Asthma in Sports: Update including mannitol

By
Chris Randolph, MD
Clinical Professor
Yale Affiliated Programs
Waterbury, CT

Disclosures
- Funding: Schering – Plough
- Speaker’s Bureau: Schering – Plough
- Glaxo Smith Kline
- Astra Zeneca
- Novartis-Genentech
- Merck
- Pfizer
- Wallace
- Alcon
- Sanofi – Aventis
- Sepracor
- Sciele Pharma, Inc
- Acredo
- Baxter

Learning Objectives
- The practicing allergist/immunologist or health care provider will understand in athletes:
  - Pathogenesis, epidemiology, presentation,
  - Diagnosis and management of known asthma with exercise induced bronchospasm (EIB) previously known as exercise induced asthma (EIA) and exercise induced bronchoconstriction alone (EIB)

Heterogenous syndromes
- Phenotypes ? genotypes of EIB:
  - Increasing levels ventilation
  - Asymptomatic-Atopy or Asthma-Overuse

HISTORY OF EIB/EIB with asthma
- Aretaeus the Cappadocian (1st century)
- 1698 John Floyer (E. Burke, R. Laennec, William IV, JFK, TR, MSanguly)
- 1962 Dr R. S. Jones - in children
- 1966 Heimlich et al treadmill
- 1966 McNeil et al refractory period
- 1972 Olympic medal denied
- 1998 Olympics on over 300% increase in use of beta agonist (BA)
- 2002 Salt Lake City: International Olympic Committee Medical Commission (IOC-MC) required objective testing for EIB or EIB with asthma:
  - NHLBI for asthma with decline in BA25% increase ICS +200%
  - 2008 IOC-MC recommendations for EIB with asthma similar to NHLBI for asthma with decline in BA25% increase ICS <200%

(Olympic is a philosophy of life... combining qualities of the body, will and mind)
I. Pathogenesis: Cases and Definition: Heterogeneity

- Definition: EIB: Transient increase in airway resistance and narrowing following vigorous exercise.
- EIA = exercise induced bronchoconstriction (EIB) as a major phenotype reflecting known asthma with FEV1 decline >/=10% following exercise
- 50% or more of asthmatics/40-50% allergic rhinitis
- Up to 50% elite athletes and 12% school children morbidity QoL and mortality
- Few studies in adults because of perceived cardiovascular risk or limitation of challenge

- Case: 20 year old Hispanic male soccer player with known asthma has cough and wheezing 5 minutes after running for 5-10 minutes.
- Case: 9 year old white female soccer player has exertional dyspnea with baseline FEV1 72% and response to bronchodilator.

EIB in athlete

- EIB = exercise induced bronchoconstriction without known asthma and normal pulmonary functions at baseline with different pathology and variable response to inhaled steroids
- 11-50% elite athletes
- Case: A 20 y/o w/f competitive distance runner has chest tightness, cough and/or wheezing only with prolonged running in cold air (<40°F)
- Anderson S Current All Asthma Reports 2005;5:116-22

I. Pathogenesis: variants

- Ventilation up to 200l/m bypass nose (30l/m) and conditioning leading to cold and/or dry air.
- Hyperosmolar environment is created with degranulation of mast cell = Exercise induced bronchoconstriction (EIB) in known asthma (EIA)

- Zetkowski Z et al Int Arch All Immunol2008;143(3):299-310

Table 2: Specific sport environments associated with exercise induced hypersensitivity disorders

<table>
<thead>
<tr>
<th>Environment</th>
<th>Hypersensitivity Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Running</td>
<td>Conjunctivitis, rhinorrhea, bronchoconstriction</td>
</tr>
<tr>
<td>Swimming</td>
<td>Conjunctivitis, rhinorrhea, bronchoconstriction</td>
</tr>
<tr>
<td>Diving</td>
<td>Conjunctivitis, rhinorrhea, bronchoconstriction</td>
</tr>
<tr>
<td>Water polo</td>
<td>Conjunctivitis, rhinorrhea, bronchoconstriction</td>
</tr>
<tr>
<td>Triathlon</td>
<td>Conjunctivitis, rhinorrhea, bronchoconstriction</td>
</tr>
<tr>
<td>Ice skating</td>
<td>Conjunctivitis, rhinorrhea, bronchoconstriction</td>
</tr>
</tbody>
</table>

Figure: Effects of refractory period on EIB


Factors affecting EIB with asthma

1. Environmental:
   - Humidity
   - Temperature
   - Aeroallergens
   - Pollutants or irritant

2. Intensity and type of exercise
   - Treadmill = Running > cycling > swimming

3. Infection


U.S. Athletes participating in the 1996 Atlanta Summer Olympics Who Were Classified As Having Either Asthma or Active Asthma.

