Objective

• Discuss the use of spirometry and bronchoprovocation testing (BPT) in management of asthma
• Discuss the testing options and process to obtain reliable results
Conflicts of interest

- I have no conflicts of interest related to this presentation
- This is purely driven by my passion about helping people with asthma

Guidelines and sources

- EPR-3 (Expert panel review 3)
  - From the NIH – NHLBI - NAEPP
  - www.nhlbi.nih.gov/guidelines/asthma/
    Or search for “EPR-3 asthma”
- GINA (Global Initiative for Asthma)
  - www.ginasthma.org/
- ERS technical standard on bronchial provocation testing
  - www.erj.ersjournals.com European Resp Journal 49(5) 2017
Focus for today’s talk

- Bronchial provocation testing by
  - Methacholine
  - Exercise challenge
  - Eucapnic Voluntary Hyperventilation

ASTHMA

DEFINITION: Asthma

- Variable and recurring symptoms
  - chest tightness, wheezing, cough, dyspnea
- Airflow obstruction:
  - Bronchial hyperresponsiveness (“twitchy airways”)
  - Underlying inflammation

Airway obstruction is partially or completely reversible either spontaneously or with treatment)
In between asthma attacks – inflammation is in the background

Exposure to a trigger causes bronchospasm in allergic (atopic) asthma. Non-allergic, non-atopic has no known cause – no trigger

Criteria for acceptable spirometry testing

- American Thoracic Society and the European Respiratory Society (ATS/ERS)
  - Set standards for accuracy and reproducibility of tests
  - Gives guidance for interpretation of tests
    - Go to www.thoracic.org – search for “Statements” - look under “Pulmonary Function and Exercise Testing”
Why Use Spirometry?

• Asthma diagnosis:
  • “Use spirometry in all patients >5 years of age to determine that airway obstruction is at least partially reversible.”

• Asthma treatment strategies:
  • For the urgent or emergency care setting: <40 percent predicted in FEV1 or PEF indicates severe exacerbation and potential benefit from use of adjunctive therapies
  • >70 percent predicted FEV1 or PEF is a goal for discharge from the emergency care setting.”

From: NAEPP – EPR 3  Guidelines for the diagnosis and management of asthma

Asthma

• EPR-3 Recommendation is to use FEV₁/FVC to assess severity and FEV₁% predicted to assess risk of exacerbation

• EPR-3 divides this between 2 age groups
  • Those 5 to 11 years old and those ≥ 12 years old through adults
    • Not mentioned in those <5 years old

• GINA uses 6-11 years-old, 11+
Issues and Opportunities

• JAMA 2016 – 33% patients diagnosed with asthma did not have it.  
• 613 patients enrolled... 203 had asthma ruled out (33%)  
• 10 Canadian Cities  
  • Used a home PEF checks, spirometry, bronchial provocation tests, and interviews to monitor symptoms


Issues and Opportunities

• 28% had no respiratory condition, others had minor issues such as heartburn or allergies  
• 80% were taking asthma medications, 35% daily  
• 49% were not given objective tests (spirometry or PEF, bronchial provocation test)  
  • Study protocol slowly reduced medications  
  • end result was 90% stopped taking meds

Issues and Opportunities

“Doctors would not diagnose diabetes without checking blood sugar levels...

but for some reason many are not ordering the spirometry tests that can definitely diagnose asthma.”

*S Aaron et. al. JAMA. 2017;317(3):269-279

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<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (Children 5–11 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2×/month</td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal FEV₁ between exacerbations</td>
</tr>
<tr>
<td></td>
<td>FEV₁/PVC &gt;80%</td>
</tr>
<tr>
<td>Risk</td>
<td>Exacerbations requiring oral systemic corticosteroids</td>
</tr>
</tbody>
</table>

*For patients not taking LTC medications

From EPR-3 Guidelines
### Classification of Asthma Severity

**Youths ≥12 years of age and adults**

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Persistent</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days/week but not daily</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>2-3x/month</td>
<td>3-4x/month</td>
<td>&gt;1x/week but not nightly</td>
<td>Often 7x/week</td>
<td></td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2x/day</td>
<td>&gt;2 days/week but not &gt;1x/day</td>
<td>Daily</td>
<td>Several times per day</td>
<td></td>
</tr>
</tbody>
</table>

| Interference with normal activity | None | Minor limitation | Some limitation | Extremely limited |

