Updates in Asthma

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Financial Disclosures

- Nothing to disclose

Objectives

- Explain the recent GINA and EPR-4 (NAEPP) recommendations concerning combined maintenance and reliver therapy (MART) to patients and prescribers
- Develop a patient care plan that incorporates recent practice changes
- Define severe asthma and describe how it differs from poorly controlled asthma
- Discuss the role in therapy of biologics and non-biologic add-on agents for severe asthma

What is New in Asthma

- Major changes to GINA in 2019
- NAEPP publishes EPR-4 updates in late 2020
- New Boxed warning for montelukast (March 2020)
- New recommendations and medications for severe asthma

NAEPP Guidance and GINA

- National Asthma Education and Prevention Program (NAEPP)
  - Funded by the NHLBI
  - Last full report was EPR-3 in 2007
  - EPR-4 is a focused update
  - EPR-4 is limited to 6 focused topic areas
- Global Initiative for Asthma – GINA
  - Collaborative effort from NIH and WHO
  - Updated annually
  - Comprehensive approach to asthma care

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2021. Available at: www.ginaasthma.org
2020 Focused Updates to the Asthma Management Guidelines. J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270.

Focus of EPR-4 Update

- Topic areas
  - Fractional exhaled nitric oxide (FeNO) in diagnosis, medication selection, and monitoring of treatment response in asthma
  - Remediation of indoor allergens (e.g., house dust mites/pets) in asthma management
  - Adjustable medication dosing in recurrent wheezing and asthma
  - Long-acting antimuscarinic agents in asthma management as add-ons to inhaled corticosteroids
  - Immunotherapy and the management of asthma
  - Bronchial thermoplasty (BT) in adult severe asthma

2020 Focused Updates to the Asthma Management Guidelines. J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270.

Defining asthma

- NAEPP still utilizes "intermittent" asthma as a grouping
  - Characterization remains unchanged since 2007 guidelines
  - Symptoms less than twice weekly
- GINA starts at mild asthma
  - Symptoms less than twice monthly
  - Characterizes severity by therapy required to obtain control

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Case 1

- MH is a 23-year-old female with mild asthma. She is currently prescribed low-dose fluticasone BID with PRN albuterol. She states that she uses the albuterol 2-3 times per week. Refill records indicate that she fills her fluticasone inhaler approximately every 3 months. Would she be an appropriate candidate for PRN BUD/FOR therapy?

Major Change for Asthma Care

- Introduced no SABA only therapy for mild asthma in GINA 2019
  - Forceful in recommendations
  - All patient should receive ICS
- Introduction of PRN ICS-formoterol as reliver
- SMART/MART therapy for STEPS 3-5
  - Single Maintenance and Reliver Therapy
- EPR-4
  - Literature review prior to PRN ICS-formoterol data in late 2018
  - Endorses SMART therapy for STEPS 3-4
  - Conditionally recommends PRN ICS and SABA for STEP 2 (12+ years)
  - SABA only remains for STEP 1

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Wait, PRN ICS? Is that really a thing? What is MART?

PRN ICS + reliever

- Ideally a combination inhaler PRN
- MUST contain ICS
- ICS-formoterol specified in GINA
- Why formoterol?
  - Available in combination with ICS
  - Suitable as reliever – fast onset
- Can I use albuterol?
  - Sure can
  - Take ICS when use albuterol
  - Two inhalers
  - EPR-4 regimen

S/MART

- Use of same inhaler for controller and reliever
- MUST contain ICS
- Vast majority of studies use ICS-formoterol, mostly budesonide
- Why formoterol?
  - Available in combination with ICS
  - Suitable as controller – long duration
  - Suitable as reliever – fast onset
- Can I use albuterol?
  - Nope, not as a controller
  - Could use as reliver in standard regimen

