Newer Approaches to Asthma Treatment, Selection, and Assessment

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Disclosures

- **Barbara Yawn, MD, MSc, FAAFP** discloses that she serves as a consultant for AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, and TEVA. She is on advisory boards related to asthma for AstraZeneca and has received travel grants for adult vaccine presentations from GlaxoSmithKline.

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Learning Objectives

At the end of this presentation, participants will be able to…

Incorporate AIR and SMART into their asthma therapies based on patient characteristics, clinical evidence, and guidelines.

Prevent asthma exacerbations requiring systemic corticosteroids.

Start or refer for biologic therapies in appropriate patients.

Be alert for new evidence on asthma remission concepts and use of **Azithromycin** for asthma management.

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Asthma overview:

- Role of primary care
- Definition
- Classifications
- Common complications
- Diagnostic process

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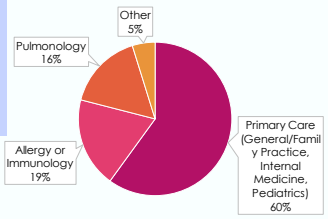
Asthma – The Role of Primary Care

60% of all asthma visits are in primary care

- The majority of patients with asthma can successfully be managed by Family Physicians



Akinbami LJ, et al. *Natl Health Stat Report*. 2019;128:1-20. Wu TD, et al. *Med Clin North Am*. 2019;103(3):435-452.

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Asthma is:

- Chronic lung disease
- Can start at any age
- Includes wheezing, cough, dyspnea, activity limitations
- Primarily inflammatory but also bronchospasm
- Heterogenous
- Variable symptoms over time
- Variable airflow limitation over time

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Available from: www.ginasthma.org

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Asthma classifications: Based on symptom frequency

- **Intermittent**: The symptoms noted by the patient come and go, so patients may not believe they need chronic treatment. (Not recognized by GINA)
- **Persistent**: The symptoms are noticed by the patient most of the time but are still likely to be variable over time.
  - **Mild**
  - **Moderate**
  - **Severe**

Asthma can also be described by phenotypes.
Allergic (Th-2 high), Non-allergic (Th-2 low), Eosinophilic, Neutrophilic, Exercise-induced, Aspirin-induced and Occupational related.

Cloutier MM, et al. *J Allergy Clin Immunol.* 2020;146(6):1217-1270; Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Available from: www.ginasthma.org

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Complications of Asthma:

Complications in children	Common to both	Complications in adults
Growth delay	Permanent narrowing of bronchial tubes	Frequent sick days from work
Higher risk for learning disabilities	Medication side effects	Higher risk for depression
	Emergency room visits	
	Higher risk of obesity	

National Health Service (NHS). Asthma Overview. Reviewed April 19, 2021. Accessed October 12, 2023. https://www.nhs.uk/conditions/asthma/

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Asthma Diagnostic Process

- **Medical History Assessment:**
  - Coughing, wheezing, and shortness of breath. Family history and potential triggers.
- **Physical Examination:**
  - Breath sounds
  - Allergic conditions like eczema or hay fever.
- **Lung Function Tests:**
  - Spirometry to assess airflow and reversibility
- **Additional Tests:**
  - Allergy testing (blood or skin)
  - Imaging (X-ray or CT scan)
  - FeNO for allergic inflammation
- **Confirmation of Asthma Diagnosis:**
  - History
  - Physical examination
  - Reversible airflow obstruction.
- **Asthma Severity/Control Assessment:**
  - Guides treatment decisions

Cloutier MM, et al. *J Allergy Clin Immunol.* 2020;146(6):1217-1270; Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Available from: www.ginasthma.org

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Asthma management/care:

- Guideline summaries
  - GINA
  - NAEPP 2020 update
- AIR
- MART
- Exacerbations
- Risks of systemic corticosteroids

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Managing Asthma in Primary Care

International guidance: 2024 GINA; US Guidelines: NAEPP 2020

- Major components of asthma management:
  - Confirm diagnosis
  - Aim for symptom control and prevention of exacerbations
    - Maintenance Rx
      AND
    - Quick reliever/rescue Rx
  - Life style changes
  - Assess and manage co-morbidities
  - Teach and review inhaler technique
  - Assess adherence
  - Address patient and family preferences and goals.

