
Albuterol		IE	IE	IE	C	C	IE
Formoterol	IE		IE	IE	C	C	C
Arformoterol	IE	IE		IE	C	C	IE
Levalbuterol	IE	IE	IE		C	C	IE
Budesonide	C	C	C	C		C	IE
Ipratropium	C	C	C	C	C		IE
Revefenacin	IE	C	IE	IE	IE	IE	

Table 1: Compatibility of aerosolized medications. C indicates compatible. IE indicates inconclusive evidence.[1]

NEBULIZED MEDICATIONS COMPATABILITY; SanoMed Pharmacy

Drug	Doses available	Frequency	Notes
Budesonide (ICS)	250, 500, 1000mcg	Twice daily	Light sensitive
Arfomoterol (LABA)	15mcg	Twice daily	Light sensitive Refrig, room temp x 6 wks
Formoterol (LABA)	20mcg	Twice daily	Light sensitive Refrig. room temp x 90 day
Revefenacin (LAMA)	175mcg	Twice daily	Light sensitive

A REVIEW OF NEBULIZED DRUG DELIVERY IN COPD. INTJ CHRON OBSTRUC PULMON DIS 2016; 11; 2585-2596

Ngim K, et al. Int J Pharm Compd, 2020; 24(3):242-245

KEY MESSAGES

- Use LAMA as initial therapy for COPD patients with symptoms.
- LAMA/LABA for patients w/continued symptoms/exacerbations on LAMA.
- Add ICS to LAMA/LABA if having exacerbations on LAMA/LABA.
- Consider De-escalation of ICS if no exacerbations in the last year.
- Educate on inhaler technique, so patients get the most out of their inhalers.

RESOURCES

- COPD foundation (Inhaler Videos) COPD Inhaler Educational Video Series
  - + app for mobile device (for Providers and Patients)
- GOLD 2024 Global Initiative for Chronic Obstructive Lung Disease
- ATS COPD (thoracic.org)
- VA/DOD COPD Guidelines Management of COPD (VA/DOD)
- VA Academic Detailing (COPD) COPD-Provider-COPDEducationalGuide

THANK YOU!

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