ALLERGY & IMMUNOLOGY
CASE PRESENTATIONS

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Disclosures

• I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

- Recognize and treat anaphylaxis
- Perform appropriate evaluation for food allergy
- Utilize appropriate diagnostic tests in the evaluation of patients for suspected immune deficiency
- Understand the risk factors involved in the development and progression of asthma
- Recommend asthma therapy based upon level of severity or control
**ABP Specifications**

- Specific recommendations from the ABP regarding Allergy & Immunology content will be denoted throughout this presentation by use of “**”
Case 1
Food Allergy
Case 1

- An 8 year old girl just finished eating lunch and develops rapid onset progressive hives and swelling of her face with one episode of vomiting.

1. What is her diagnosis?

2. What is the best treatment?
What is Anaphylaxis?**

- Prior lack of universal agreement on definition
- NIAID/FAAN convened worldwide symposium in 2004
- Here’s what they came up with:
  
  “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.”

- Developed criteria to help patients, lay personnel, EMS, and physicians

• Skin symptoms occur in >80% of cases of anaphylaxis**

• Absence of skin symptoms does not exclude anaphylaxis

• These criteria will satisfy almost all cases
Two or more that occur rapidly after exposure to likely allergen:

**Skin and/or Mucosa**
- Pruritus
- Flushing
- Hives
- Angioedema

**Respiratory Compromise**
- Dyspnea
- Wheeze
- Stridor
- Hypoxemia

**Hypotension/End-organ Dysfunction**
- Collapse
- Syncope
- Incontinence

**Persistent GI Symptoms**
- Vomiting
- Abdominal Pain

- If patient is *KNOWN* to have allergy *and* exposure, then GI symptoms more applicable
After exposure to known allergen for that patient:

Hypotension

- This applies to the *RARE* patient with acute hypotension *AND* known allergy *AND* known exposure
  - Most children do not have hypotension
  - Unlikely to apply in the field
    - i.e. symptoms after receiving allergen immunotherapy injection in office setting
Things to Consider

- Scromboid poisoning**
  - Almost always fish: tuna, mackerel
  - Others eating same meal will suffer symptoms as well
- MSG reactions
- Non-IgE mediated food intolerance
Case 1

- 911 was called and this girl was treated with epinephrine by the emergency responders and all symptoms resolved within 15 minutes.

3. What is the proper dosage?

4. How should epinephrine be administered?

5. Should she be transported to the nearest Emergency Department?

6. Is any additional follow up needed?
Epinephrine Autoinjectors

Adrenaclick®

Auvi-Q™

EpiPen®
Epinephrine and Anaphylaxis

- First line therapy
- Provides rapid resolution of all symptoms
- Side effects are minimal when administered IM at recommended dosages**
  - 0.15 mg ≤ 25 kg
  - 0.3 mg > 25 kg

- Majority of deaths from anaphylaxis are associated with delayed or lack of epinephrine administration
Treatment of Anaphylaxis**

- Epinephrine administered into lateral aspect of thigh
- When in doubt, give epinephrine!
- Antihistamines are second line therapy
- Corticosteroids *ARE NOT* helpful!!!

- In controlled setting – epinephrine should still be administered IM
  - Dose = 0.01 mg/kg (max 0.5 mg) every 5 minutes as necessary to control symptoms
- Supportive care as deemed necessary

Disposition

- Recommended observation in ED at least 4 to 8 hours
- Decision to admit individualized
  - More than 1 dose of epi, IV fluids for hypotension, laryngeal edema, severe asthma, ingestion as trigger → consider admission
- If symptoms fully resolved, discharge to home
  - No evidence to support routine therapy with antihistamines or steroids if symptoms have completely resolved

Case 1

- She has no known history of food allergies
- Lunch consisted of a turkey sandwich, salad with strawberries, shredded cheese, raspberry walnut dressing, candied pecans, and a cookie from a local bakery.
- She also took ibuprofen 5 hours earlier for a headache

7. What else would you like to know?
8. What was the cause of her symptoms?
Case 1

9. Did this girl experience a food allergy reaction?

10. Was the timing right?

11. Did she have the right symptoms?

12. Did she eat the right food?

13. Is there any testing that you want to perform? For what?
Case 1

- You obtain serum IgE testing to evaluate for tree nut allergies
- Order a ‘childhood allergy profile’
- Results (kU/L):
  - Milk 1.19
  - Egg 0.87
  - Peanut 6.65
  - Walnut 47.91
  - Almond 13.49
  - Pistachio 8.54
  - Cashew 9.32

