Special Issues in Asthma Management

February 4, 2021

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Issues

1. What is EIB and how is it best managed?
2. What is the effect of pregnancy on asthma and what are the recommendations for treatment?
3. Are there special considerations in managing older patients with asthma?

Issues (cont'd)

4. How should aspirin-exacerbated respiratory disease be managed?
5. What are modifiable risks for asthma management?
6. How are severe and exacerbation-prone asthma phenotypes defined? What are treatment options?

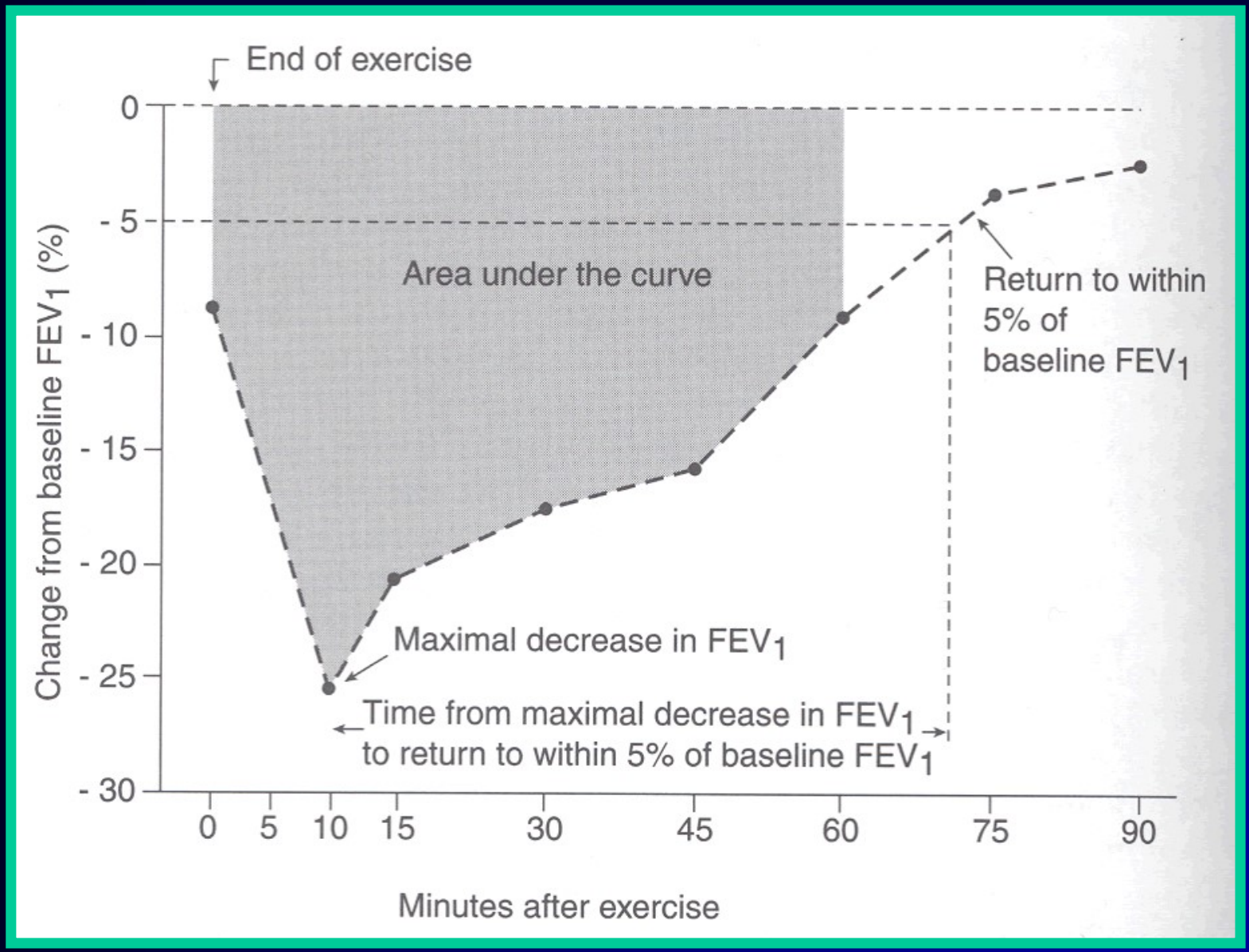
Pathophysiology of Exercise-Induced Bronchoconstriction (EIB)