<table>
<thead>
<tr>
<th>Event</th>
<th>Asthma/total athletes (%)</th>
<th>Active asthma/total athletes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Track</td>
<td>9/36 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Swimming, synchronized swimming</td>
<td>16/36 (44.4%)</td>
<td>19/36 (52.8%)</td>
</tr>
<tr>
<td>Rowing, kayaking, rowing, sailing, kayaking</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Rowing, kayaking, rowing, sailing, kayaking</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Rowing, rowing, sailing, kayaking</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Fencing, gymnastics, rhythmic gymnastics</td>
<td>6/36 (16.7%)</td>
<td>15/36 (41.7%)</td>
</tr>
<tr>
<td>Baseball, softball</td>
<td>5/30 (16.7%)</td>
<td>10/30 (33.3%)</td>
</tr>
<tr>
<td>Basketball, field hockey, lacrosse, tennis, soccer</td>
<td>10/30 (33.3%)</td>
<td>15/30 (50.0%)</td>
</tr>
<tr>
<td>Diving, water polo</td>
<td>3/30 (10.0%)</td>
<td>5/30 (16.7%)</td>
</tr>
<tr>
<td>Field hockey, baseball, soccer, tennis</td>
<td>1/30 (3.3%)</td>
<td>5/30 (16.7%)</td>
</tr>
<tr>
<td>Handball, water polo</td>
<td>10/30 (33.3%)</td>
<td>15/30 (50.0%)</td>
</tr>
<tr>
<td>Synchronized swimming</td>
<td>16/36 (44.4%)</td>
<td>19/36 (52.8%)</td>
</tr>
<tr>
<td>Synchronized swimming</td>
<td>16/36 (44.4%)</td>
<td>19/36 (52.8%)</td>
</tr>
<tr>
<td>Track and field</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Track and field</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Track and field</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Track and field</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Track and field</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Track and field</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Track and field</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>Track and field</td>
<td>2/36 (5.6%)</td>
<td>12/36 (33.3%)</td>
</tr>
</tbody>
</table>

* Asthma was defined as athlete-reported use of an asthma medication and/or previous diagnosis of asthma by a physician. Active asthma was defined as either permanent or very permanent use of asthma medication at the time of the study. Modified from Storms WW Med Sci Sports Exercise 2003;35(9):145. Approved for reproduction from Beadle, Wilber, Lemanske. Exercise Induced Asthma; Human Kinetics, 2002.
Epidemiologic Factors for EIB with asthma

- Personal or family history of asthma
- African American race
- Socioeconomic status
- Cystic fibrosis
- Bronchiectasis
- Asthma control/presence of infection
- Asthmagenicity of exercise
- Environment and time of day ie humidity, temperature, aeroallergens, pollutants

Modified from Carver TW Current Allergy and Asthma Reports 2008;8:500-4

II. Presentation

- Symptoms: cough, wheezing, chest pain and/or chest tightness as well as common postrace cough in elite athletes and sore throat, stomach ache in the young child. (Storms, 2005)
- Dyspnea alone is usually not asthma but a differential diagnosis:
  - Vocal cord dysfunction or other psychogenic etiologies with only 8% EIB positive treadmill (Abu-Hassan et al, Annals Allergy Asthma Immunol 2005;94(3):366-71)

Exercise induced dyspnea

- 74/117 (52%) normal treadmill:
  - 15% (15%) above normal conditioning
  - 27 (19%) within normal conditioning
  - 26 (18%) with poor conditioning
  - 11/117 (8%) EIA=EIB with asthma
  - 15 (11%) restrictive
  - 13 (9%) VCD
  - 2 (1%) Laryngomalacia
  - 1 (0.5%) Hyperventilation
  - 1 (0.5%) SVT


FDEIA (Food dependent exercise induced anaphylaxis)

- Case: 14 year old male brought in by paramedics from a public swimming pool with hypotension, generalized urticaria, angioedema and wheezing with improvement with epinephrine im. He had ingested wheat pasta 20 minutes prior to swimming class and previously tolerated wheat and exercise.
- Evaluation: positive prick skin test to wheat 4mm and wheat specific IgE WAS 6.7Ku/L
- Exercise challenge after eating two slices of wheat bread was positive with urticaria and angioedema (+) DBFC wheat (Toit GD Ped All Immunology 2007;18:455-463)

