Asthma in Adults: A Breathless Update

COL Douglas Maurer, DO, MPH, FAAFP

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Learning Objectives
1. Use evidence-based criteria to order and interpret appropriate tests for asthma.
2. Analyze environmental triggers for asthma with patients and select factors to reasonably avoid or control them.
3. Develop system-wide interventions that promote patient adherence to long-term management of chronic asthma.
4. Collaborate with asthma patients to develop an asthma action plan that encourages adherence.
Associated Session

• Asthma in Adults: PBL

How many asthma patients do you see?
How do you normally treat them?
How comfortable are you treating them?

Current Guideline Review

2007 NHLBI + 2017 GINA

AES Poll Question #1

Which of the following is the correct spirometry criteria to diagnose asthma?
A. Non-reversible obstruction of at least 10% FEV1
B. Reversibility of at least 12% in baseline FEV1
C. Reversibility of at least 5% in baseline FEV1
D. Non-reversible obstruction of at least 20% FEV1

Asthma Diagnosis

• Reversibility: 12% in baseline FEV1 or 10% of percent predicted FEV1
• Methacholine challenge most sensitive test
• Positive: decrease in FEV1 > 20% at 8 mg/mL
• Decreased FEV1/FVC suggestive of dz
• Normal spirometry does not exclude asthma!
Got Asthma? (Really?!)  
- Patients (N = 701) underwent spirometry and symptom monitoring  
- Patients without asthma per spirometry underwent medication weaning over 4 visits  
- Repeat testing ruled out asthma in 203 (33%)  
- After 1 year, 6 (2.9%) resumed treatment  
- 12 with serious alternative diagnoses

Risk Factors for Asthma  
- Wheezing before age 3 years  
- Atopy, allergic rhinitis  
- Environmental: tobacco smoke, pets, gas cooking, mold, cockroach, dust-mites, cleaning, farming  
- Perinatal: preterm delivery, maternal smoking  
- Respiratory infections early in life  
- Meds: aspirin/NSAIDs (sensitivity only), acetaminophen?  
- Other: genetics, day care, overweight/obesity

Acute Asthma Treatment  
- SABA's drug of choice for acute exacerbations  
- Systemic corticosteroids reduce relapse, hospitalization, and SABA use  
- Initial treatment: O2, SABA's, ipratropium bromide, and systemic corticosteroids*  
- Severe exacerbations: IV magnesium or heliox

Chronic Asthma Treatment  
- 4 categories (NHLBI):  
  - Mild intermittent  
  - Mild persistent  
  - Moderate persistent  
  - Severe persistent  
- 3 Categories (GINA):  
  - Mild  
  - Moderate  
  - Severe

AES Poll Question #2  
First line maintenance therapy for mild persistent asthma is which ONE of the following?  
A. Short acting beta agonists (SABA)  
B. Long acting beta agonists (LABA)  
C. Oral prednisone  
D. Inhaled corticosteroids (ICS)  
E. Leukotriene receptor antagonists (LRA)

Chronic Asthma Treatment  
- Stepwise treatment of categories  
  - SABA only as needed for all categories  
  - ICS preferred controller  
  - LABA preferred add-on agent after ICS  
  - LRA acceptable controller
GINA Stepwise Management

**Components of Severity**

- **Classification of Asthma Severity**

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**Symptoms**

- Shortness of breath
- Wheezing
- Chest tightness
- Coughing

**Risk**

- History of severe asthma
- High risk occupation
- High environmental exposure
- High socioeconomic status
- Family history

**Recommendations: Step by Step Initial Treatment**

- **Step 1**: Low dose ICS
- **Step 2**: Low dose ICS + LTRA
- **Step 3**: Med/high dose ICS
- **Step 4**: Professional advice/management
- **Step 5**: Add-on treatment

**GINA Stepwise Management**

- **Remember To...**
  - **Provide guided self-management education**
  - **Treat modifiable risk factors and comorbidities**
  - **Advise about non-pharmacological therapies and strategies**
  - **Consider stepping up if uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first**
  - **Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is 70% predicted**
  - **Consider stepping down if symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.**