14. What is your advice?
15. Do you need more information?
Sensitization ➔ Allergy

- Sensitization
  - The detection of specific IgE toward an allergen through skin prick, intradermal, or serum specific IgE testing

- IgE mediated hypersensitivity
  - Characteristic clinical symptoms upon exposure to an allergen AND…
  - The detection of specific IgE toward that allergen
IgE Mediated Food Allergies

- Cow’s milk, egg, soy, wheat, peanuts, tree nuts, fish, and shellfish account for > 90% of all food allergy**
- Reactions are objective, immediate onset and reproducible with every exposure to the offending food, no matter what form**
- Typical symptoms:
  - Urticaria
  - Angioedema
  - Emesis
  - Rhinorrhea
  - Wheezing
  - Hypotension
  - Anaphylaxis
- Uncommon causes of allergy:
  - Strawberries, fruits/vegetables, natural food additives, artificial preservatives
Serum Specific IgE Testing

- Levels of IgE specific for food and/or inhalant allergens can be obtained through routine venipuncture
- Test offers convenience
- Commercial panels widely available and marketed as excellent screening tools

- Results reported in a range from 0.1 kU/L – 100 kU/L
  - Also reported as arbitrary classes (1 through 5)

- A big “!” will accompany any value reported > 0.10 kU/L
## Specific IgE Cutoff Points

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Decision Point (kU/L)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7</td>
<td>98</td>
<td>38</td>
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<tr>
<td>Milk</td>
<td>15</td>
<td>95</td>
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<tr>
<td>Peanut</td>
<td>14</td>
<td>100</td>
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<tr>
<td>Fish</td>
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<td>56</td>
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<tr>
<td>Soybean</td>
<td>30</td>
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<td>82</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>74</td>
<td>87</td>
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</tbody>
</table>

A Quick Word About IgG…

• Serum IgG antibodies towards foods touted by many practitioners as a tool to diagnose food allergy/intolerance
• IgG may actually be a marker for food tolerance, not intolerance
  • Early recovery from cow’s milk allergy associated with increasing IgG₄

• “IgG and IgG subclass antibody tests for food allergy do not have clinical relevance, are not validated, lack sufficient quality control, and should not be performed”

Case 1

• Mom is pregnant and her due date is in 2 months. Mom has a history of allergic rhinitis and asthma.

16. What risk factors influence the development of allergic disease in the baby?

17. Is there anything she can do now to prevent the onset of allergies in this baby?
Prevalence of Food Allergy

- Many reports have listed food allergy in **17-30%** of the general population
  - Self reported measures without confirmation through appropriate testing

- DBPCT performed with appropriate testing and confirmed with food challenges place prevalence between **5-8%** of general population
  - On average, at least one child in every classroom in America

Risk Factors for Development of Food Allergy**

- Eczema
- Asthma
- Environmental allergies
- Family history of allergies
Natural History of Food Allergies**

• IgE mediated food allergies
  • Milk, egg, wheat, soy → majority develop tolerance by school age
  • Peanut, tree nuts, seafood → 80-90% remain for life

• Milk protein induced proctocolitis
  • Improves by 12 months of age
  • No testing indicated

• Food protein induced enterocolitis
  • Often improves prior to school age
Case 1

18. At what age should the following foods be introduced to the new baby:
   - Milk
   - Egg
   - Wheat
   - Peanut
   - Tree nuts
   - Seafood
## 2008 vs 2000 AAP Recommendations**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>2008</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define ‘high risk’</td>
<td>Parent or sibling with atopy</td>
<td>Both parents or 1 parent and sibling</td>
</tr>
<tr>
<td>Avoidance of foods during pregnancy</td>
<td>Lack of evidence</td>
<td>Possibly peanut</td>
</tr>
<tr>
<td>Exclusive breast feeding until</td>
<td>Evidence for 3-4 mos</td>
<td>6 months</td>
</tr>
<tr>
<td>Avoidance of foods during lactation</td>
<td>Some evidence for reduced atopic dermatitis</td>
<td>Peanuts, tree nuts and consider egg, milk, fish and “other foods”</td>
</tr>
<tr>
<td>Prevention formulas</td>
<td>Certain hydrosylates may delay onset compared with cow’s milk based, not soy</td>
<td>“Hypoallergenic” formulas, not soy</td>
</tr>
<tr>
<td>Types of solid foods</td>
<td>Evidence to wait until 4-6 mos; no evidence for specific foods</td>
<td>No solids until 6 mos, milk til 1 yr, egg til 2 yrs, peanuts, nuts, fish til 3 yrs</td>
</tr>
</tbody>
</table>
What’s the Deal with Peanuts?