#### Normal FEV₁/FVC:
- 0.10–0.19 yr: 85%–95%
- 0.20–0.39 yr: 80%
- 0.40–0.59 yr: 75%
- 0.60–0.79 yr: 70%

#### Lung Function
- Normal FEV₁ between exacerbations
- FEV₁ < 80% predicted
- FEV₁/FVC normal
- FEV₁/FVC reduced 5%
- FEV₁/FVC reduced > 5%

#### Risk
- Exacerbations requiring oral systemic corticosteroids
- EIB (see note)
- 0-1 year (see note)
- >1 year (see note)

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*For patients not taking LTC medications

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### Classification of Asthma Control

**5-11 years of age**

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days/week but not more than once on each day</td>
<td>&gt;2 days/week or multiple times a week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤1x/month</td>
<td>&gt;2x/month</td>
<td>&gt;2x/week</td>
</tr>
</tbody>
</table>

| Interference with normal activity | None | Some limitation | Extremely limited |

#### Short-acting beta-agonist use for symptom control (not prevention of EIB)
- ≤2 days/week
- >2 days/week

#### Lung Function
- FEV₁ or peak flow >80%
- FEV₁/FVC >80%
- 60–80% predicted/ personal best
- 50–60% predicted/ personal best
- <50% predicted/ personal best

| Exacerbations requiring oral systemic corticosteroids | 0-1 year (see note) | >1 year (see note) |

#### Risk
- Evaluation requires long-term follow-up.
- Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.

#### Recommended Action for Treatment

(See figure 4-1b for treatment steps.)

- Maintain current step.
- Consider step down if well controlled for at least 3 months.
- Step up to at least 1 step and intensify in 2-4 weeks.
- For side effects, consider alternative treatment options.
- Consider short course of oral systemic corticosteroids.
- Step up to 1-2 steps, and intensify in 2 weeks.
- For side effects, consider alternative treatment options.
Criteria for acceptable spirometry testing

- **Acceptable spiromgrams**
  - No cough during first second
  - Maximal effort given
  - No leak at mouthpiece or nose
  - No obstructed mouthpiece
  - ≥6 seconds for FVC for adults
  - Reach a “plateau” for exhalation

- **Best test = highest sum of FEV₁ + FVC**
  - Alternate – Select highest FVC, select highest FEV₁ (which determines the remaining values)
  - QC – a. FEV₁ ± 150 mL, b. FVC ± 150 mL, c. PEF ± 10%

- When testing, keep each recorded effort until good clinical judgment justifies dropping the poor recordings. Save the best three.
Evaluate: BPT indicated if spirometry results are normal & patient has symptoms

“Normal” F/V loop often shows up in asthma when between attacks

“No BPT – Pre/post needed”

“Obstruction” pattern during asthma attack. If seen in testing, bronchoprovocation (BPT) is NOT INDICATED. Instead, a Pre/Post is needed

Pre-post F/V loops and V/T curves – NO BPT needed

These tracings reflect obstruction in the “Pre” test BPT is NOT INDICATED and shows a (significant) pre/post response to a bronchodilator
Obstruction at the outset & Significant change Pre/Post (minimum 12% and 200 mL increase in FEV₁ or in FVC) – NO BPT

FVC : 3.14 – 2.52 = 620 ml response and 25% change
FEV₁: 2.14 – 1.59 = 550 ml response and 35% change

Definition of Bronchial Hyperresponsiveness (BHR)

• BHR – exaggerated bronchoconstriction
  • Allergens: dust mites, pollen, dander, mold, cockroach
  • Pollutants: exhaust fumes, smog
  • Irritants: tobacco or wood smoke, chemicals
  • BHR also linked to exercise, cold air, sulphur dioxide, non-isotonic aerosols.

• These stimuli cause the airways to narrow when BHR is present
• BHR is the acute pathology in asthma and is linked to the inflammatory process
Asthma Is a Chronic Inflammatory Disorder

- Airway inflammation is the underlying pathology in asthma
- Inflammation leads to:
  - Airway hyperresponsiveness – rapid and exaggerated response to triggers
  - Obstruction due to bronchoconstriction – usually at least partially reversible
  - Symptoms – cough, wheeze, dyspnea, chest tightness
  - Further inflammation, airway remodeling
- Symptoms are easily appreciated, but inflammation is often overlooked


Why do Bronchial Provocation Testing?