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GINA – Rationale for Change

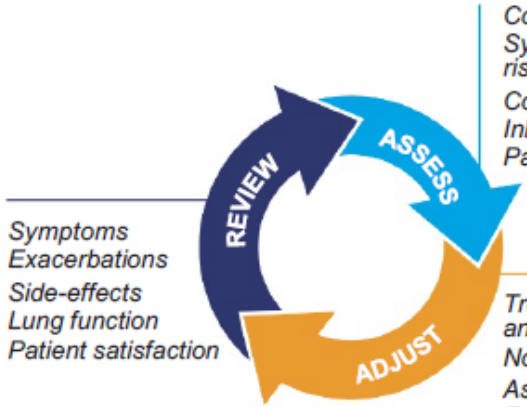
- Over-use of SABA associated with increased risk of death
- ICS known protective effect and improved QOL
- Adherence to ICS is low (25-35%)
- Messaging to patients in Step 1 vs Step 2 (symptom relief vs asymptomatic daily therapy)
- Formoterol widely available with ICS, SABA not

Eur Resp J 2019;53:1901046

Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review
for individual patient needs



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down/up/between tracks)
Education & skills training

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	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
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	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	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				

Other controller options for either track

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects*

Figure I.d: Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
Treatment	**STEP 1**	**STEP 2**	**STEP 3**	**STEP 4**	**STEP 5**	**STEP 6** ■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

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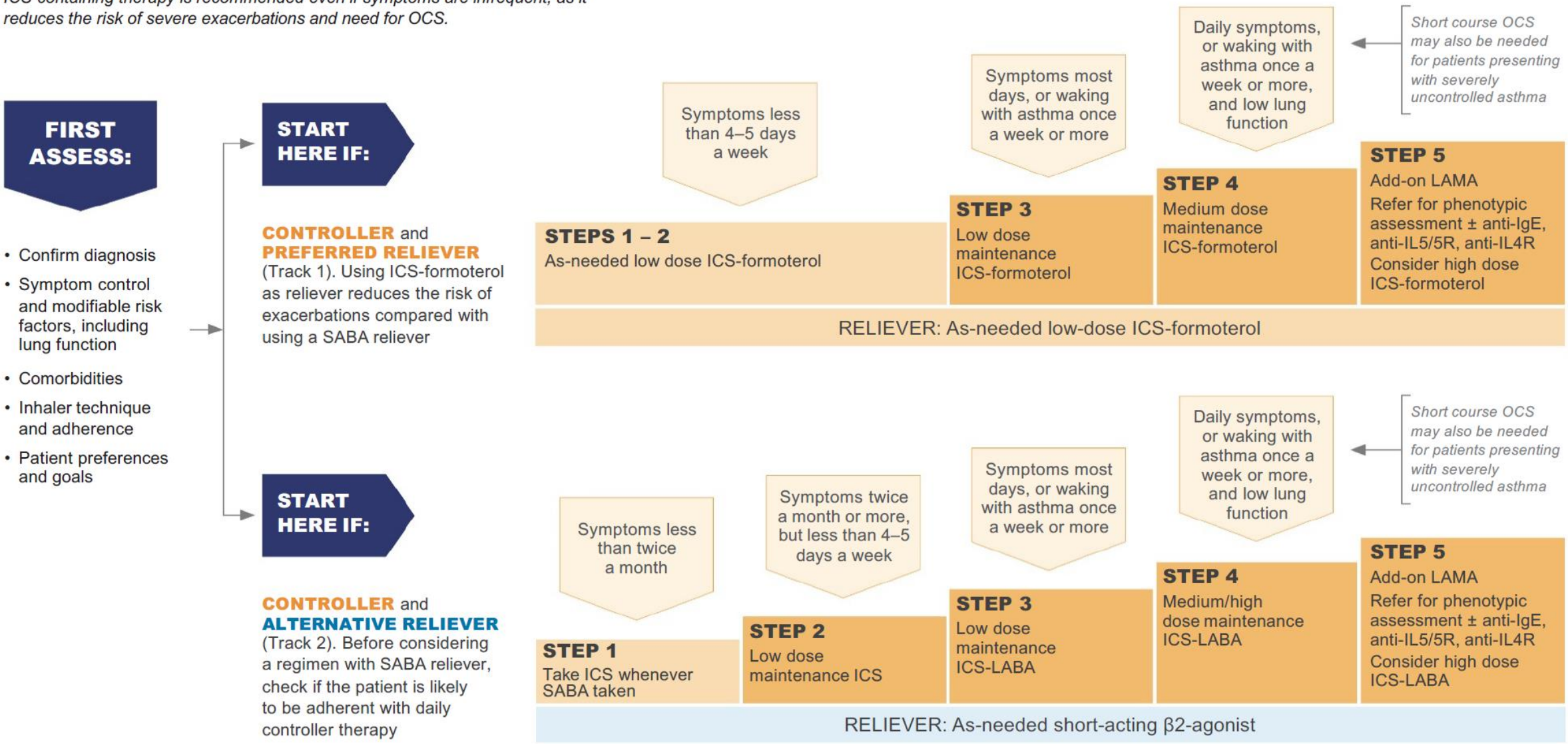
STARTING TREATMENT