- Prevalence of food allergy has doubled in past decade
- Food allergy:
  - Overall, affects 5-8% of children
  - Peanut allergy ~1%
- 2008 Study: Prevalence of peanut allergy in Israeli children 10-fold less than in United Kingdom
  - ARR: 9.8 (95% CI, 3.1-30.5)
- Median monthly consumption of peanut in infants 8-14 months old
  - Israel = 7.1 grams
  - UK = 0 grams

Learning about Early Introduction of Peanuts (LEAP) Study

- **Landmark** food allergy study
- Demonstrated that early introduction of peanut may protect against development of peanut allergy

**Protocol:**
- Infants 4-11 months of age
- Moderate-to-severe eczema and/or egg allergy
- Skin prick test (SPT) and in office challenge
- 640 infants randomized (median age 7.8 months)
  - 542 SPT negative
  - 98 SPT positive (1-4 mm wheal)
    - Consume 2 grams peanut 3 days/week until age 5
    - Peanut avoidance
- Follow up challenge at 5 years of age

LEAP Results

- SPT & consumed peanut = 86% Reduction
  Primary Prevention

+ SPT & consumed peanut = 70% Reduction
  Secondary Prevention

New Guidelines

- Goal is to introduce age appropriate peanut containing foods to all infants before 11 months of age
- Does not apply to anyone who already has peanut allergy!!!
- Only small subset need IgE testing before introduction
  1. History of severe eczema and/or egg allergy → serum IgE or skin prick to peanut 4-6 months of age then introduction.
  2. Mild to moderate eczema → introduce at home without testing ~6 months of age.
  3. No eczema or food allergy → introduce at home without testing ~6 months of age.
New Guidelines

Severe eczema
Or
Egg allergy
Or
Both

Peanut serum specific IgE

<0.35
- Majority will have (-) SPT to peanut.
  - Risk of reaction low.
  - Options:
    1. Introduce at home
    2. Supervised feeding in office based upon parent/provider preference

≥0.35
- Refer to allergist for consultation/SPT protocol

Peanut skin prick test (SPT)

0-2 mm
- Risk of reaction low
  - (95% will not have peanut allergy)
  - Options:
    1. Introduce at home
    2. Supervised feeding in office based upon parent/provider preference

3-7 mm
- Risk of reaction variable
  - Options:
    1. Supervised feeding in office
    2. Graded oral food challenge in specialist facility

≥8 mm
- Infant likely allergic to peanut.
  - Peanut avoidance recommended
  - Consider referral to allergist.
Case 1

- Mom has questions about her oldest son, who is 8 years old. He has food allergies to egg and shellfish. She would like for him to receive the influenza vaccine and wants to know if he can ever have a CT scan with contrast.

19. What vaccines does he need to avoid?

20. What is the risk of shellfish allergy and radiocontrast media?
Vaccines Prepared with Egg - Background

- Hen’s egg embryos used for enriched media to grow viruses used in the production of several vaccines
  - MMR, Rabies, Yellow Fever, and Influenza vaccines
  - Picograms or micrograms of egg protein may be introduced into the vaccines

- Vaccines can also contain several other ingredients that may provoke an IgE mediated reaction
  - Gelatin
  - Neomycin
Safety of MMR Vaccine in Egg Allergic Patients

- **2016 Red Book:**
  - Skin testing of children for egg allergy is not predictive of reactions to MMR vaccine and is not required before administering MMR or other measles-containing vaccines.
  - Children with egg allergy may be given MMR or MMRV vaccines without special precautions.
Safety of Influenza Vaccine in Egg Allergic Patients

- General agreement regarding overall safety of influenza vaccine

- JCAAI:
  - Egg allergy is not a contraindication to administration of the influenza vaccine, regardless of history
  - Waiting periods are not warranted
  - Referral to an allergy specialist is not necessary

- AAP:
  - All children with egg allergy can receive influenza vaccine with no additional precautions from those of routine vaccinations.
Contrast Media and Shellfish Allergy Origins

- 1975 report by Shehadi:
  - Patients with a history of *any allergy* = 2.2 x more likely to have reaction to contrast media
  - Number 1 allergy listed = seafood (15%)

- Oh, by the way:
  - Other allergies listed, also at 15% include:
    - Egg
    - Milk
    - Chocolate
  - All allergies listed by self report, no confirmatory testing was ever performed

Shellfish and Iodine

- Origins of this association unclear
- Likely *created by physicians* linking history of shellfish allergy and iodinated contrast

- Iodine is not and cannot be an allergen
  - Present throughout all of our bodies
  - Not large enough to cross link IgE antibodies

- Fish and shellfish contain iodine, but this is not the source of allergens
  - Muscle proteins cause IgE mediated reactions
  - Tropomyosin and parvalbumin
Case 2
Immune Deficiency
Case 2

• A 2 year old boy has a history of recurrent otitis media with prior tympanostomy tube insertion at 15 months of age, one prior episode of pneumonia, and has been treated with antibiotics 3 times in the past 6 months for sinusitis.