GINA, Global Initiative for Asthma; NAEPP, National Asthma Education and Prevention Program

Cloutier MM, et al. *J Allergy Clin Immunol.* 2020;146(6):1217-1270. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Available from: www.ginasthma.org

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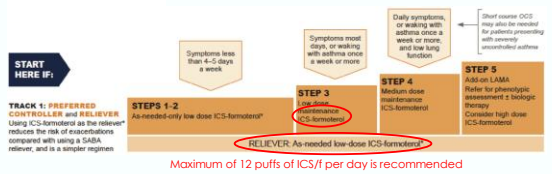
GINA Treatment Approach – Track 1

MART—formerly SMART



Maximum of 12 puffs of ICS/f per day is recommended

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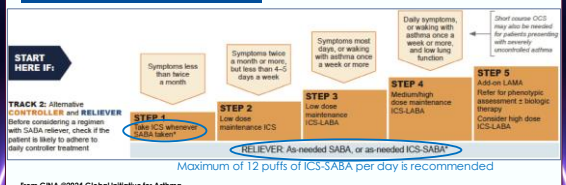
GINA Treatment Approach – Track 2

AIR—using ICS with quick reliever/rescue



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Why MART or AIR Patient Perspectives to Improve Adherence.

- **INSPIRE – 3415 adults with asthma asked about their perceptions of treatment[4]**
  - Most patients (90%) wanted treatments that work quickly
  - About 74% used a SABA daily despite being prescribed maintenance therapy
  - 38% thought they didn't need to take asthma medication daily when they were feeling well
- **Patients often prefer symptom-driven treatment, creating a paradox**
  - Historically, SABA-only rescue therapy has been the main symptom-driven treatment
  - Does not help decrease exacerbations if used without ICS

1. Guevara JP, *et al. BMJ.* 2003;324(7402):1308-1309. 2. Gibson PG, *et al. Cochrane Database Syst Rev.* 2003;1:CD001117. 3. Wilson SR, *et al. Am J Respir Crit Care Med.* 2010;181(6):566-577. 4. Partridge MR, *et al. BMC Pulm Med.* 2009;6:13.

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The Importance of ICS: Rescue/Reliever Therapy

ICS have both nongenomic and genomic anti-inflammatory effects

- Both contribute to lowering airway inflammation related to an exacerbation

Nongenomic Effects (Rapid onset – seconds to minutes)	Genomic Effects (Delayed onset – 4–24 hours)
Decreased airway mucosal blood flow	Increased transcription of anti-inflammatory genes
Decreased airway edema	Decreased transcription of inflammatory genes
Immune cell activity modulation	
Potentiation of bronchodilator effects	

Panettieri RA, *et al. Trends Pharmacol Sci.* 2019;40(1):38-49. Alangari AA. *Ann Thorac Med.* 2010;5(3):133-139.

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The Role of MART--ICS + fasting acting LABA

Budesonide-formoterol fixed dose combination studies

- Across asthma severities
- Compared with PRN SABA, budesonide-formoterol as maintenance and rescue or as rescue alone:
  - Reduced ICS exposure
  - Better symptom control
  - Improved lung function
- Collectively, trials demonstrate reductions in asthma exacerbations with PRN budesonide-formoterol compared to PRN SABA alone

Formoterol is considered a LABA; however, onset of action is within 3 minutes, similar to SABAs

