Exercise Effects of Asthma in Kids

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Disclosures
1. Dr. Gregory is on the speakers bureau for Novartis, ALK, and Monaghan which will not influence her presentation.
2. Dr. Bowman is retired from the Med Univ S Carolina; he is on the speakers bureau for Monaghan and a consultant for Thermo-Fisher. Neither will influence his presentation.
3. In the presentation, both speakers will only speak about medications in accord with their licensure.
4. It is important for members of the audience to recognize the relative chaos of licensure of asthma medications in children.

Educational Objectives
Members of the audience will be able to:
1. Describe mechanisms by which asthma may impair a patient’s exercise ability.
2. Outline the recommended approaches for effective treatment of exercise impairment caused by asthma.
3. Describe alternative approaches to manage asthma-related exercise impairment besides use of short-acting beta–agonists before exercise.
4. Identify ways they plan to use exercise tolerance as a marker of severity and control of asthma in their own practice / work setting.
**Exercise Effects of Asthma in Kids**

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**Exercise-Induced Bronchoconstriction (EIB)**

Transient and reversible acute airway narrowing that occurs during or after exercise in the presence or absence of clinically recognized asthma

Clinical Pearl:  
- The term exercise-induced asthma (EIA) is not used as it may imply incorrectly that exercise causes rather than exacerbates or triggers asthma symptoms

1. Bhumika, 2018  
2. Parsons, 2013  
3. Weiler, 2016

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**Prevalence of EIB in Children**

- General population approximately 5–20%  
- Approximately 40% to 60% of individuals with asthma have EIB  
- Affects up to 80% of children with asthma  
- Prevalence is greater in high-performance athletes than in the general population owing to prolonged inhalation of cold, dry air, aeroallergens and airborne pollutants

1. Khan, 2012  
2. Caggiano, 2017  
**EIB: The Facts**

- Exercise is one of the most common triggers of bronchoconstriction.
- EIB can occur without a diagnosis of asthma.
- EIB is frequently documented with asthma and reflects insufficient control of underlying asthma.
- Exercise-induced respiratory symptoms have a poor predictive value for bronchoconstriction.

**Pathobiology**

During exercise-related hyperventilation, transient osmotic change at the airway surface occurs causing reduction in epithelium liquid volume.

- Hypersmolar environment leads to:
  - Mast cell degranulation
  - Mast cell-mediated release: leukotrienes, histamine, tryptase, prostaglandins
  - Airway smooth muscle contraction
  - Increased mucus production
  - Microvascular permeability
  - Sensory nerve activation

**Bronchoconstriction, Airway edema**

**Role of Mast Cells, Eosinophils, and Mediators**

- Mast cells and eosinophils appear to play a major role in the pathogenesis of EIB.
- Peripheral blood eosinophil counts are associated with severity of EIB.
- Patients with asthma and EIB are more likely to have a greater concentration of eosinophils in sputum than those without EIB.
**EIB: Osmotic vs Thermal Theory**

**Osmotic theory**
- Mucosal dehydration
- Increased osmolarity
- Cell volume changes
- Mediators released
- Smooth muscle contraction
- Vascular leakage
- Edema

**Thermal theory**
- Mucosal cooling
- Vasoconstriction
- Rapid re-warming of the airway
- Reaction hyperemia
- Vascular engorgement
- Vascular leakage & edema

**Exercise-induced Bronchoconstriction**

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**Clinical Symptoms of EIB in Children**

**Most Common**
- Wheeze
- Chest tightness
- Dyspnea
- Cough
- Chest pain (primarily in children)
- Excessive mucus production

**Non-specific**
- Chest pain
- Poor exercise performance
- Avoidance of activity
- Difficulty keeping up with peers

**Impact of EIB in Pediatric Asthma**

- Physical activity is fundamental for growth and long-term development in children!
- Associated with physical and emotional burden
- Significantly reduces participation in physical activity/sports
- Negative association with QoL regardless of the severity of asthma symptoms
- Stop exercising because of EIB symptoms
- Children may experience
  - fear
  - bullying
  - social isolation
  - depression
  - anxiety
  - poor health
  - obesity

**Generally occurs during or within 5 to 30 minutes after intense exercise**

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**Which Sport is Best for Children with EIB?**

Sports and activities most likely to cause EIB symptoms are those requiring constant activity or performed in cold weather.

- **Low-risk**: short duration; high ventilatory levels are not reached.
- **Medium-risk**: alternation of aerobic and anaerobic phases; brief periods of continuous high-intensity exercise (5–8 min).
- **High-risk**: endurance and winter sports; physical effort high ventilatory levels are reached.