• Weight 5\textsuperscript{th} percentile, Height 5\textsuperscript{th} percentile
• Total serum IgG = 486 mg/dL
Case 2

1. Does he have an immune deficiency?

2. What other conditions can contribute to recurrent infections?
Primary Immune Deficiency

- Rare in general population\textsuperscript{1,2}
  - Estimates of incidence: 1 in 2,000-10,000 live births
  - Prevalence: 1 in 10,000
- Most common\textsuperscript{1,2}
  - Selective IgA Deficiency: 1 in 300-500 live births
- Very rare\textsuperscript{3}
  - Chronic Granulomatous Disease: 1 in 200,000 live births

History is the Key

- Use the history to decide if/what type of evaluation is indicated
- Age of presentation
- Family history
- History of severe or recurrent infections
History is the Key

- How were infections diagnosed?
- Why were antibiotics prescribed?
- How does his growth compare to other siblings or parents?
Recurrent Infections

- Difficult to assign precise frequency or number of infections that reflects an impaired immune response

- Majority of “typical” infections are viral
  - Average child: 6-8 URI’s/year

- Consider increased exposure to infections
  - Daycare
  - School
  - Siblings
Clues for Abnormal Infections

- Unusual site
- Unusual severity
- Unusual microbe
Co-Morbid Conditions Associated with Immune Deficiency

- Autoimmune disease
- Malignancy
- Cytopenias
- Thymoma
- Hypocalcemia
- Congenital heart disease
- GI disease
- Vasculitis
- Arthritis
Secondary Causes of Recurrent Infections

- Allergic rhinoconjunctivitis
- Cystic fibrosis
- COPD
- Ciliary dyskinesia
- Diabetes mellitus
- Protein losing enteropathy
- Nephrotic syndrome
- Malnutrition
- Asplenia or hyposplenism
- HIV infection
- Resistant organisms - MRSA
- Trauma or burns
- Aging
- Medications
- Stressful life events
- Tobacco use and/or exposure
- Illicit drug use

You need to rule out secondary immune deficiency before you can diagnose primary immune deficiency.
Clues on Physical Exam

- Gender
- Poor growth
- Muscle wasting / failure to thrive
- Lack of tonsils or other lymph nodes
- Diffuse lymphoid hyperplasia
- Dysmorphic facies
- Hepatosplenomegaly
- Severe eczema
Case 2

3. What types of immune deficiency should you consider for this patient?

4. What historical factors can help determine which immune deficiencies to consider?
Four Main Components to Human Immune System

- Humoral Immune System
  - B cells and immunoglobulins

- Cell Mediated Immunity
  - T cells

- Phagocytes

- Complement
Humoral Immune System

- Adaptive Immunity
- Largely responsible for clearing bacterial infections
- 5 types of immunoglobulin:
  - IgG, IgA, IgM, IgE, IgD
Examples of Humoral Immune Deficiency

- Bruton’s agammaglobulinemia
- Selective IgA deficiency
- Common variable immune deficiency
- Selective antibody deficiency
- Transient hypogammaglobulinemia of infancy
Presentation of Humoral Immune Deficiency**

- May not present until 3rd, 4th, 5th decade of life
  - Rarely presents before 6 months of age**

- Repeated pyogenic infections with gram positive encapsulated bacteria
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Staphylococcus aureus*

- Can also see gram negative infections
  - *Pseudomonas*
Presentation of Humoral Immune Deficiency**

• Typical anatomic location is sinopulmonary tract

• Repeated episodes of otitis media, pneumonia, sinusitis

• Do not typically succumb to opportunistic, viral, or fungal infections
  • Increased susceptibility to enterovirus
  • Meningoencephalitis
Cell Mediated Immunity

- Principally involved with host defense against viral, mycobacterial, and fungal infections

- Also play a critical role in adaptive immunity
  - Recruit and activate B cells to stimulate antibody production
Examples of Cell Mediated Immune Deficiency

- DiGeorge syndrome
- Ataxia telangiectasia
- Wiskott-Aldrich syndrome
- Chronic mucocutaneous candidiasis
- IFN-\(\gamma\) receptor defects
- X-linked hyper IgM syndrome
Presentation of Cell Mediated and Combined Immune Deficiency