in adults and adolescents with a diagnosis of asthma

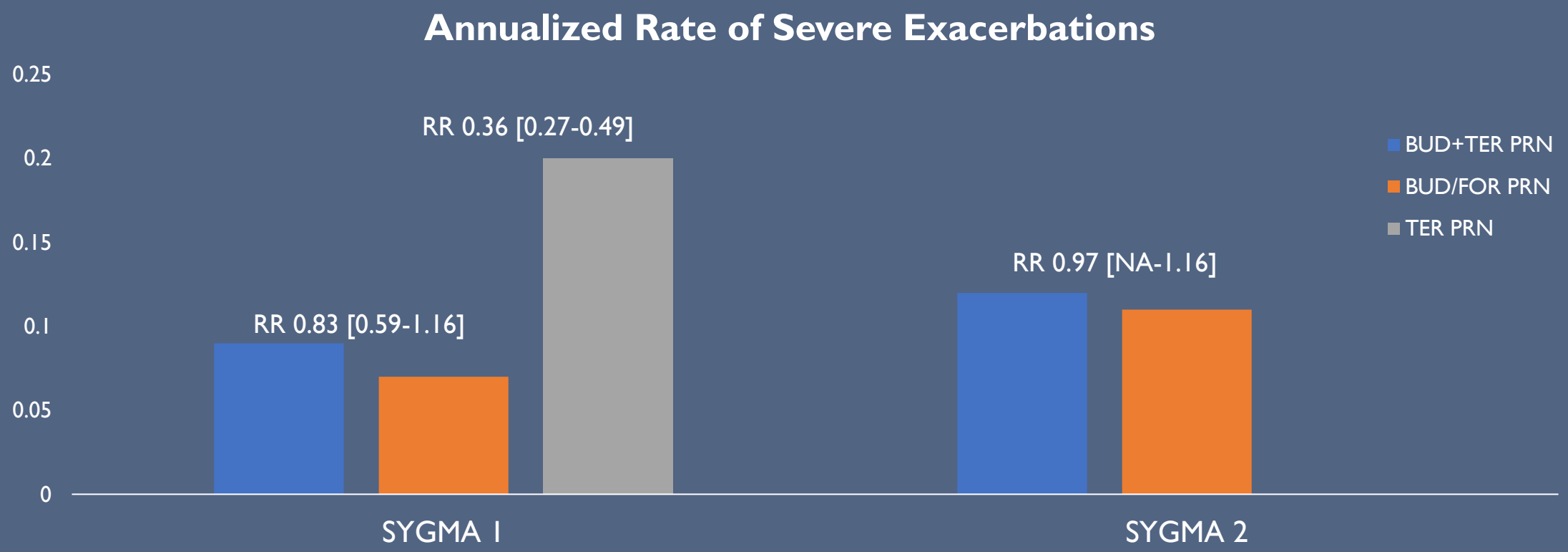
Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS.