**Severe Asthma**

- **Definition:**
  - Requires high-dose ICS PLUS second agent OR
  - Oral steroids for ≥ 50% of previous year
- **Eval and tx comorbidities:** sinusitis, polyps, GERD, OSA, obesity, smoking, etc.
- **Consider steroid resistance and eosinophilia**
- **Tx with ICS/LABA plus low dose theophylline or montelukast or omalizumab**
AES Poll Question #3
Treatments for exercise-induced bronchoconstriction (EIB) include which of the following EXCEPT?
A. Short acting beta agonists (SABA)
B. Long acting beta agonists (LABA)
C. Cromolyn
D. Ipratropium bromide
E. Leukotriene receptor antagonists (LRA)

Exercise-Induced Bronchoconstriction
• Formal post-exercise spirometry for diagnosis
• SABA 15 min prior to exercise
• Alternant: mast cell stabilizer, anticholinergic
• NO LABA’s!
• If use SABA daily: ICS or LRA
• Nondrug: warm up first, use mask or scarf

Latest Evidence on Acute Asthma Management

ER Management
• Nebulizers no better than MDI’s via spacer
• Inhaled mag sulfate: no benefit; stick with IV
• Ketamine showed NO benefit in its only RCT
• Weak data for IV beta agonists + inhaled
  – NO benefits for adults
  – Limited evidence in children

ER Management
• ICS in the ER for acute exacerbations
  – Reduced admissions if not treated with oral or IV
  – May reduce admissions when added to systemic
• Increasing ICS as part of an action plan ineffective
• Choice of oral steroid?
  – Prednisone vs. dexamethasone

Dexamethasone for Exacerbations
• 2016 RCT (N=456) adults < 56 years presenting with acute asthma to ER with acute exacerbation
• Randomized to prednisone 60 mg daily for 5 days vs 12 mg of dexamethasone x 1 and 4 days placebo
• After 2 weeks, relapse in 12.1% dexamethasone vs 9.8% prednisone (diff 2.3%; 95% CI, -4.1% to 8.6%)
• No difference in hospitalizations between groups (3%)
• More side effects in the prednisone group
Azithromycin for Asthma Exacerbations?

- 2016 RCT (N=199 — 4383 excluded!) with asthma exacerbations requiring steroids
- Randomized to azithromycin 500 mg daily or placebo for 3 days and standard care
- No difference in mean asthma symptom scores at day 10 between the 2 groups (P>0.05)
- No differences in QOL or lung function
- Results consistent with current guidelines: no abx!

Latest Evidence on Chronic Asthma Management

Symptom-Based ICS?

- Govt funded nonblinded RCT with 342 participants
- Randomized into 3 groups:
  - Physician adjusted based on 2007 guideline
  - Biomarker adjusted based on exhaled nitric oxide
  - Symptom-based ICS matched puff to puff to SABA
- Symptom-based group with similar outcomes
- Used half the dose of steroids as the other groups
- 2015 Cochrane: less steroid, no loss of control
  - Mild asthma patients only, need more studies

ICS for Everyone?

- 2016 industry-funded RCT (N=7100, ages 4-66) mild asthma
  - Randomized to budesonide or placebo daily x 3 years
  - ICS group with 50% fewer severe asthma-related events vs placebo regardless of symptom frequency at baseline
  - ICS group with 8 fewer adverse events per 1000 patient-years
  - Absolute difference: small; could consider ICS in patients with infrequent symptoms (2 days/week or less)
- Guidelines still rec ICS only for patients with symptoms on 3 or more days/week

ICS plus LABA...Right Away?

- 2013 Cochrane Review, 27 trials, N=8050
- RCT’s comparing ICS + LABA with ICS alone
- Combo ICS/LABA no better than ICS alone
- Higher dose ICS superior to add-on LABA
- Children responded similarly to adults
- No difference in adverse events

Single Inhaler Therapy (SiT)

- Combo formoterol/budesonide (SiT)
- 13 studies of over 13,352 patients; no children < 12
- All industry funded
- SiT reduced:
  - Asthma exacerbations requiring oral steroids
  - ER visits and hospitalizations
  - Adverse events/discontinuation higher in SiT group
- NNT 100 to prevent admission or ER visit
ICS plus LABA…Then Again…I!
- 2016 industry funded RCT, 11,751 pts, > 12 yrs
- All patients with moderate-severe asthma
- Fluticasone vs fluticasone-salmeterol BID
- Primary outcome: first severe asthma exacerbation
- Combo reduced exacerbations more than ICS alone (8% vs 10%, NNT = 50 over 26 wks)
- No difference in intubations or deaths