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**Sports and Potential Risks of EIB**

<table>
<thead>
<tr>
<th>Low-risk sports (5–8 minutes effort)</th>
<th>Medium-risk sports (5–8 minutes effort)</th>
<th>High-risk sports (&gt;5 minutes effort and/or in cold/dry environment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Track and field:</td>
<td>Soccer</td>
<td>Track and field:</td>
</tr>
<tr>
<td>• sprint</td>
<td>• long distance (10,000→15,000 m)</td>
<td>• Long distance (5000–10,000 m)</td>
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<tr>
<td>• hurdles</td>
<td>• endurance</td>
<td>• Endurance</td>
</tr>
<tr>
<td>• jumps</td>
<td>• interval training</td>
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<tr>
<td>Tennis</td>
<td>Rugby</td>
<td>Tennis</td>
</tr>
<tr>
<td>Fencing</td>
<td>American football</td>
<td>Fencing</td>
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<tr>
<td>Gymnastics</td>
<td>Basketball</td>
<td>Gymnastics</td>
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<tr>
<td>Downhill skiing</td>
<td>Baseball</td>
<td>Downhill skiing</td>
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<tr>
<td>Boxing</td>
<td>Field hockey</td>
<td>Boxing</td>
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<tr>
<td>Golf</td>
<td>Swimming</td>
<td>Golf</td>
</tr>
<tr>
<td>Weightlifting</td>
<td>Swimming</td>
<td>Weightlifting</td>
</tr>
<tr>
<td>Martial arts</td>
<td>Swimming</td>
<td>Martial arts</td>
</tr>
</tbody>
</table>

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**Swimming and EIB**

Studies do not show consistent effect of swimming, asthma risk and EIB:

- Swimming has been considered safe and recommended for patients with asthma.
- Conflicting data:
  - Increased risk of EIB
  - Competitive swimmers show a high prevalence of asthma and EIB

Possible rationale:

- Increased risk of EIB with swimming and pool attendance
- Association shown between chlorinated pools and prevalence of childhood asthma
- Chlorine has strong oxidizing potential and has been shown to cause epithelial damage
Medical treatment regimen and physical activities must be adapted to each situation.

The most important thing is to choose a sport the child enjoys!

Management of EIB

- Prevent and treat bronchoconstriction
- Non-Pharmacological Management
- Patient education

Management of EIB

Management of EIB is based on the understanding that EIB susceptibility varies widely among patients with asthma and in the absence of asthma.
Management of EIB: Treating Bronchoconstriction

- Management of EIB protocols are well established.¹
- Short-acting β-agonist (SABA) bronchodilators are treatment of choice.²,³
  - Inhaled SABAs should only be used in response to an EIB episode or up to 2–4 times per week ahead of exercise likely to induce EIB.
  - Daily use of SABA can quickly result in tolerance and limits its effectiveness.
- Leukotriene receptor antagonists should be considered.³,⁴
- Uncontrolled EIB requires further evaluation by an asthma specialist.
- Guideline-based use of combination therapy.
- Poor response to therapy.³,⁴
  - Poor adherence, improper inhaler technique and exposure to environmental triggers.

Management of EIB: Non-Pharmacological

- Avoid exercise in an at-risk environment.
- Good conditioning and aerobic fitness.¹
  - Regular exercise prevents rapid and abrupt increased in minute ventilation which is more likely to trigger EIB.²
- Gradual warm-up and cool-down periods.¹
- Use of face mask.
- Modifications to the activity or sport, if possible, can be helpful when the symptoms are limiting the child’s participation.³

Management of EIB: Patient Education

- Child and parents must understand:
  - the mechanisms causing EIB
  - associated symptoms associated
  - activities that causes prolonged rapid breathing
  - treatment regimen – Asthma Action Plan
  - Correct inhaler technique
- Identify activities that exacerbate symptoms
- Identify therapeutic interventions
- Adherence
- EIB should not limit participation.
Comprehensive Asthma Action Plan

Includes:
- Management of EIB
- Daily treatment regimen
- Recognizing worsening symptoms
- Pre-medicating before sports or exercise

Current Literature Review

Periostin and EIB in Children with Asthma

- Significance of periostin as a biomarker of TH2-induced airway inflammation, and as a measure of the response to therapy\(^1\)\(^2\)
- Periostin is induced by IL-13 and can induce proinflammatory cytokines, including thymic stromal lymphopoietin (TSLP)\(^1\)\(^2\)
- TSLP in combination with IL-33 increases mast cell formation\(^1\)
- Prognostic relationship between periostin and risk of asthma exacerbations has been observed in clinical studies

1. Masuoka, 2012
2. Izuhara, 2016
Periostin and EIB in Children with Asthma

86 children 6-15 years old from US, Japan and Korea
asthmatic group (n = 56) and healthy controls (n = 30)

1 Measured periostin levels in serum
1 Performed pulmonary function test:
   baseline measurements, post-bronchodilator inhalation tests, exercise bronchial provocation tests (BPTs), and mannitol BPTs

56 asthmatic children were divided into four groups:

- asthmatics with + BPT and + mannitol BPT (n = 30)
- asthmatics with + BPT but - mannitol BPT (n = 7)
- asthmatics with - BPT but + mannitol BPT (n = 10)
- asthmatics with - BPT and - mannitol BPT (n = 9)