Evaluation of Evidence for GINA STEPS 1-2

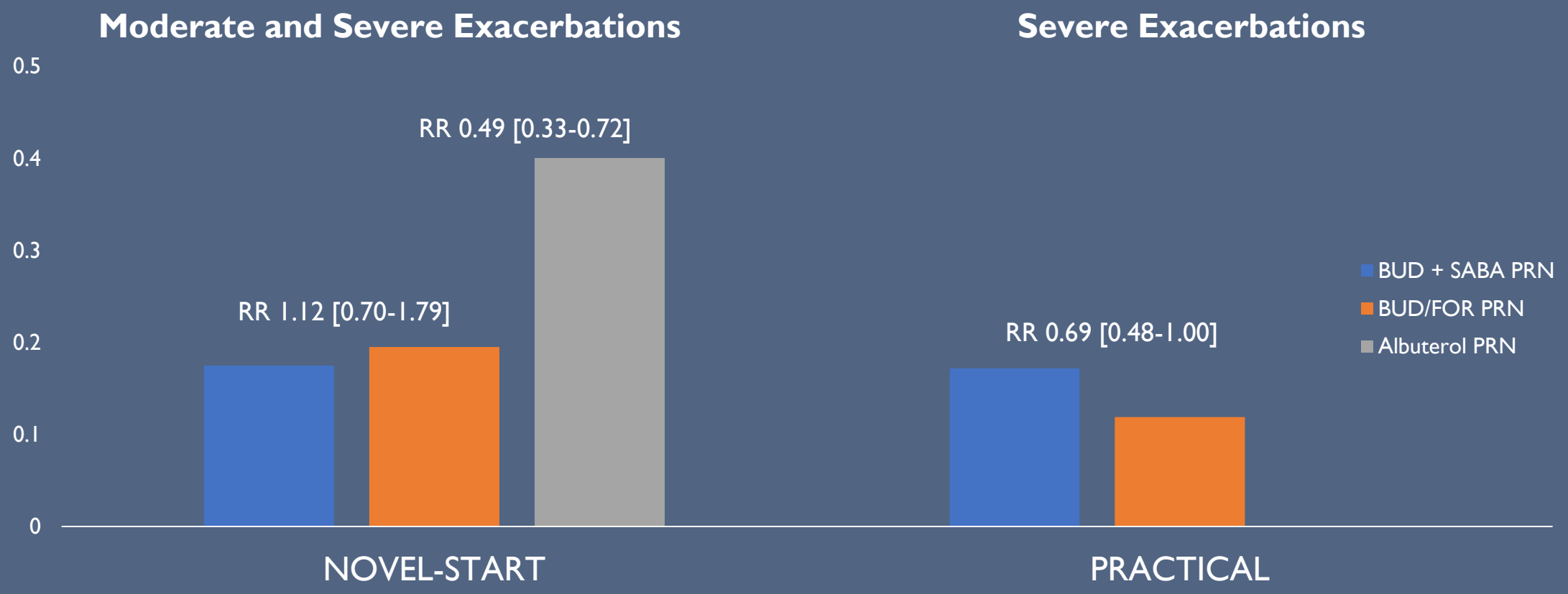
- Outcomes of interest
  - Frequency of severe exacerbations
  - Measures of asthma control
  - Corticosteroid exposure
  - Adherence to daily ICS