Budesonide-formoterol is not currently FDA-approved for PRN use in the US

O'Byrne PM, et al. *N Engl J Med*. 2018;378(20):1865-1876. O'Byrne PM, et al. *Lancet Respir Med*. 2021;9(2):149-158. Bateman ED, et al. *N Engl J Med*. 2018;378(20):1877-1887. O'Byrne PM, et al. *Am J Respir Crit Care Med*. 2005;171(2):129-136. Scicchitano R, et al. *Curr Med Res Opin*. 2004;20(9):1403-1418. Rabe KF, et al. *Chest*. 2006;129(2):246-256. Kuna P, et al. *Int J Clin Pract*. 2007;61(5):725-736. Beasley R, et al. *N Engl J Med*. 2019;380(21):2020-2030.

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Select (MART) budesonide-formoterol studies

SYGMA Trials (mild asthma)

SYGMA 1
- 65% reduction in annualized exacerbation rate compared to PRN terbutaline
- Equally effective as budesonide maintenance therapy for preventing exacerbations
- Post-hoc analysis: a single day of treatment with ≥2 PRN inhalations of budesonide-formoterol reduced short-term risk of severe exacerbations

SYGMA 2
- Equally effective compared to budesonide maintenance therapy for preventing exacerbations
- 75% reduction of inhaled corticosteroid exposure

MART uses budesonide-formoterol or mometasone-formoterol.

Neither combination is FDA approved for MART.

O'Byrne PM, et al. *N Engl J Med*. 2018;378(20):1865-1876. O'Byrne PM, et al. *Lancet Respir Med*. 2021;9(2):149-158. Bateman ED, et al. *N Engl J Med*. 2018;378(20):1877-1887.

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ICS + SABA or **AIR** Studies

PREPARE Trial (moderate to severe asthma)

1400+ Black or Hispanic Adults

Randomly assigned to:
- ICS + SABA for rescue plus usual maintenance therapy (AIR)
  or
- SABA alone for rescue plus usual maintenance

Patients who used AIR had a **lower annualized rate of severe exacerbations** than the control group
(HR 0.85; 95% CI 0.72–0.999; *P* = .048)

Intervention group also had better asthma control and fewer missed days of work, school, and usual activities

Israel E, et al. *N Engl J Med*. 2022;386(16):1505-1518.

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ICS + SABA –AIR Studies

MANDALA Trial (moderate to severe asthma)

3132 **adolescent** and adult with moderate-to-severe asthma

Key patient groups:
- AIR (albuterol 180 mcg + budesonide 160 mcg) plus maintenance
- PRN albuterol 180 mcg plus maintenance

AIR vs SABA only rescue:
- 27% reduction of severe exacerbations (HR 0.73; 95% CI 0.61–0.88)
- Lower mean annualized total dose of SCS (86.2 ± 262.9 mg prednisone equivalents versus 129.3 ± 657.2 mg)
- Improvement in asthma control (ACQ)OR, 1.22; 95% CI, 1.02 to 1.47)
- Improved asthma-related QoL (AQLQ+12; OR, 1.23; 95% CI 1.02–1.48)

Papi A, et al. *N Engl J Med*. 2022;386(22):2071-2083.

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FDA Approval of Albuterol/Budesonide

January 2023

- The FDA approved the combination inhaler albuterol/budesonide "for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older."

- **Strength**: albuterol 90 mcg and budesonide 80 mcg per inhalation
- **Dosing**: 2 inhalations as needed
  - **Maximum dose: 12 inhalations in 24 hours**

Airsupra [Package Insert]. Updated January 2023, accessed November 13, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214070s000lbl.pdf. US Food & Drug Administration. FDA approves drug combination treatment for adults with asthma. Updated January 11, 2023, accessed November 13, 2023. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-combination-treatment-adults-asthma