When to Stop a LABA?
- Black box: stop LABA once asthma controlled
- Meta-analysis: 5 studies, 1292 pts says “No”
  - Patients did WORSE after stopping LABA
  - Lots of drop-outs due to poor control
- 2015 Cochrane: temporary loss of control

How to Stop a LABA?
- Prescriber’s Letter recommends:
  - Step up tx, go to medium ICS before LABA
  - Step down tx, go to lower dose of combo first
  - Stop LABA, keep ICS same or double dose
  - Still symptomatic, restart combo ICS/LABA

Risks of LABA’s
- Cochrane Reviews of LABA safety
  - 6 deaths in combo formoterol vs. 1 in ICS alone
  - No difference in non-fatal events
  - Salmeterol deaths all occurred with drug alone
  - No diff in head to head comparisons
- Ongoing FDA surveillance studies…

The Return of the LABAs
- 2016 RCT (N=11,693) evaluated formoterol + budesonide (Symbicort) vs budesonide alone in adults > 12 yrs
  - Combo reduced exacerbations 16.5% (HR 0.84; 95% CI, 0.74-0.94)
  - No diff in serious asthma-related side effects (43 vs 40); 2 deaths in combo group
- 2016 RCT (N=6028) evaluated salmeterol + fluticasone (Advair) vs. fluticasone alone in children 4-11
  - Combo non-inferior to fluticasone alone; no diff in serious asthma-related side effects (21 vs. 27); no deaths in either group
  - No benefit to add on LABA, but safety was primary endpoint

Adult Height and ICS
- Risks appear mild; still concern about height
- Govt funded RCT of 1000 children ages 5-13
- Treated with ICS, nedocromil or placebo for 4.3 yrs then enrolled in follow-up study
- Height measured in adulthood (mean age 25)
- ICS caused modest height reduction of 1.2 cm
- Most pronounced in girls
- GINA recs checking height annually in children
LRA as Monotherapy?
- Industry study: LRA’s “equivalent” to ICS/LABA
  - Outcomes DOE’s not POEM’s
  - All “improvements” gone by 2 years
- Cochrane: 65 studies, 10K adults, 3K children
  - LRA’s more asthma exacerbations (NNH 28)
  - LRA’s more dropouts for poor control (NNH 31)
- LRA ONLY as add-on to ICS and LABA

Tiotropium for Asthma?
- 2012 industry funded RCT (N=900)
  - All with asthma not controlled on LABA or ICS
  - DOE improvements of pulmonary function
  - POEM decrease in exacerbations
    - 1 less exacerbation after 8 yrs of treatment
- Multiple Cochrane Reviews in 2015/2014
  - LAMA add-on therapy improves lung function
  - No difference in exacerbations of LAMA vs. LABA

Omalizumab, Reslizumab, Mepolizumab
- 2013 Cochrane Review found omalizumab:
  - Reduces asthma exacerbations
  - Reduces hospitalizations
  - Well tolerated
  - Reduce/withdraw steroids
- Adjunct to ICS and steroid tapering
- FDA approved for ages 6+ with pos skin test
- Expensive! One vial: $826!

Dupilumab
- Monoclonal antibody targeting IL-4Ra
- 104 adults, 18-65 years, persistent asthma
- Randomized to dupilumab or placebo x 16 wks
- Decreased exacerbations when ICS and LABA tapered off BUT no difference as add-on tx!
- Not FDA approved for asthma (atopic derm)

Bronchial Thermoplasty
- Only FDA approved nondrug asthma therapy
- Tube with four RF wires that destroy excess smooth muscle via bursts of heat
- One study showed 78% decrease in ER visits!
- Risk of exacerbation from procedure itself!
- Reserved only for severe asthmatics not controlled on ICS and LABA
Prevention