Periostin and EIB in Children with Asthma

• Periostin levels were significantly correlated with both the maximum decrease in %FEV₁ and mannitol PD₁₅ value
• Serum levels of periostin in asthmatic children with both positive exercise and mannitol BPT were significantly greater than those in asthmatic children with both negative exercise and mannitol BPT and also greater than in healthy controls
• Periostin levels may serve as a clinically useful biomarker for identifying EIB in asthmatic children

Fraction of Exhaled Nitric Oxide (FeNO) in EIB

• Schoos et al. examined the predictive value of elevated FeNO for the presence of EIB on standardized testing in 7-year-old children at risk of asthma
• FeNO and EIB were linearly associated
• FeNO cutoff of 27 parts per billion (ppb) had a specificity and a positive predictive value (PPV) of 100% for EIB
• Study supports the presence of EIB is likely in children with an elevated FeNO

Studies confirmed respiratory symptoms are a poor predictor of EIB
Anaphylaxis and Exercise

Exercise-induced anaphylaxis (EIAn)
- anaphylaxis occurs only in association with physical exertion

Food-dependent, exercise-induced anaphylaxis (FDEIAn)
- Symptoms develop only if exercise takes place within a few hours of eating
- In most cases, symptoms present only if a specific food to which the patient is sensitized is eaten during the pre-exercise period

Exercise induced anaphylaxis (EIAn) is a rare and potentially fatal condition. Approximately 2–15% of all anaphylactic episodes are caused by or associated with exercise.

Food-dependent Exercise-Induced Anaphylaxis (FD-EIAn)
- EIAn is more frequently occurs in atopic individuals
- Diagnoses of FD-EIAn relies on a rigorous clinical history
- Symptoms occur from 10 minutes up to 4 hours after food allergen intake
- Generally occurs if a specific food is eaten; wheat tends to be more reactive
- Mast cell release of vasoactive mediators during EIAn may have a role in the pathogenesis
- Gastric permeability increases during exercise, which may permit increased entry of intact or incompletely digested allergens into the circulation
- Avoid any potential trigger foods at least 4–6 hours before exercise and one hour after exercise

Summary
- EIB is described as acute airway narrowing that occurs as a result of exercise
- EIB is observed in 40 to 90% of children with asthma
- Current ATS guidelines recommends use of SABA 15 minutes before exercise
- Intensity, duration, and type of exercise is associated with occurrence of EIB with higher prevalence rates in endurance sports, winter sports, possibly swimming
- Environmental factors such as temperature of inhaled air, the humidity and intensity of exercise have a significant effect on the induction of bronchoconstriction
- When properly managed, EIB does not restrict exercise performance
Clinical Perspectives on Exercise Tolerance in Children with Asthma

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Key Issues About Exercise

• Multiple causes of exercise intolerance exist, which vary markedly among children.
• What does “exercise intolerance” mean?
• Issues change over time, season, duration, environment, degree of asthma control.
• Has asthma been diagnosed?
• Does the patient know what s/he is feeling?
• We expect a child with asthma to have totally normal exercise tolerance.
Exercise Intolerance

• Practically speaking, a child won’t play hard
• Does it mean they won’t, don’t have the opportunity, can’t, or see no reason to do so?
• What are they feeling? Why are they feeling that way?
• If they feel bad, do they know that’s abnormal?
• Many kids say nothing about it.
• If they do say anything, how is it interpreted?

Key Issues About Exercise

• Many factors influence how hard a child plays
  ➢ Competition and challenges
  ➢ Instructions
  ➢ Enjoyment
• Who observes the child, at what time?
• Are there any external symptoms or noises, and when? (remember cough = wheeze)
• What is the setting? (ill, weather, outdoors, etc.)
• How long does it last; does rest make it go away?
• Does it recur predictably? Symptom variation

Has Asthma Been Diagnosed?

• Some say that if you want to find who in a school has asthma, you should ask the PE teachers who they think is lazy.
• Motivation, fitness, asthma influence activity.
• Key issue for asthma – response to SABA (prevent and/or resolve symptoms)
• Obesity <-> asthma <-> exercise intolerance
• A child should be able to play hard every day.
• If they don’t exercise and hide symptoms, we often underestimate the severity of their asthma.
**Asthma Symptoms**

- What does the patient describe?
- Wheezing makes it really obvious.
- Cough is observable, but often misunderstood.
- “I can’t breathe” must be evaluated.
- Parents can often observe when their child is having trouble, but they need to be present.
- Pulmonary function tests and peak flow meters can be almost diagnostic (> 5 yo) for asthma.
- Exercise intolerance is often not included as a marker of poor control.
- Exercise is a major QOL feature.

**What to do for Exercise Problems**

- Recognize them; adjust parent / child expectations; provide rescue; make diagnosis.
- Increase overall treatment – controllers may be needed.
- EIB often responds to altered warm-up routine.
- Obesity and asthma are particularly challenging.
- Elite athletes on combination meds may have new problems when they start having workouts and games late in the day. Moving the evening dose of ICS/LABA to pre – exercise can help.

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QUESTIONS?