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Biologics for asthma

	OMALIZUMAB (XOLAIR)	MEPOLIZUMAB (NUCALA)	BENRALIZUMAB (FASENRA)	RESLIZUMAB (CINQAIR)	DUPILUMAB (DUPIXENT)	TEZEPELUMAB-EKKO (TEZSPIRE)
Molecule/ Target	IgE/Anti-IgE monoclonal antibody	IL-5/Anti-IL-5 monoclonal antibody	IL-5 receptor/ Anti-IL-5 receptor monoclonal antibody	IL-5/Anti-IL-5 monoclonal antibody	IL-4 and IL-13/ Anti-IL-4R alpha monoclonal antibody	TSLP/Anti-TSLP monoclonal antibody
Age Approved for Asthma Indication	6+	6+	6+	18+	6+*	12+
Asthma Indication	Moderate-to-severe persistent asthma and + positive skin test or in vitro reactivity to a perennial aeroallergen (allergic asthma)	Severe eosinophilic asthma	Severe eosinophilic asthma	Severe eosinophilic asthma	Moderate-to-severe eosinophilic asthma and OCS-dependent asthma	Severe asthma
Mode of Administration	Subcutaneous injection (shot)	Subcutaneous injection (shot)	Subcutaneous injection (shot)	Intravenous infusion (IV)	Subcutaneous injection (shot)	Subcutaneous injection (shot)
Setting of Administration	Clinic or home	Clinic or home	Clinic or home	Clinic	Clinic or home	Clinic or home
Dosing Interval	Every two to four weeks	Every four weeks	Every four weeks for the first 3 doses, and then every 8 weeks thereafter	Every four weeks	Every one to four weeks	Every four weeks

Abbreviations used: immunoglobulin E (IgE), interleukin (IL), oral corticosteroids (OCS), thymic stromal lymphopoietin (TSLP)

Up to 30% of user change biologics at least once

Most common reasons:
- Insurance/costs 12.8%
- Failure to respond/adhere 6.4%
- Side effects 2.1%

Lopez M, White A. Switching biologics for asthma. Ann Allergy Asthma Immunol. 2022 Nov;129(5 Suppl S1):121. doi:10.1016/j.anai.2022.08.643

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Real world data for biologics

- **Omalizumab**[1]
  - Exacerbations decreased by 33.6%, overall OCS use decreased 20.3%
- **Mepolizumab**[2]
  - Exacerbations decreased by 38%, OCS use decreased 8%
- **Benralizumab**[3]
  - Exacerbation decreased by 55%, OCS use decreased by 40%
- **Mepolizumab**[4]
  - Exacerbations decreased by 38%, OCS use decreased 8%
- **Dupilumab**[5]
  - Exacerbation decreased by 44%, OCS reduced by 48%
- **Tezepelumab**
  - Effectiveness study (PASSAGE) – underway

1, Ke X, et al. Clin Ther. 2018 Jul;40(7):1140-1158.e6. 2. Llanos JP et al J Asthma Allergy. 2020 Jan 29;13:77-87. 3. Chung Y et al. Ann Allergy Asthma Immunol. 2022 Jun;128(6):669-676.e6. 4. Pamettieri, Reynold et al. Journal of Allergy and Clinical Immunology, Volume 145, Issue 2, AB26 5. Blaiss M, et al. Ann Allergy Asthma Immunol. 2024 Apr;132(4):463-468.

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Exacerbations:

Managing
Preventing
- Critical time
- Major goal in asthma care

Adverse effects of OCS

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Exacerbations

- **Exacerbations**--**progressive increase in symptoms and decrease in lung function**
  - Change from usual status--requires a change in treatment
- **Symptoms** are a sensitive measure of exacerbation onset
  - Small portion of patients--poor perception of airflow limitation may have significant lung function decline without change in symptoms - consider routine lung function monitoring, as this especially affects patients with a history of near-fatal asthma

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Available from: www.ginasthma.org