Asthma Action Plans (AAP)
- 2017 CR of 15 RCTs N=3062 (AAP vs no AAP: N=2602; AAP plus education vs education alone: N=460)
- Ages 22-49; most studies 6 months long
- No benefit or harm with AAPs on ED visits or hospitalizations (OR 0.75; 95% CI, 0.45-1.24; N=1385)
- No benefit or harm with AAP + education on ED visits or hospitalizations (OR 1.1; 95% CI, 0.27-4.32; N=70)
- Similar results with AAPs on steroids, symptoms, function
- Overall evidence rated “low/very low”

AES Poll Question #4
Which of the following has been associated with the prevention of asthma and/or asthma exacerbations?
A. Probiotics
B. Influenza vaccine
C. Vitamin C
D. Nuts
E. All of the above

Influenza Vaccine
- 2013 Cochrane Review of 18 trials
  - No reduction in influenza-related exacerbations
  - No apparent risk from inactivated vaccine
  - No risk from live intranasal influenza vaccination
  - Vaccines do not worsen asthma
- Insufficient evidence to determine if asthma attacks prevented by influenza vaccination

Asthma and Supplements
- Probiotics during pregnancy or early infancy do not prevent asthma
  - Meta-analysis of 20 RCTs included 4866 children
  - Various combinations/doses of probiotics
  - Followed children from 2 to 6 years after birth
  - No evidence of benefit
- Vitamin C not beneficial in asthma
  - 9 studies, 330 participants
  - One study with drop in FEV1 post-exercise
**Asthma and Supplements**
- Vitamin D MAY prevent exacerbations
  - 250 pt RCT: vitamin D vs placebo; no difference in time to 1st exacerbation
  - 2016 Cochrane: 9 trials, 435 children, 658 adults showed reduction in exacerbations, ER visits and hospitalizations
- Caffeine improves airways function for up to four hours
  - 7 studies of 75 patients
  - Improved FEV1 by 12-18%
  - May need to avoid caffeine for at least four hours prior to spirometry

**Nuts and Pregnancy**
- Avoiding nuts during pregnancy controversial
- Danish Birth Cohort of 101,045 pregnancies
- Self-report data from validated questionnaire
- Nut intake inversely associated with asthma
- Consumption may decrease risk of allergies
- Nut consumption not harmful

**Fish Oil in Pregnancy**
- 2016 RCT in Danish women (N = 695): LCPUFA during pregnancy to reduce wheezing disorders in children
- Compared 1g of fish oil to identical olive oil
- Supplementation 22-26 weeks’ gestation until 1 week after; children followed at least 5 years
- Wheezing disorders lower in fish oil group (16.9% vs 23.7%; HR 0.69; 95% CI 0.49 - 0.97, NNT 15)
- Women with lowest baseline LCPUFA levels benefited most (17.5% vs 34.1%; HR 0.46; 0.25 - 0.83, NNT 5.6)
- No reduction in exacerbations, allergic sensitization, or eczema

**AES Poll Question #5**
Which of the following is the preferred controller agent for persistent asthma in pregnancy?
- A. Budesonide
- B. Albuterol
- C. Salmeterol
- D. Fluticasone
- E. Tiotropium bromide

**Asthma and Pregnancy**
- Asthma may improve, worsen or stay the same
  - Mild: 12.6% exacerbation / 2.3% hospitalization
  - Moderate: 25.7% / 6.8%
  - Severe: 51.9% / 26.9%
- 15-20% increased risk of complications
  - Mortality, pre-e, preterm delivery, low birth weight
- Monitor peak flows bid +/- spirometry

**Smoking cessation!**

**Medication safety**
- Albuterol (C), ICS (B/C), LABA (C), LRA (B), Ipratrop (B)
- Carboprost (avoid!)
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### Practice Recommendations

- No changes in current NHLBI asthma guideline
- New EIB guideline favors SABA’s not LABA’s
- Symptom-based ICS or SiT use may be “OK”
- Careful using LABA’s (but don’t stop them!)
- Don’t use LRA’s as monotherapy
- Tx asthma exacerbations same in pregnancy!

### Learning Summary

- Reviewed current NHLBI asthma guideline
- Discussed new EIB guideline
- Evaluated latest evidence for asthma treatment
- Discussed prevention of asthma
- Reviewed some asthma in pregnancy pearls

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