- Onset early in infancy
- Recurrent infections with fungal, viral, and mycobacterial pathogens
- Opportunistic infections
- Failure to thrive
- Seborrheic dermatitis
- Fatal infections after live virus vaccines
- GVHD from blood transfusions
- Increased incidence of malignancy
Phagocytes

- Innate immune response
- Phagocytes, neutrophils, natural killer cells
- Responsible for engulfing and destroying bacteria
- Recognize bacterial cell wall constituents
Examples of Phagocytic Disorders

- Chronic granulomatous disease
- Leukocyte adhesion deficiency
- Chediak Higashi syndrome
- Hyper IgE syndrome
Clinical Presentation of Phagocytic Dysfunction**

- Infections with minimal or no pus
- Infections with formation of abscesses or granulomas
- Recurrent infections with bacteria of low virulence
- Catalase producing organisms
Clinical Presentation of Phagocytic Dysfunction**

• Infections at sites where the body interfaces with the environment
• **Skin infections**, furuncles, organ abscesses, lymphadenitis, gingivostomatitis
• Poor wound healing
• Delayed separation of umbilical cord
  • 2-3 months+ before concern
Complement

- Cascade of 9 principal and several regulatory proteins
- 3 separate pathways
  - Classical
  - Mannose binding lectin
  - Alternative
Clinical Presentation of Complement Disorders**

- May not result in increased frequency or severity of infections
  - Lupus
  - Hereditary angioedema

- Early complement deficiency (C1, C4, C2)
  - Encapsulated bacteria

- Late complement deficiency (C5-9)
  - Increased susceptibility to Neisseria
Case 2

- You decide to evaluate for possible immune deficiency.

5. What test(s) should you order to help with the diagnosis?
Immunologic Testing

- Use history to guide testing
  - Rarely a need to perform ‘shotgun’ testing
- Use age specific normal ranges for interpretation
- Acute illness often alters results
- Always want to evaluate production AND function
- Don’t treat the test result, treat the patient!
Evaluation of Humoral Immunity**

• Ability to **produce** antibody
  • Serum Immunoglobulin levels
  • Use appropriate “normal range” for age
  • Physiologic nadir 2-6 months
  • IgA often not produced until 3-4 years of age

• **Antibody function**
  • Response to protein and polysaccharide antigens
    • Diphtheria
    • Tetanus
    • Pneumococcus
Laboratory Evaluation of Cell Mediated and Combined Immune Deficiency**

- ~90% of SCID patients have lymphopenia

- Lymphocyte enumeration studies - production
  - CD3 – all T cells
  - CD4 – T helper cells
  - CD8 – Cytotoxic T cells
  - CD56 – Natural Killer cells
  - CD19 – B cells

- In vitro and in vivo analysis of function
  - Mitogen stimulation
  - Anergy panel
    - May be negative in infants or patients receiving immune suppression
Laboratory Evaluation of Phagocytic Disorders**

- CBC with differential – production
  - Neutropenia
  - Leukocytosis
    - Can see elevated WBC at baseline and > 100,000 during acute infection with LAD
    - Look at the smear (or have someone who knows what they’re doing look at it)
- Function
  - Neutrophil Oxidative Burst Assay
  - Neutrophil chemotaxis assay
- Adherence
  - CD11/18 deficiency – flow cytometry with monoclonal Ab against CD11b/18
Evaluation of Complement**

- Typically start with function – normal result indicates all proteins are present and accounted for
  - $\text{CH}_{50}$ assay
  - $\text{AH}_{50}$ assay

- Hemolytic activity is very sensitive to heat degradation

- Measure individual proteins for production
  - Rarely indicated
Case 2

- Laboratory results reveal inadequate titers towards pneumococcal vaccination.

6. What is the next step in evaluation and/or treatment?
Evaluation of Humoral Immunity**

- If specific antibody titers are low – revaccinate and check titers 4-6 weeks later
  - Absolute response that indicates intact immune system is not known

- Expect at least 2-4 fold increase to 50% of serotypes
  - No response indicates antibody dysfunction
    - Subset of general population may not respond robustly to vaccines
    - Conjugated vs. polysaccharide vaccines
Case 3
Asthma
Case 3

- A 4 year old girl presents with a history of recurrent episodes of prolonged cough during upper respiratory infections. She was hospitalized with bronchiolitis as an infant and has been diagnosed with pneumonia twice in the past 3 years. Parents have never heard her have wheezing.