- Exercise initially causes bronchodilation, lasting up to 3 minutes
- EIB occurs after exercise, reaches its peak within 5-10 minutes after stopping, and generally resolves in another 20-30 minutes
- Defined as a drop in FEV_1 of ≥10% of pre-exercise value
- Exact pathogenesis unknown; heat loss and/or water loss from the central airways seem key
- EIB is more easily provoked in cold, dry air; warm, humid air can blunt or block it
- Refractory period of up to 2 hours after exercise (not consistent between or within individuals)
- EIB is a reflection of the increased bronchial hyperresponsiveness (BHR) of asthmatics

Prevalence of EIB

- EIB, preferred over EIA
- EIB affects 70-90% of asthmatics
- Estimated 5-20% of general population w/o atopy have EIB
- Some patient groups with BHR (e.g., after viral infections, cystic fibrosis, allergic rhinitis) show bronchoconstriction after exercise to a lesser degree (5-10%)
- Elite athletes have a higher prevalence of EIB than the general population (30-70%)

Endpoints Used to Assess the Degree of EIB



Asthmogenic Characteristics of Activities and Sports

HIGH (associated with high minute ventilation)	HIGH (associated with cold, dry environment)	LOW	
Cycling	Cross-Country Skiing	Baseball	Racquetball
Distance Running	Figure Skating	Boxing	Sprinting
Rugby	Hockey	Diving	Swimming
Soccer	Speed Skating	Downhill Skiing	Tennis
		Football (±)	Volleyball
		Golf	Weightlifting
		Gymnastics	Water Polo
		Handball	Wrestling
		Karate	

Specific Issues in the Management of Asthma in Athletes

- Poor recognition of or difficulties in assessing Sx
- Unrecognized alterations in lung function
- Increased prevalence of coexisting conditions e.g. rhinitis, GER, hyperventilation syndrome
- Undertreatment, overtreatment, or poor control with current Tx
- Need to avoid development of tolerance to beta2-agonists (e.g. regular or frequent use)
- Difficulties in reducing exposure to sensitizers and irritants (e.g. allergens, pollutants, cold, chlorine)

Boulet LP & O'Bryne PM. N Engl J Med 2015; 372(7): 641-648.

Treatment of Asthma & EIB in Athletes

- Main treatment goals
  - Achieve & maintain asthma control
  - Inhibit or minimize EIB to avoid affecting performance
  - Prevent risk for exacerbations
  - Reduce risk of ↓ lung function
  - Ensure compliance with sports-authorities' regulations (www.wada-ama.org)
- General measures
  - ID possible triggers & inducers & suggest environmental control measures
  - ID & treat coexisting conditions
  - Provide asthma education & guided self-management abilities

Boulet LP & O'Bryne PM. N Engl J Med 2015; 372(7): 641-648.

Treatment of Asthma & EIB in Athletics (Cont'd)

- Prevention of EIB
  - Ensure effective asthma control
  - Engage in pre-exercise warm-up
  - Use pre-exercise (15 min. prior) SABA (2-4 hrs. protection)
- Pharmacologic treatment
  - Follow asthma guidelines
  - Provide rescue Rx eg SABA
  - Provide maintenance Rx (1st choice ICS; 2nd choice LTRA)
  - Rx combination Rx if low-dose ICS inadequate

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Exercise, Asthma, and Doping

- Permitted substances
  - Albuterol
  - LABAs (salmeterol, formoterol)
  - ICS
  - LTRAs
  - Cromones (not readily available in U.S.)
  - Omalizumab
  - Inhaled anticholinergics
- Therapeutic use exemption for prohibited substances
- Prohibited substances
  - Terbutaline
  - All β_2 agonists orally or by injection
  - All glucocorticoids oral, IV, IM
- World Anti-Doping Agency Prohibited List

ATS Clinical Practice Guideline: EIB, Am J Respir Crit Care Med 2013; 187(9): 1016-27

NAEPP Expert Panel Report Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004

(NIH Publication No. 05-3279)

Web: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm

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Management of Asthma During Pregnancy

www.uptodate.com,Nov2019

Effect of Asthma on Pregnancy

- Asthma affects 8-14% of pregnant women
- Maternal asthma may increase the risk of perinatal mortality, preeclampsia, preterm birth, need for cesarean delivery, LBW infants, and maternal morbidity and mortality (15-20% ↑ risk)
- More severe asthma associated with increased risks on pregnancy (30-100% ↑ risk)
- When asthma is controlled, outcomes for mother and fetus are similar to the general population
- Rare in 1st trimester and last 4 weeks; primarily 17-37 weeks (peak = 6 months)