Rate of Severe Exacerbations - SYGMA Trial Program



SYGMA 1 N Engl J Med 2018;378:1865
SYGMA 2 N Engl J Med 2018;378:1865

Rate of Exacerbations – Pragmatic Trials



Novel-START: N Engl J Med 2019;380:2020
PRACTICAL: Lancet 2019;394:919

Symptom Control

Trial	ACQ Mean Difference [95% CI]*	
	BUD/FOR vs. BUD	BUD/FOR vs. SABA
SYGMA 1	0.15 [0.10 to 0.20]	-0.15 [-0.20 to -0.11]
SYGMA 2	0.11 [0.07 to 0.15]	NA
NOVEL-START	0.14 [0.05 to 0.23]	-0.15 [-0.24 to -0.06]
PRACTICAL	0.06 [-0.005 to 0.12]	NA

*Minimally important change in ACQ score is a reduction of 0.5

SYGMA 1 N Engl J Med 2018;378:1865
SYGMA 2 N Engl J Med 2018;378:1865
Novel-START: N Engl J Med 2019;380:2020
PRACTICAL: Lancet 2019;394:9

Exposure to Systemic Corticosteroids

Trial	Reporting Method	BUD/FOR	BUD	SABA
SYGMA 1	Total days with CS	465 days	500 days	1237 days
SYGMA 2	Median days with CS	6 days	6 days	NA
NOVEL-START	Mean prednisone use	7.5 mg	14.5 mg	17.4 mg
PRACTICAL	Percentage prescribed CS for ≥ 3 days	78%	72%	NA

SYGMA 1 N Engl J Med 2018;378:1865
SYGMA 2 N Engl J Med 2018;378:1865
Novel-START: N Engl J Med 2019;380:2020
PRACTICAL: Lancet 2019;394:9

Adherence to Daily ICS

Trial	Mean Percentage of Doses Taken (SD)
SYGMA 1	79 (22)
SYGMA 2	63 (29)
NOVEL-START	56 (NR)
PRACTICAL	76 (NR)

- Real-world adherence rates reported closer to 35% for daily ICS

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SYGMA 2 N Engl J Med 2018;378:1865
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Case 1

- MH is a 23-year-old female with mild asthma. She is currently prescribed low-dose fluticasone BID with PRN albuterol. She states that she uses the albuterol 2-3 times per week. Refill records indicate that she fills her fluticasone inhaler approximately every 3 months. Would she be an appropriate candidate for PRN BUD/FOR therapy?
- What if she refilled her fluticasone regularly and only used her albuterol 2-3 times per month?

EPR-4 Recommendations

- Keep SABA monotherapy option for STEP 1
- STEP 2 – two preferred options
  - Traditional ICS controller with SABA reliever
  - PRN concomitant ICS and SABA
- STEP 3 and 4 – Preferred option is MART
  - STEP 3 – daily and PRN low-dose ICS-formoterol
  - STEP 4 – daily and PRN medium-dose ICS-formoterol

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Evidence for MART

- MART with ICS-formoterol reduces risk of severe exacerbations compared to regimens with SABA reliver
  - Example: fluticasone/salmeterol twice daily + albuterol PRN
- MART reduces severe exacerbations compared
  - Same dose ICS-LABA
  - Higher dose ICS-LABA
- MART led to significant reductions is corticosteroid use
- No effect on asthma QOL or asthma control

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Managing Worsening Asthma

Considering a temporary increase in controller therapy

Case 2

- PH is on MART therapy with ICS-formoterol and is experiencing a “flare-up” of his asthma. He checks his action plan and notices he is in the yellow zone. How should he manage this situation?

Recommendations

GINA 2021

- Recommends a short increase in maintenance therapy – differs based on controller
- Does not recommend short course of ICS with URI

EPR-4

- Children 0-4 who wheeze with URI, start short course of ICS with SABA at onset of URI symptoms
- Recommends against short-term increase of ICS in patients 4 years and older for worsening asthma

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GINA Increases in Controller