FoodDependent/Exercise-induced Anaphylaxis

- FD-EIA:
  - Rare physical allergy
  - Subtype of food allergy induced by exercise
  - Symptoms typically generalized urticaria, shock or hypotension
  - Associated foods wheat most common in Japan with alpha amylase inhibitor most important wheat allergen
  - Also:
    Grains, cereals, sea foods, nuts, peanut, vegetables, meat, foods contaminated with aeroallergen, and miscellaneous

Ozol D et al Current Opinion in Pulmonary Medicine 2008;14:9-12
Notice: Huckleberry Finn

• “Persons attempting to find a motive in this narrative will be prosecuted; persons attempting to find a moral will be banished; persons attempting to find a plot will be shot”. By order of the author (Mark Twain)

Diagnosis: Question

• History and/or therapeutic trial of medication is adequate for diagnosis of EIB with asthma
  • True
  • False

III. Diagnosis

• Comprehensive medical history;
  • Questionnaire is no better than "a coin toss"
  • In elite athletes 10-20% may have asthma while 50% of recreational runners report symptoms of allergy and/or asthma but often in denial
• Physical rarely helpful but may help rule-out differential with history.
• Diagnostic testing: Exercise or surrogate (Indirect) challenge with spirometry
• Treadmill (concentration 90% negatives) free running or sports challenge or cycle ergometry
• Hyperosmolar (surrogate) challenges in EIB (Eucapnic hyperventilation) are more specific but may be more sensitive than methacholine (Direct) for EIB. Mannitol is 92% specific and 96% sensitive to identify positive response to EIB.

Optimal exercise challenge

• 8 minutes running or cycling >90% (95% for elite) of HR max by 2 minutes and maintain for 6 minutes (<22°C, RH<50%)
• HR and oxygen saturation monitor with pulse oximetry
• Monitor pulmonary functions pre, baseline, 2 minutes and then every 5 minutes out to 30 minutes post exercise. Positive if >10% decline continue monitoring until 50% decline then bronchodilator and monitor until 95% of baseline. Calculate FEVI 10% fall, 50% alert/95% return value from pre exercise
• Mannitol advantages: safe, graduated, useful for diagnosis and monitoring asthma completed in 30 minutes, dose response, inexpensive, minimum equipment but awaiting approval (Rundell et J All Clin Immun 2008;122:238-246)
**Mannitol challenge**

- Mannitol sugar alcohol in vegetables derived from manna and seaweed
- Smooth muscle contraction by release mediators from airway cells
- Indirect challenge: reflects airway neural and cellular contribution
- Graduated capsules delivered in doubling doses of 5mg, 10mg, 20mg, 40mg, 80mg, 160mg, 160mg and 160mg until 
  \(\text{ FEV1} \geq 15\% \text{ decline} \) or between dose fall \(\geq 10\% \) or cumulative \(635\text{mg} \). Sensitivity Specificity \(>90\%\) EVH Sensitivity Specificity \(90\%\) Spector S 2008 J All Clin Immunol 2008;121;2(abstract #805 S210 /Rundell J All Clin Immn 2008;122(2)238-246)

**Therapy Question**

- Beta agonist alone is adequate therapy for EIB with asthma either as needed or continuously.
- True
- False

**Mannitol Correlation with Asthma Severity**

**Management for EIB**

- Nonpharmacologic:
- Sufficient warm-up / warm-down
- Avoidance of triggers
- Nasal breathing
- Mask in cold environment
- Pharmacologic:
  - Long(LABA) and/or short acting beta agonists
  - Leukotriene receptor agents(LRA)
  - Nonsteroidal: Cromolyn Like Compounds(Intal)
  - Inhaled steroids (CCS)/Combination LABA/CCS

Stepped Approach to EIB with known asthma
(Modified from Storms,2005)

- 1.a. Education of the athlete and trainers+ in avoidance, warm-up
  warm-down, face mask and nasal breathing, prn beta agonists
  b. Albuterol 2pff 15minutes prior to exercise if not improved.
  • 2. Add Intal 4pff just prior to exercise
  • 3. Add Inhaled CCS,LABA if not improved with Intal
  • 4. Evaluation and therapy for inhalant allergy
  • 5. Consider alternative diagnoses: exercise challenge, methacholine
  challenge, rhinolaryngoscopy as indicated
  • 6. Follow up to evaluate response to intervention


Effect of continuing or finishing high-level sports on
airway inflammation, bronchial hyperresponsiveness, and
asthma: a 5-year prospective follow-up study of 42 highly
trained swimmers.