- Asthma is often misdiagnosed
  - No stand-alone blood test, X-ray, lab test
  - Many things mimic asthma (CHF, VCD, COPD, etc)
  - Subjective estimates of asthma correlate poorly to objective measures ...“poor perceivers”
  - BPT helps to rule in or rule out asthma (but it is still not a definitive test)
When is BPT needed?

• Symptoms suggest asthma but a normal PFT...
  • Questionable case (EIB, cough variant asthma)

• Objectively findings - treat effectively at the lowest cost
  • Occupation or recreational activity where hyperresponsive airways could be a potential problem
  • May be useful to “step down” in treatment

2 types of BPT

1. Direct tests:
   • Acts directly on the bronchial smooth muscle to cause bronchoconstriction.
     • Agents: Inhaled methacholine or histamine to cause a measurable change
   • Direct test tends to **RULE OUT** asthma when negative

2 types of BPT

2. Indirect tests:
- Cause a change in the airway and this affects mast cells
- Brings out release of histamine, leukotrienes, prostaglandins, etc.
  - Agents: Exercise-induced bronchospasm (EIB), Eucapnic voluntary hyperventilation (EVH)
  - Agents: Inhaled agents (mannitol, hypertonic saline, adenosine monophosphate)
- Indirect tests tend to **RULE IN** asthma when positive

Exercise/Eucapnic Voluntary Hyperventilation

Respiratory Water Loss

Mucosal Dehydration

Airway cooling

Increase in $[\text{Na}^+], [\text{Cl}^-], [\text{Ca}^{2+}], [\text{K}^+]$

Cough

Increase in osmolarity

Sensory nerves

Airway surface liquid

Epithelial Cells

Submucosa

and in the presence of inflammation (eosinophils, mast cells)

Mediators released from inflammatory cells

Bronchial smooth muscle contraction in those with hyperresponsive airways

Inhaled Mannitol, hypertonic saline

Methacholine

Bronchial provocations tests

- **Why?** History and symptoms point to asthma but *spirometry is normal*
- **How?** Challenge or provoke airways to spasm
  - BUT - If obstruction is present stop and do a pre/post test.
  - For inhaled agents, step up in strength and check FEV$_1$ at each step
  - For exercise, perform then - then begin serial FEV$_1$ measurement
- **What?** Look for a 20% drop from baseline = positive test
  - methacholine – 20%
  - mannitol - 15% or 10% drop between 2 consecutive doses
  - exercise 10-15%
- **Report?** Provocative dose (PD$_{20}$)
Contraindications for BPT (from ERS J 2017)

- **Airflow limitation**
  - $\text{FEV}_1 < 60\%$ predicted (adults or children) or 1.5 L (adults)
  - $\text{FEV}_1 < 75\%$ predicted (adults or children) for exercise or EVH challenge

- **Spirometry Quality** – Can’t do the PFT test

- **Cardiovascular problems**
  - MI or stroke in last 3 months
  - Uncontrolled HTN, known aortic aneurysm
  - Recent eye surgery or risk for elevating ICP

- **General** – Can’t do the provocation test

Relative contraindications

- Pregnancy or nursing mothers
- Patient is using cholinesterase inhibitor medication (e.g. for myasthenia gravis)
- Recent viral infection (may cause temporary increase in airway responsiveness and false-positive results)
Preparations

• Quality and Safety
  • Spirometer is calibrated
  • Vials for testing are prepared by pharmacist or qualified, well-trained staff using sterile technique
  • Vials are clearly labeled, refrigerated until 30 minutes prior to testing (use at room temperature)
  • Observe Infection control precautions (hand-washing, spirometer has new filter/mouthpiece, sterile solutions, new or sterilized nebulizer)
  • Patient informed consent obtained (may cause chest tightness or cough)
    • DON’T state that test induces asthma attack – may bias the results