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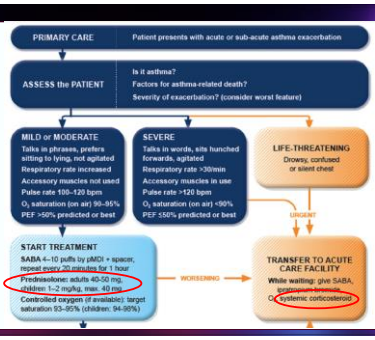
Managing Exacerbations in Primary Care - GINA



O_2, oxygen; PEF, peak expiratory flow

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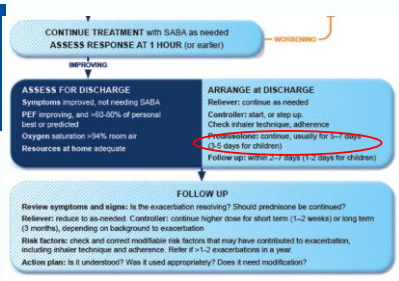
Managing Exacerbations in Primary Care – GINA (cont)



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Better to Prevent Exacerbations

Preventing exacerbations is a key asthma outcome

- Fewer exacerbations leads to:
  - Fewer visits to the emergency department
  - Lower rates of hospitalization
  - Lower mortality rates
  - Improvement in quality of life
  - **Lower exposure to oral/systemic corticosteroids.**
- **Regular ICS (maintenance therapy)** use leads to reductions in exacerbations across asthma severity levels
- **Adding ICS to a fast-acting bronchodilator as rescue or maintenance and rescue** therapy has demonstrated additional benefit

Suissa S, et al. *N Engl J Med*. 2000;343(5):332-336. Adams NP, et al. *Cochrane Database Syst Rev*. 2005;(1):CD002738. Bateman ED, et al. *N Engl J Med*. 2018;378(20):1877-1887. Israel E, et al. *N Engl J Med*. 2022;386:1505-1518. Chipps BE, et al. *BMJ Open Respir Res*. 2021;8(1):e001077.

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Systemic Corticosteroid related Risks:

- **Findings from a US based retrospective cohort study**
- Suggest that each prescription for an OCS results in a cumulative burden on current and future health, regardless of dosage and duration
- The incidence of adverse events appears to increase with each year of exposure
  - Particularly for patients with 4 or more prescriptions of OCS per year (even in case of short-term bursts of OCS use)
  - Results in a greater risk of an adverse effect during the current year

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Systemic Corticosteroids in children

- **Recent reviews show OCS widely prescribed in children**
- 2015, US-based study of 69,000 children with asthma
  - 42% had ≥1 OCS prescription, 10% had ≥2 OCS prescriptions, and 3% had ≥3 OCS prescriptions
- Another US based study reported that 23% of patients with non-severe and 64% of patients with severe asthma were prescribed OCS
- Socioeconomic status is a contributing factor: children with asthma living in poor urban areas tend to have a higher rate of oral corticosteroid use compared to children in other demographics
- OCS AE related to pediatric population: suppression of the HPA axis function can delay growth and puberty; weight gain

Arabkhazaeli A, et al. J Asthma. 2016 Dec;53(10):1012-7., Farber HJ, et al. Pediatrics. 2017 May;139(5):e20164146, Arellano FM, et al. Pediatr Allergy Immunol. 2011 Aug;22(5):469-76. https://www.aispjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A2040, Liu D, et al. Allergy Asthma Clin Immunol. 2013 Aug 15;9(1):30.

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Adverse Effects of SCS: Well-established for Decades

- Short term AEs:
  - Sleep disturbances
  - Risks of infection (pneumonia, sepsis)
  - Peptic ulcers
- Long term AEs
  - Metabolic: obesity, type 2 diabetes
  - CV: hypertension, hypercholesterolemia
  - Bone related: osteoporosis, increased risk of fracture
  - Psychiatric and affective disorders: anxiety and depression, irritation, agitation
  - Other: cataracts, adrenal suppression

Bleecker ER, et al. World Allergy Organ J. 2022 Dec 10;15(12):100726, Sullivan P, et al. J Allergy Clin Immunol. 2018;141:110–116, e7. Bleecker ER, et al. Am J Respir Crit Care Med. 2020 Feb 1;201(3):276-293.