Helenius I, Rytilä P, Sarna S, Lumme A, Helenius M, Remes

Swimmers who discontinued high level training
experienced attenuation or resolution of asthma and
bronchial HR. Those who continued swimming
experienced exacerbation of eosinophilic inflammation.

Metanalysis: Swimming in elite athletes(>30h/week)
exacerbates asthma not in adolescents<20hour
/week(Goodman Met al J Asthma 2008;45:639-47

Table 3: PHARMACOTHERAPEUTIC OPTIONS FOR EIB

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Timing of administration</th>
<th>Duration of protective effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA (e.g. albuterol)</td>
<td>Taken 15 minutes before exercise</td>
<td>May prevent symptoms for up to 3 hours</td>
</tr>
<tr>
<td>LABA (e.g. formoterol, salmeterol)</td>
<td>Taken 230 minutes before exercise</td>
<td>May prevent symptoms for up to 12 hours</td>
</tr>
<tr>
<td>Mast-cell stabilizers (e.g. cromolyn sodium, nedocromil sodium)</td>
<td>Taken just before exercise</td>
<td>May prevent symptoms for up to 2 hours</td>
</tr>
</tbody>
</table>

LABA, long-acting  β2-agonist receptor agonist SABA, short-acting β2-agonist receptor agonist EIB, exercise-induced bronchoconstriction.

Figure 2: Changes in forced expiratory volume in 1 second (FEV1) after exercise challenge at baseline and after pre-treatment with albuterol and montelukast.

Daily use beta agonist detrimental

1) Significant minority of asthmatics EIB with known asthma not prevented with B2 agonist
2) Daily treatment B2 agonist enhances severity EIB with known asthma
3) LABA qd decreases duration of protection. Bronchoprotection wanes before bronchodilation because BA receptors mast cell sm ms
4) Recovery from EIB with known asthma slower with standard dose B agonist
5) BHR induced or enhanced
Resolve within 72 hours discontinuation

Anderson S et al: Clinical Reviews All Immunol 2006;31:163-180
Reproduced by permission from publisher Humana Press 3/28/07

Reproduced perm AAAAI

Weiler J et al. Annals Allergy, Asthma, Immunology 2005;94:65-72
Questions

• EIB alone is differentiated from EIB with asthma by the absence of known asthma T F

• EIB alone management is by limitation of training

• EIB with asthma is managed by controller medications including steroids and prn beta agonists T F

Conclusions

1. EIB with and without known asthma is common, exacerbating with allergens and/or irritants, and controlled with achievement of a healthy lifestyle.

2. Exercise testing with pulmonary function confirmation is recommended for diagnosis of EIB and to monitor therapy

3. EIB with known asthma requires treatment for entire airway with leukotriene modifier and/or inhaled steroids or nonsteroidal ie cromolyn and relevant training. Beta agonist use prn

Thank you for listening. I will take questions

ASTHMA MEDICATIONS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Possible Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol DPI +</td>
<td>1 puff bid</td>
<td>Tremor/Tachycardia</td>
</tr>
<tr>
<td>Cromolyn MDI</td>
<td>4 puff bid</td>
<td>None</td>
</tr>
<tr>
<td>Nedocromil MDI</td>
<td>2 puff bid</td>
<td>Offensive Taste</td>
</tr>
<tr>
<td>Inhaled CS MDI</td>
<td>1-16 puff/day++</td>
<td>Candida/Dysphonia</td>
</tr>
<tr>
<td>Formoterol DPI</td>
<td>1 puff bid</td>
<td>Tremor/Insomnia</td>
</tr>
<tr>
<td>Combination *</td>
<td>1-2 puff bid</td>
<td>as with ICS/LABA</td>
</tr>
<tr>
<td>Leukotriene Mod</td>
<td>1 tablets qd-bid</td>
<td>headache/nausea</td>
</tr>
</tbody>
</table>

*Inhaled CS+LABA/LABA pm only except combination Modified from Storms reference below ++may be once a day but usually bid (Storms, WW. Medical Science and Sports Exercise (1Suppl):S33-8.1999.)