1. Does she have asthma?

2. What is the definition of asthma?

3. What are common signs and symptoms of asthma?
What is Asthma?

- A chronic inflammatory disorder of the airways that causes variable and reversible recurrent episodes of airway obstruction

- Airway hyperresponsiveness
- Obstruction

- Airway remodeling may occur in long standing disease
  - May lead to incomplete reversibility of airflow limitation
Asthma Symptoms

- Coughing (night or early morning)
  - Post-tussive emesis
- Wheezing
- Breathlessness
- Chest tightness
- Chest pressure
- Difficulty breathing
- Increased work of breathing
- **Respiratory distress**

- “Do you feel better with albuterol?”
Case 3

- You learn that she has a history of atopic dermatitis as an infant, which has improved with age. She also has itchy, watery eyes each spring and summer. Both parents have a history of asthma as children.

4. What causes asthma?

5. What are risk factors that contribute to the development of asthma?
What Causes Asthma?**

- Complex (poorly understood) gene-environment interactions
- Consensus is that early life (even *in utero*) exposures greatly determine future risk
  - Nutrition
  - Allergen exposure
  - Endotoxin
  - Pollutants
  - Microbiome
  - Psychosocial factors
- Th2 dominant pathway in many asthmatics
  - IL-4, IL-5, IL-13

Case 3

- You suspect that she may have asthma.

6. Is she old enough to be diagnosed with asthma?

7. Are there any diagnostic tests that may help confirm whether she has asthma?

8. What are common asthma triggers in children?

9. Should she have allergy testing performed?
Asthma Diagnosis**

• To establish a diagnosis of asthma, the clinician should determine that:
  
  • Episodic symptoms of airflow obstruction or airway hyper-responsiveness are present
  
  • Airflow obstruction is at least partially reversible, measured by spirometry. Reversibility is determined by an increase in FEV1 of >200 mL **and** 12% from baseline measure after inhalation of short-acting b2-agonist (SABA)

Journal of Allergy and Clinical Immunology. 2007;120(5):S94-138
Diagnosing Asthma in Young Children**

- **Episodic symptoms** of airflow obstruction or airway hyperresponsiveness are present

- **Episodic**: Do symptoms recur over time? (at least 4 episodes)

- **Symptoms**: Coughing, wheezing, difficulty breathing, shortness of breath

- **Hyperresponsiveness**: What has been the response to albuterol and/or systemic corticosteroids? If unknown, use as a diagnostic and therapeutic trial
Spirometry and Asthma

• Use spirometry to obtain objective measures of lung function
• Perform spirometry at the following times:
  • At the initial assessment
  • After treatment is initiated and symptoms have stabilized
  • During periods of progressive or prolonged loss of asthma control
  • At least every 1 to 2 years; more frequently depending on response to therapy

Reduced:

- FEV1
- FEV1/FVC ratio
- FEF 25-75%

***Spirometry may be completely normal****

Pre and post-albuterol results can help determine the presence of bronchial hyper reactivity: 12% and 200 ml improvement in FEV1
Common Asthma Triggers

- Upper respiratory infections*
  - Autumn asthma spikes
- Weather changes
- Allergens
- Environmental irritants (pollution, ozone)
- Cigarette smoke
- Aerosols, perfumes, cleaning products, essential oil diffusers
- Emotions
- Exercise
Allergies and Asthma

- 60-80% of children with asthma have inhalant allergies

- Can trigger acute or chronic symptoms

- + IgE to aeroallergens predicts
  - Persistent asthma
  - Improved response to inhaled corticosteroids
Exercise Induced Bronchospasm**

- Doesn’t occur in everyone with asthma
- 1st line treatment:
  - Pretreatment with albuterol 2 puffs with spacer at least 15 minutes prior to exercise
  - Brief warm up period may help

- If symptoms still occur:
  - You DO NOT need to wait 4 hours before using albuterol again!
  - Rest, use 2-4 more puffs of albuterol immediately
  - Do not resume activity until symptoms completely resolve

- May be weather/season dependent
Case 3

- You decide that she has asthma and would like to prescribe treatment. You learn that in addition to prolonged cough with upper respiratory infections, which occurs every 1-2 months, that she also has difficulty with exercise, wakes at night due to cough once a week, and always comes home coughing after visiting her grandparents, who have 3 cats.