Effect of Pregnancy on Asthma

- General rule: 1/3 get worse, 1/3 get better, 1/3 stable during pregnancy
- Consistent effect with subsequent pregnancies
- Severe asthma is more likely to get worse during pregnancy
- 75% revert to pre-pregnancy status within 3 mos. postpartum

Treatment of Asthma in Pregnancy

- 2007 NAEPP guidelines and Up to Date 11/2019
  - Albuterol is preferred SABA
  - ICS are preferred controller (esp. low-med. doses)
    - Budesonide 1st choice (Class B)
    - Reassuring fluticasone data
    - Salmeterol is LABA of choice; reassuring data for formoterol
    - Montelukast or Zafirlukast is alternative, not preferred Tx
    - Ipratropium considered safe; limited data with LAMAs
    - Omalizumab (Class B)
- Oral corticosteroids
  - ↑ risk of LBW and pre term birth
  - Pre-eclampsia (2 x risk)
  - Oral clefts (3 – 6x with 1st trimester exposure)
  - ?gestational diabetes and HTN
  - ? Drug effects vs severe or uncontrolled asthma ("disease effect")
  - Acute exacerbations – treatment recommendations essentially the same
  - Biologics
    - Safety & efficacy unknown
    - Prospective observational registry of omalizumab

Recommendations

- Safer to treat with asthma medications compared to risk of exacerbations/asthma symptoms
- Routine (monthly) objective monitoring of lung function and assessment of asthma symptoms are recommended; asthma action plan recommended; coordinated care
- Goal is to maintain oxygenation of the fetus
- Use of ICS, S(L)ABA's, theophylline, antihistamines, prednisone OK w/breastfeeding
- Flu shot highly recommended
- Control environmental triggers
- STOP SMOKING!

Considerations for Managing Older Patients with Asthma

- Presence of coexisting diseases (COPD, CHF, chronic rhinosinusitis, sleep apnea, GERD)
- Increased risk for complications of influenza and community-acquired pneumonia
- Cognitive and physical barriers to device use
- Increased risk for side effects due to high-dose ICS
  - Osteoporosis
  - Cataracts
  - Glaucoma
  - ?Pneumonia
- Need for beta-blockers, ACE inhibitors, NSAIDs/ASA

Aspirin Exacerbated Respiratory (AER) Disease

- Formerly known as aspirin-induced asthma or aspirin-intolerant asthma (AIA)
- Characterized by recalcitrant mucosal inflammation of the upper and lower respiratory tract, after ingestion of ASA and most NSAIDs ("aspirin triad")
- Associated with progressive rhinosinusitis, nasal polyposis, and asthma, despite avoidance of ASA and NSAIDs (COX-1)
- Difficulty drinking alcoholic beverages (upper & lower-airway reactions)
- 5-20% asthmatics, more often in women, rarely in children; increased risk with severe asthma
- Onset in 3rd or 4th decades of life

Clinical Features and Diagnosis of Aspirin Insensitivity

- Chronic rhinitis
- Anosmia
- Chronic sinusitis with aggressive polyposis
- Oral or high-dose inhaled and nasal corticosteroid-dependent
- Severe bronchospasm and/or rhinorrhea provoked by small doses of ASA or other NSAIDs (non-IgE mediated hypersensitivity reaction) – reaction within 20 mins – 3 hrs
- Diagnosis confirmed by ASA challenge
- Presumed mechanism-inhibition of COX-1 and a resulting imbalance of prostaglandin E2 and leukotrienes

Treatment of AER Disease

- Aggressive Tx asthma and sinus disease; add LTRA if moderate-severe asthma (? Biologics)
- Absolute avoidance of ASA and other NSAIDs that inhibit COX-1 (tartrazine does not cross-react)
- COX-2-selective drugs usually tolerated
- Provision of a safe list of drugs for patients
- Aspirin desensitization, followed by daily ASA (sometimes daily NSAID)

NSAIDs that Cross-React with ASA in AER

Highly selective COX-1 inhibitors: Cross reactions occur both with first exposure and low doses. Contra-indicated in AER.