Preparations

• Directions for withholding medications are followed
  • Including no alcohol within 4 hrs., no smoking within 1 hr.
  • Note: Normal dietary servings of caffeine, chocolate have no effect
  • Minimize exposure of challenge agent to staff (filtering exhaled air, two room air turn-overs/hour, etc.)
  • Medical director or physician close at hand (to treat acute bronchoconstriction)
  • In testing area:
    • epinephrine (subcutaneous injection) albuterol and delivery device, oxygen, plus resuscitation supplies, stethoscope, sphygmomanometer, pulse oximeter
  • Patient always attended throughout testing ....and not sent home unless within 10% of baseline (pre-testing) spirometry values
Withholding medications/ methacholine

<table>
<thead>
<tr>
<th>Medication</th>
<th>Acronym</th>
<th>Withhold time prior to testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting β-agonists in conventional inhaled doses</td>
<td>SABA</td>
<td>6 hrs</td>
</tr>
<tr>
<td>(e.g. albuterol 200 μg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting β-agonists (e.g. salmeterol)</td>
<td>LABA</td>
<td>36 hrs</td>
</tr>
<tr>
<td>Ultra-long-acting β-agonists (e.g. indacaterol, vilanterol, olodaterol)</td>
<td>LABA</td>
<td>48 hrs</td>
</tr>
<tr>
<td>Ipratropium (Atrovent 40 μg)</td>
<td>SAMA</td>
<td>12 hrs</td>
</tr>
<tr>
<td>Long-acting anti-muscarinic agents (e.g. tiotropium)</td>
<td>LAMA</td>
<td>≥168 hrs (7 days)</td>
</tr>
<tr>
<td>Oral theophylline</td>
<td></td>
<td>12–24 hrs</td>
</tr>
</tbody>
</table>

From ERS J (2017)

Quadrupling concentrations of methacholine

Label Vial A – add diluent to starting vial (100 mg product). Label 4 empty vials B, C, D, E with correct letter and strength of solution. Label 2 syringes: “Diluent” and “methacholine”. Keep them “pure”

<table>
<thead>
<tr>
<th>Label strength</th>
<th>Take</th>
<th>Add NaCl (0.9%)</th>
<th>Obtain dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>100 mg powder</td>
<td>6.25 mL</td>
<td>A: 16 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution A to make B</td>
<td>9 mL</td>
<td>B: 4 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution B to make C</td>
<td>9 mL</td>
<td>C: 1 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution C “ ” D</td>
<td>9 mL</td>
<td>D: 0.25 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution D “ ” E</td>
<td>9 mL</td>
<td>E: 0.0625 mg·mL⁻¹</td>
<td></td>
</tr>
</tbody>
</table>

Store powder between 59° - 86° F. Shake each vial well after preparing. Store A – E at 36° to 46° F – no more than 2 weeks. Give 30 min. pre-test to reach room temp.
Bronchial Provocation Testing

• Dosimeter or Tidal Breathing?
  • Dosimeters are becoming obsolete
  • Breath-actuated nebulizers or vibrating mesh nebulizers are now being used – must know the dose delivered
  • Use noseclips for inhalation and FEV₁

Dosimeter

• Dosimeter – 5 inhalations from FRC to TLC and hold 5 seconds
• FEV₁ and FVC at 30 and 90 seconds after inhalation of product – use the highest number
• Stop if FEV₁ drops below 80% of baseline FEV₁
• Report Provocative dose - PD₂₀
  • Old method of reporting was the PC₂₀
Tidal Breathing

- Tidal Breathing for 1 minute
  - 2 minutes? 12 seconds? --- depends on the nebulizer efficiency and output
  - Manufacturer should have aerosol output and particle size specified for the nebulizer used
- FEV\textsubscript{1} and FVC at 30 and 90 seconds after inhalation of product – use the highest number
- Stop if FEV\textsubscript{1} drops below 80% of baseline FEV\textsubscript{1}
- Report Provocative dose - PD\textsubscript{20}