10. What is her level of asthma severity?

11. What medication would you recommend?

12. What role do leukotriene modifiers have in the treatment of asthma?
Classification of Asthma Severity**

• Intermittent
• Persistent
  • Mild
  • Moderate
  • Severe
Determination of Asthma Severity**

• Symptoms

• Nighttime awakenings

• Short acting beta-adrenergic agonist use (NOT exercise)

• Interference with normal activity

• Lung function
<table>
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<tr>
<th></th>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tr>
<td><strong>Symptoms</strong></td>
<td>≤2 days/wk</td>
<td>&gt;2 days/wk,</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>not daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nighttime awakenings</strong></td>
<td>≤2 x/month</td>
<td>3-4x/month</td>
<td>&gt;1x/week but not nightly</td>
<td>Often 7x/wk</td>
</tr>
<tr>
<td><strong>Beta-agonist use for symptoms</strong></td>
<td>≤2 days/wk</td>
<td>&gt;2 days/wk but not daily, not more than 1x on any day</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td><strong>Interference with normal activity</strong></td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td>FEV$_1$ &gt; 80% pred FEV$_1$/FVC normal</td>
<td>FEV$_1$ &gt; 80% pred FEV$_1$/FVC normal</td>
<td>FEV$_1$ &gt; 60% but &lt; 80% pred FEV$_1$/FVC reduced 5%</td>
<td>FEV$_1$ &lt; 60% pred FEV$_1$/FVC reduced &gt; 5%</td>
</tr>
</tbody>
</table>
Stepwise Approach to Medications

**Step 1**
*Preferred:* SABA prn

**Step 2**
*Preferred:* Low dose ICS

*Alternative:* Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 3**
*Preferred:* Medium dose ICS + LABA

*Alternative:* Medium dose ICS + either LTRA, Theophylline or Zileuton

**Step 4**
*Preferred:* High dose ICS + LABA

*AND*
Consider Omalizumab for patients who have allergies

**Step 5**
*Preferred:* High dose ICS + LABA + oral steroids

*AND*
Consider Omalizumab for patients who have allergies

**Step 6**
*Preferred:* High dose ICS + LABA + oral steroids

*AND*
Consider Omalizumab for patients who have allergies
Stepwise Approach to Medications

- Use severity to **initiate** medications
- Use control to **adjust** medications
- Highlights:
  - Inhaled corticosteroids are **preferred** agent for initiating controller therapy
  - Leukotriene receptor antagonists are **alternative** or **add on** agents
  - Consider **addition of a Long Acting Beta Agonist to ICS** if not well controlled and need step up in therapy
Leukotriene Modifiers**

• Indicated as add on therapy or alternative therapy when inhaled corticosteroids cannot be used
  • Not a 1st line therapy

• Black box warning re: side effects
  • Possible behavioral side effects
  • Increased aggression, nightmares, possible depressive symptoms
  • Typically occurs early in treatment (60 days) and not after prolonged use
  • FDA indication for allergic asthma or exercise induced asthma
Case 3

- She comes back to see you 2 months after starting controller therapy. Overall, she is improved but still coughs occasionally. She has not experienced an upper respiratory infection since her last visit.

13. How can you assess her level of asthma control?

14. Aside from discussing the role of her medications, are there any tools you can use to help her family manage her asthma when she starts to have symptoms?
Classification of Asthma Control**

- Well controlled
- Not well controlled
- Very poorly controlled
Assessment of Control**

- Symptoms
- Nighttime awakenings
- Interference with normal activity
- Short acting beta-adrenergic use (NOT exercise)
- FEV$_1$ or peak flow
- Validated questionnaires
  - ATAQ
  - ACQ
  - ACT
<table>
<thead>
<tr>
<th></th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>≤2 days/wk</td>
<td>&gt;2 days/wk</td>
<td>Throughout the day</td>
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<tr>
<td><strong>Nighttime awakenings</strong></td>
<td>≤2 x/month</td>
<td>1-3x/week</td>
<td>≥4 x/week</td>
</tr>
<tr>
<td><strong>Interference with normal activity</strong></td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td><strong>Short acting beta-agonist use</strong></td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times/day</td>
</tr>
<tr>
<td><strong>FEV₁ or peak flow</strong></td>
<td>&gt;80% pred/personal best</td>
<td>60-80% pred/personal best</td>
<td>&lt;60% pred/personal best</td>
</tr>
<tr>
<td><strong>Questionnaires</strong></td>
<td><strong>ATAQ</strong></td>
<td><strong>ACQ</strong></td>
<td><strong>ACT</strong></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
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<td></td>
<td>≤0.75</td>
<td>≥1.5</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>16-19</td>
<td>≤15</td>
</tr>
</tbody>
</table>
Asthma Action Plans**

• Asthma action plans typically follow a “traffic light” model
  • Green – daily management when symptoms are well controlled
  • YELLOW – FOREWARNS ACUTE LOSS OF CONTROL AND IMPENDING EXACERBATION
  • Red – onset of severe exacerbation requiring course of systemic corticosteroids and contact with health care provider

• Every patient should be provided with an asthma action plan
• Include instructions for recognition of loss of control AND activation of the yellow zone intervention plan
Case 3

• Parents are reluctant to use daily medications and ask whether she will outgrow her asthma as she gets older.