Usual medication regimen	1 – 2 week change for worsening asthma
Maintenance + reliever ICS-formoterol	Continue maintenance ICS-formoterol and increase reliever ICS-formoterol PRN
Maintenance ICS with SABA as reliever	Adults and adolescents: quadruple maintenance ICS dose
Maintenance ICS-formoterol with SABA as reliever	Quadruple maintenance ICS-formoterol
Maintenance ICS + other LABA with SABA as reliever	Step up to higher dose formulation of ICS + other LABA Adults: consider adding separate ICS inhaler to quadruple ICS dose

- Maximum recommended daily dose of formoterol is 54 mcg – 12 puffs of budesonide-formoterol

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2021. Available at: www.ginaasthma.org

Studies Evaluating Increase in Controller

- Quadruple dose of ICS
  - Adolescents and adult patients
  - Severe exacerbations reduced with intensified controller regimen
  - Increased time to first severe exacerbation, first use of OCS, and first unscheduled healthcare consultation
  - Increased rates of thrush with intervention
- Quintupling of ICS
  - Children 5-11 years
  - No significant difference in rate of severe exacerbations, treatment failure, albuterol use or symptom scores
  - Highly adherent population with maintenance ICS

N Engl J Med 2018;378:891-901
N Engl J Med 2018;378:902-10

Case 2

- PH is on MART therapy with ICS-formoterol and is experiencing a “flare-up” of his asthma. He checks his action plan and notices he is in the yellow zone. How should he manage this situation?

Wheezing with URI (0-4 years)

- Intermittent ICS with SABA reduced risk of exacerbations needing systemic corticosteroids by 33% compared to SABA alone
- No impact on acute care visits
- No impact on asthma-related hospitalizations
- Conditional recommendation in EPR-4
- GINA states it may be useful, but cautions against widespread use

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FDA boxed warning for montelukast

- Boxed warning added for serious mental health side effects
  - Examples: agitation, attention problems, vivid dreams, depression, anxiety, irritability, memory problems, suicidal actions, tremor
- Earlier communication/warnings indicated risk (2008-2009)
- Boxed warning increases awareness of risk
- FDA Sentinel study did not find greater risk of mental health side effects compared to ICS
- Should not be first-line therapy as alternatives more effective

ICS: inhaled corticosteroids

FDA Drug Safety Communication March 4, 2020. Available from: www.fda.gov

Severe Asthma

Severe Asthma – Defined

- Severe asthma – uncontrolled despite adherence with high-dose ICS-LABA treatment, or worsens when high-dose treatment is decreased
- It is not
  - Uncontrolled asthma
    - Poor symptom control, frequent exacerbations
  - Difficult-to-treat asthma
    - Uncontrolled despite prescribing medium or high-dose ICS-LABA or that requires high-dose to maintain control
    - Modifiable risk factors uncorrected (inhaler technique, adherence, smoking, comorbidities)
- ATS/ERS – similar definition

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Management of Severe Asthma: A ERS/ATS guideline. Eur Respir J 2020;55:1900588

GINA Decision Tree for Difficult-to-Treat Asthma

- Confirm diagnosis
- Identify factors contributing to poor symptoms
- Optimize management
- Review response after 3-6 months
- Assess severe asthma phenotype
  - Is type 2 inflammation present?
  - Is type-2 biologic available or affordable?
- Consider add-on biologic type 2 targeted treatments

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Type 2 Inflammation

- Classic inflammatory phenotype of asthma
- Characterized by
  - Eosinophilia
  - Increased FeNO
  - Allergen driven
  - Responds well to ICS
- Cytokines
  - IL-4, IL-5, and IL-13 predominate
  - Targets for newer biologics
- Type 2 inflammation necessary for newer agents

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Type 2 inflammation

- Are any of the following present during high-dose ICS therapy?
  - Blood eosinophils ≥150 cells/μL
  - FeNO ≥20 ppb
  - Sputum eosinophils ≥2%
  - Allergen driven
  - Need for maintenance OCS
- If present and adherent to therapy consider biologic therapy for severe asthma