Airway response to methacholine

<table>
<thead>
<tr>
<th>PD\textsubscript{20} μ mol (μg)</th>
<th>PC\textsubscript{20} mg.mL\textsuperscript{-1}</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 (&gt;400)</td>
<td>&gt;16</td>
<td>Normal</td>
</tr>
<tr>
<td>0.5 - 2.0 (100 – 400)</td>
<td>4-16</td>
<td>Boderline AHR</td>
</tr>
<tr>
<td>0.13 - 0.5 (25 – 100)</td>
<td>1-4</td>
<td>Mild AHR</td>
</tr>
<tr>
<td>0.03 – 0.13 (6 – 25)</td>
<td>0.25 – 1</td>
<td>Moderate AHR</td>
</tr>
<tr>
<td>&lt;0.03 (&lt;6)</td>
<td>&lt;0.25</td>
<td>Marked AHR</td>
</tr>
</tbody>
</table>

ERS Technical Standards from ERJ 2017 49: 1601526
From the revised GINA Report, Global Strategy for Asthma Management and Prevention (2007), available on the Global Initiative for Asthma (GINA) website

*Airway responsiveness to inhaled methacholine or histamine in a normal subject, and in asthmatics with mild, moderate, and severe airway hyperresponsiveness. Asthmatics have an increased sensitivity and increased maximal broncho-constrictor response to the agonist. The response to the agonist is usually expressed as the provocative concentration causing a 20% decline in FEV₁ (PC20).

Methacholine Challenge Report

Start low and work up in increasing doses. Check FEV₁ x 2 after each dose.
Bronchial provocation testing – positive methacholine test

Positive test that occurred between the 5 mg and 10 mg dose. 20% fall from the baseline in the FEV1
Bronchial provocation testing - positive methacholine test

Exercise Challenge

• Usefulness:
  • The real stimulus that produces the symptoms
  • High positive predictive value for asthma
  • Likely to be the most common trigger of an attack
  • Appropriate for assessing drug effects
Exercise Protocol

- 6 to 8 minutes at high level of exercise
  - Targeting a percentage of max HR based on age
- Monitor continuous ECG and SpO2
  - Some labs monitor F/V loops, minute ventilation and tidal volume during exercise to assess workload
- Environmental conditions should be controlled:
  - Temp <25°C (77°F), relative humidity ≤ 50%
  - Nose clips needed to reduce gas conditioning by nose
- Spirometry recorded at 1 to 2 minutes post exercise then at 5, 10, 15, 20, and 30 minutes
- Positive test: 10% to 15% drop in FEV₁ from baseline

Exercise Challenge

**Limitations:**
- Exercise choice is limited
- Unable to exercise for the test?
- Elite athletes may be difficult to reach maximum exercise
- Exercise may need to be sports specific
  - Rowing vs cross-country skiing
- ‘Dry’ air for best results
- Safety issues
  - May have severe bronchospasm post exercise (greater risk for large falls in FEV₁)
  - If using a treadmill – required speeds are high...safety?
- Cost and resources
Eucapnic Voluntary Hyperventilation (EVH)

- **Usefulness**
  - High sensitivity to identify EIB
  - Protocol and inspired air conditions can be adjusted to simulate conditions of a specific sport (e.g. rowing, cross country skiing, cycling)
  - Negative test = low risk of EIB
  - Mediators the same as for EIB
  - Equipment less expensive compared with exercise

Protocol for EVH

- Cold air (relative humidity near 0%) breathed at high level of ventilation
  - Target ventilation is between 30 to 70% of the MVV
- CO\textsubscript{2} levels kept stable by using special gas mixture
  - 5% CO\textsubscript{2} 21% O\textsubscript{2} balance N\textsubscript{2}
- Hyperventilation maintained for 4 to 6 minutes
- Spirometry measured at 1, 5, 10, 15, 20 minutes post exercise
- 15% decrease in FEV\textsubscript{1} from baseline is positive
EVH Limitations

• Special gas mixture needed (5% CO₂ 21% O₂ balance N₂)
• Less sensitive if <6 minutes or if Vₑ < 30 x FEV₁
• 6-min protocol 30 x FEV₁ can provoke severe fall in FEV₁
Conclusion

• Bronchial provocation testing is useful as another tool to help rule in or rule out asthma
  • Agents include methacholine, mannitol, cold air, EVH, Exercise challenge
  • If AFO is seen in routine PFT – BPT is not needed... do a Pre/post to check response to β agonist (albuterol)
  • Watch or other causes (i.e. vocal cord dysfunction)
• Be safe and be accurate in testing!

Thank you for listening

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