15. What advice can you offer them?

16. Can you predict whether her asthma will be persistent or transient?
Childhood Asthma Phenotypes**

- 40% of toddlers will wheeze at some point
- But only 30% go on to develop asthma
- Phenotypes
  - Never/infrequent 59%
  - Transient early 16%
  - Late 16%
  - Prolonged early 9%
  - Persistent 7%
  - Intermediate 3%

Asthma Predictive Index**

- Primary: > 4 wheezing episodes per year

- Secondary:

  At least 1 Major:
  - Parental asthma
  - Physician diagnosed eczema
  - +IgE to at least aeroallergen

  At least 2 Minor:
  - Wheezing apart from colds
  - Peripheral eosinophils ≥4%
  - +IgE to milk, egg, or peanut

Application of the API

- Positive API by 3 years of age
  - 77% chance of having asthma from 6-13 years of age
- Negative API by 3 years of age
  - Less than 3% chance of developing active asthma during their school years

- Can help provide earlier diagnosis of asthma
- Initiate daily controller therapy sooner
- Can also help with parental discussion, prognosis, etc

Case 3

- She does well for the next 2 months but then becomes ill with an upper respiratory tract infection and develops severe cough along with wheezing, dyspnea, and intercostal retractions.

17. What treatment should you administer?

18. What signs indicate severe obstruction during an acute asthma exacerbation?
Severe Asthma Exacerbations**

- Can affect any child with asthma at any time
- Highest risk:
  - Poor asthma control
  - Higher disease severity
  - Prior hospitalizations/PICU admissions
  - Non-adherence to therapy/avoidance measures
- Mortality rates declining 0.21 → 0.14 per 1000 persons in past decade
Severe Asthma Exacerbations**

- Status Asthmaticus = no response to repetitive or continuous administration of short acting inhaled $\beta_2$ adrenergic receptor agonists

- “Near fatal” and “Catastrophic” asthma =
  - Hypercapnia
  - Hypoxemia
  - Impending respiratory arrest
Case 3

- She is not responding well to continuous administration of beta adrenergic agonists with continued diminished breath sounds and increased work of breathing. She has also developed tachycardia.

19. What is the pathophysiology underlying asthma exacerbations?

20. What clinical features are associated with toxicity to adrenergic agonists?

21. What other treatment can be administered at this time?
Airflow Limitation in Severe Asthma

- Bronchoconstriction
- Airway hyperresponsiveness
- Airway swelling
- Increased mucus production
Beta-Adrenergic Agonist Toxicity**

- Dose effect phenomenon
- Risk for:
  - Tachycardia
  - Lower mean arterial blood pressure
  - Lower diastolic blood pressure
  - Hypokalemia
  - Arrhythmias
- Perception of side effects often > observation of side effects
  - Concern mainly with continuous nebulization
Asthma Treatment: Exacerbations**

| 1st tier therapies: | Inhaled beta agonists |
|                    | Inhaled anti-cholinergics |
|                    | Systemic corticosteroids |

| 2nd tier therapies: | IV magnesium loading |
|                    | IV aminophylline |
|                    | IV salbutamol |
|                    | Non-invasive ventilation |
|                    | Heliox |
|                    | IV magnesium continuous infusion |

| 3rd tier therapies: | IV ketamine infusion |
|                    | Inhaled anesthetics |
|                    | ECMO |

Steroids: Not All are Created Equal**

- Dexamethasone vs prednisone

- Advantages of dexamethasone
  - Longer half-life
  - Shorter treatment course
  - Increased adherence with single dose administration
  - Less vomiting
Dexamethasone: Meta Analysis

- 6 pediatric studies (all mild-to-moderate asthma)
  - IM dose in 3
  - Single PO dose in 1
  - Multiple PO doses in 2

- Primary outcome – unscheduled return visit
  - 5 days: RR (95% CI) = 0.90 (0.46-1.78)
  - 10-14 days: RR (95% CI) = 1.13 (0.77-1.67)

- Secondary outcome – vomiting
  - In the ED: RR (95% CI) = 0.29 (0.12-0.69)
  - At home: RR (95% CI) = 0.41 (0.17-0.99)

Changes You May Wish to Make in Practice

- Review proper use of self-injectable epinephrine with patients at risk for anaphylaxis at every visit
- Obtain directed quantitative and qualitative immunologic tests when evaluating patients for suspected immune deficiency
- Diagnose asthma for young children with recurrent respiratory symptoms and associated risk factors
- Assess asthma severity at diagnosis and control at every visit thereafter to prescribe and adjust appropriate therapy
Thank You