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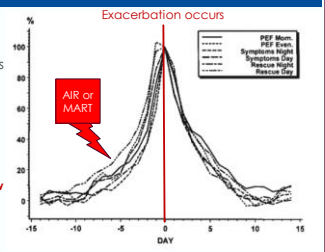
Preventing Exacerbations: The Window of Opportunity

10-14 days before an exacerbation:

- Peak expiratory flow worsens
  - (inverse relationship shown in figure)
- Symptoms increase
- SABA use increases

The time leading up to an exacerbation may offer a window of opportunity to mitigate exacerbation occurrence or severity with anti-inflammatory therapy (ICS)



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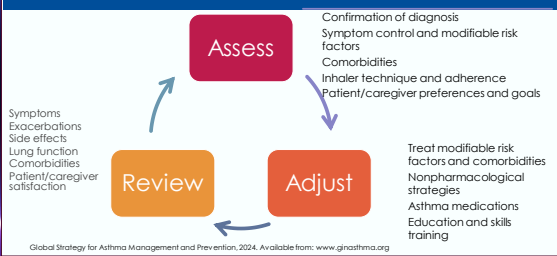
GINA Asthma Management Strategy



Global Strategy for Asthma Management and Prevention, 2024. Available from: www.ginasthma.org

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"Advances":

- Control score that assess burden and risk
- Asthma remission
- Role for Azythromycin therapy
- Newer biologic---longer acting

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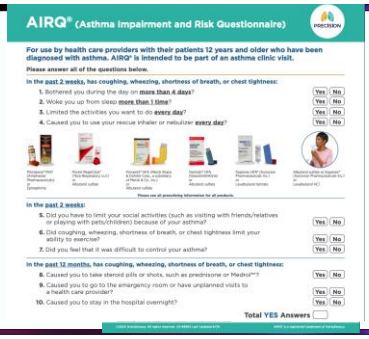
AIRQ, a validated tool to assess symptoms and exacerbation risk



AIRQ® (Asthma Impairment and Risk Questionnaire)

For use by health care providers with their patients 12 years and older who have been diagnosed with asthma. AIRQ® is intended to be part of an asthma clinic visit.

Please answer all of the questions below.

In the past 2 weeks, has coughing, wheezing, shortness of breath, or chest tightness:

1. Bothered you during the day on more than 4 days? Yes / No
2. Woke you up from sleep more than 1 time? Yes / No
3. Limited the activities you want to do every day? Yes / No
4. Caused you to use your rescue inhaler or nebulizer every day? Yes / No

In the past 2 weeks:

5. Did you have to limit your social activities (such as visiting with friends/relatives or playing with pets/children) because of your asthma? Yes / No
6. Did coughing, wheezing, shortness of breath, or chest tightness limit your ability to exercise? Yes / No
7. Did you feel that it was difficult to control your asthma? Yes / No

In the past 12 months, has coughing, wheezing, shortness of breath, or chest tightness:

8. Caused you to take steroid pills or shots, such as prednisone or Medrol®*? Yes / No
9. Caused you to go to the emergency room or have unplanned visits to a health care provider? Yes / No
10. Caused you to stay in the hospital overnight? Yes / No

Total YES Answers

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AIRQ scoring and linked to tools.

AIRQ. Accessed November 13, 2023. Available from: https://www.asthmaresourcecenter.com/home/for-your-practice.html

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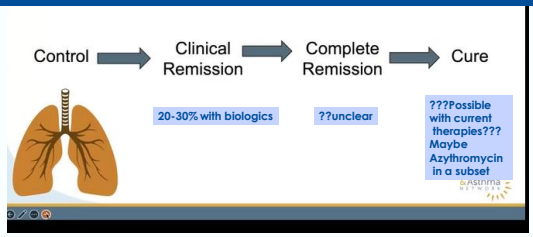
Possible progression in asthma????