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Biologic Options

Class/MOA	Agent	Age	Indication	Eligibility	Predictors of good response
Anti-IgE	Omalizumab	6+	Add-on for ***severe allergic asthma***	• Sensitization to inhaled allergen • Total serum IgE and body weight within dosing range • Repeated exacerbations	• Blood EOS ≥260/µL • FeNO ≥20 ppb • Allergen driven symptoms • Childhood onset
Anti-IL-5/IL-5R	Mepolizumab	6+	Add on for ***severe eosinophilic asthma***	• Repeated exacerbations • Blood EOS above locally specified levels (e.g., serum eosinophils 150-300/µL or more)	• Higher blood EOS • More exacerbations in previous year • Adult-onset • Nasal polyposis
	Reslizumab	18+			
	Benralizumab	12+			
Anti-IL-4R	Dupilumab	12+	Add on for ***severe eosinophilic asthma OR OCS dependent***	• Repeated exacerbations • Blood EOS ≥150/µL OR FeNO ≥25 ppb • Maintenance OCS	• Higher blood EOS • Higher FeNO

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Example Criteria for Omalizumab (BCBS AL)

Moderate-to-severe persistent allergic asthma † [1-3,20]

- Patient is at least 6 years of age; **AND**
- Will not be used for treatment of acute bronchospasm, status asthmaticus, or allergic conditions (*other than indicated*); **AND**
- Patient has a positive skin test or in vitro reactivity to a perennial aero-allergen; **AND**
- Patient must weigh between 20 kg (44 lbs.) and 150 kg (330 lbs.); **AND**
- Patient has a serum total IgE level, measured before the start of treatment, of either:
  - ≥ 30 IU/mL and ≤ 700 IU/mL in patients age ≥ 12 years; **OR**
  - ≥ 30 IU/mL and ≤ 1300 IU/mL in patients age 6 to <12 years; **AND**
- Patient has documented ongoing symptoms of moderate-to-severe asthma* with a minimum (3) month trial on previous combination therapy including medium- or high-dose inhaled corticosteroids **PLUS** another controller medication (e.g., long-acting beta-2 agonist, leukotriene receptor antagonist, theophylline, etc.); **AND**
- Baseline measurement of at least one of the following for assessment of clinical status:
  - Use of inhaled rescue medication
  - Use of inhaled or systemic corticosteroids
  - Reported disease severity symptoms (e.g., number of hospitalizations, ER visits, unscheduled visits to healthcare provider due to condition, asthma attacks, chest tightness or heaviness, coughing or clearing throat, difficulty taking deep breath or difficulty breathing out, shortness of breath, sleep disturbance, night wakening, or symptoms upon awakening, tiredness, wheezing/heavy breathing/fighting for air, etc.)
  - Forced expiratory volume in 1 second (FEV_1)

https://www.bcbsal.org/web/pharmacy/guidelines.html

Non-biologic Add-on Therapy

- Primary options are LAMA and azithromycin
- Add-on LAMA
  - STEP 5 in GINA and EPR-4
  - ATS/ERS recommend adding in patients with uncontrolled asthma despite GINA/NAEPP STEP 5 therapy
- Add-on macrolide
  - GINA recommends it only in those not responding to standard treatment
    - Cautions against resistance
  - ATS/ERS recommends a trial to reduce exacerbations in persistently symptomatic patients, but against chronic use

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Self-assessment question 1

- Which of the following is an example of MART therapy?
  A. As needed ICS-LABA
  B. Twice daily ICS with as needed SABA
  C. Twice daily ICS-LABA and as needed formoterol
  D. Twice daily ICS-formoterol and as needed ICS-formoterol

Self-assessment question 2

- Which of the following agents is the anti-IL-4R antibody?
  A. Omalizumab
  B. Dupilumab
  C. Reslizumab
  D. Benralizumab

Self-assessment question 3

- For what age group does the NAEPP recommend intermittent ICS at the onset of URI?
  A. 0-4
  B. 5-11
  C. 12 and older