Generic Names:

Acetylsalicylic Acid
Diclofenac
Etodolac
Fenoprofen
Flurbiprofen
Ibuprofen
Indomethacin
Ketoprofen
Ketorolac
Meclofenamate
Mefenamic acid
Naproxen
Oxaprozin
Piroxicam
Sulindac
Tolmetin

NSAIDs that Cross-React with ASA in AER

	Generic Names:
Weakly selective COX-1 inhibitors: Will provoke reactions at high doses in a small number of AER patients	Acetaminophen Salsalate Diflunisal
Highly selective COX2 inhibitors	Celecoxib
Preferentially selective Cox-2 inhibitors: (Cox-1 inhibition at high doses)	Meloxicam

White AA & Stevenson DD. N Engl J Med 2018; 379(11): 1060-1070

Potential Candidates for ASA Desensitization

- Uncontrolled respiratory Sx despite optimal medical management (including LTRAs)
- Respiratory inflammatory disease, which can only be controlled with daily doses of systemic corticosteroids
- Multiple polypectomies and/or sinus surgeries
- Requirement for ASA or NSAIDs for treatment of other diseases (e.g., arthritis, coronary artery disease)

Risks with ASA Challenges and Desensitization

- Severe bronchospasm
- Gastric irritation and/or ulceration with prolonged ASA-administration
- Bleeding (bruising, nosebleeds, hematuria, GI bleeds)

ASA Challenge Protocol

- Performed in a controlled setting, able to treat an acute, severe respiratory reaction
- Stable airways at time of challenge: $FEV_1 \geq 70\%$ predicted
- Withhold most asthma/allergy meds
- Start with full day of placebo challenge
- Incremental oral challenge: starting at 40.5 mg and increasing dose over a period of 1-3 days.
- Target dose: ≥ 325 mg/day; continue 325-650 mg bid
- Approaches to decrease desensitization times under study (goal=1 day)

White AA & Stevenson DD. N Engl J Med 2018; 379(11): 1060-1070

Rapid Desensitization for Patients with CV Disease and ASA Hypersensitivity

- Completed over ≤ 6 hours in a well-controlled environment (ICU or CCU)
- Silberman protocols
  - Protocol 1: ASA 1, 2, 4, 8, 16, 32, 64, 100 mg every 30 minutes
    Success rate 86% (6/7 patients)
  - Protocol 2: ASA 5, 10, 20, 40, 75 mg every 30 minutes
    Success rate 100% (27/27 patients)
  - B-blockers D/C prior to desensitization protocols
- Wong Protocol
  - Protocol 1: ASA 0.1, 0.3, 1, 3, 10, 30, 40, 81, 162, 325 mg q 10-20 min.
    Success rate 92% (11/12 patients)
    Used pretreatment with an oral antihistamine
- Enrolled patients had AER or urticaria as clinical manifestations

Page NA and Schroeder WS. Ann Pharmacother 2007; 41

Post-Challenge Protocol

- Continued daily Tx with ASA ≥ 81 mg maintains the tolerant state allowing for cardioprotection
- Decreasing airway inflammation and nasal polyps often requires doses of 650 mg ASA bid
- Patient becomes concomitantly cross-desensitized to COX-1 NSAIDs
- **If therapy is interrupted for > 48 hours, patients are no longer tolerant of ASA or NSAIDs**
- Elective surgery: decrease ASA dose to 325 mg daily for 7 days, and withhold ASA only on day of surgery
- Reassess patient periodically to ascertain if ASA-desensitization has decreased airway disease

Long-term Tx with ASA Desensitization in Asthmatic Patients with AER

- 172 patients, with F/U 1995-2005, after ASA desensitization & daily ASA
- 6 month outcomes
  - ↓ # sinus infections
  - ↓ # short courses of prednisone
  - ↑ sense of smell & ↑ nasal & asthma Sx improvement
- Results persisted for 1-5 years
  - ↓ prednisone daily dose from mean of 10.8 mg at baseline, to 8.1 mg at 6 mos., and 3.6 mg at ? 1 year
- 14% D/C ASA due to side effects
- 67% responded to ASA Tx; 87% response if Tx ? 1 year

Berges-Gimeno MP, et al. J Allergy Clin Immunol 2003; 111: 180-6

Modifiable Risks for Asthma Management

- Smoking
- Allergic rhinitis
- Chronic sinusitis
- Gastroesophageal Reflux Disease (GERD)
  - Not indicated for uncontrolled asthma in the absence of GERD symptoms
  - Safety concerns for long-term PPI use in children
- Obstructive Sleep Apnea
- Obesity