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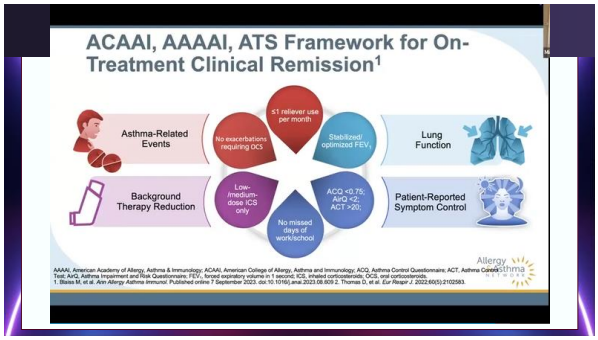

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Remission rates are low even on therapy

- A concept in motion
- Exact criteria not agreed upon
- All agree---no systemic corticosteroids in at least 12 months
- Excellent asthma and stable lung function (??normal) are basis
- Remission occurs in children but many relapse in adulthood
- Biologics only give 20-30% remission on therapy
- Early observation data suggests remission off therapy may occur in adults

- Badhel M et al. J Allergy Clin Immunol. 2020;145(3):757-765.

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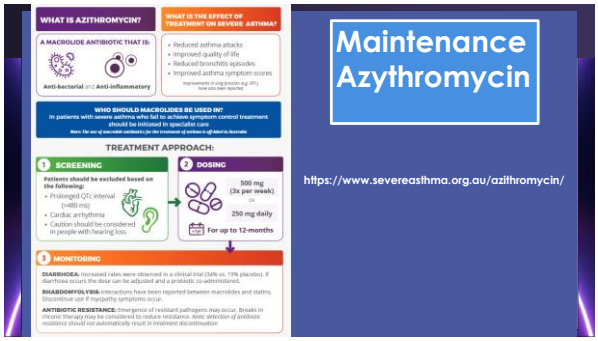

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Longer acting biologic for severe asthma:

▶Depemokimab

- Affinity for IL-5
- Lasts up to 6 months
- Met outcome goals for exacerbation reduction
- FDA to review
- New studies to review outcomes after switching from other biologics

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48-year-old woman with moderate/severe asthma (GINA Step 4)

- On medium-dose maintenance ICS-LABA—good adherence
- Adequate inhaler technique
- Complaints of worsening shortness of breath.
- 2 exacerbations in past 12 months
- AIRQ 6
- Wants albuterol refill—uses "regularly"
- Has allergic rhinitis--??controlled
- Blood eosinophils---340 cells/ml

Candidate for MART or AIR?
Won't give up purple inhaler
Candidate for biologics?
Candidate for Azythromycin?

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70-year-old Black woman with mild asthma (GINA Step 2)

- Has Medicare Part D prescription insurance
  - $50+ copay for preferred brand medications
- On low-dose ICS and as-needed SABA
  - Instructed to take her ICS when she uses her SABA
  - Says she follows her regimen as prescribed
  - No exacerbations this year and AIRQ 1
- Says her daughter is getting $35 inhaler

What are alternatives? Using AIR. ???MART
Medicare often has only tier 2-4 ICS inhalers.
Maybe low dose budesonide/formoterol for MART?

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35-year-old Hispanic male with moderate asthma (GINA Step 3)

- Presents to your FQHC to establish care; in the US for about 3 years
- Asthma not well-managed/controlled
  - Two ED visits in the last 3 months
  - AIRQ 6
- On no asthma medication---ran out of recent ED drugs
- No refills given

Could you use AIR or MART?
Pharmaceutical programs
$35 AIR
Samples?

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Thank you. Questions?

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