THE ATOPY TRIAD IN CHILDREN:  
A FOCUS ON THERAPIES

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DISCLOSURE/CONFLICT OF INTEREST

I, Lea S. Eiland, have no actual or potential conflict of interest in relation to this program.

OBJECTIVES

- Participants will be able to list the three disease states involved in the atopy triad.
- Participants will be able to design a therapeutic plan for a child with atopic dermatitis (eczema).
- Participants will be able to compare and contrast first line treatment options for allergic rhinitis in a child.
- Participants will be able to analyze safety concerns of common chronic medication used for asthma management in children.
- Participants will be able to compare and contrast drug information resources for medication use in children.
JT is a 9 mo AA male, is brought to the pediatrician's office by his mother for a rash on his face that won't go away.

During the day and night she sees him rub his face.

Mother has tried her face creams on his face, but they seem to make it worse.

PMH: Born at full term, uncomplicated delivery, breastfed x 6 months.

Family History: Father, asthma; Sister, seasonal allergies.

Social History: Lives at home with mother, father and sister, age 4.

No current medications.

No known drug allergies.

PE: Skin generally dry; patches on cheeks and in scalp, few excoriations from scratching.

*remainder of exam normal*
**ATOPIC DERMATITIS**

- Commonly known as “eczema”
- Chronic, relapsing and usually intensely pruritic inflammatory disease
- Most common form of dermatitis of children
- Onset occurs prior to 1 year of age in 65% of children and prior to 5 years of age in 85% of children
- Pathogenesis
  - Skin Barrier Dysfunction
  - Environmental factors
  - Genetic predisposition
  - Immune dysfunction

**DIAGNOSIS**

- Clinical diagnosis - biopsies and labs are usually not helpful
- Exclude other inflammatory skin conditions, especially if patient not improving with therapy
  - Contact dermatitis
  - Seborrheic dermatitis
  - Psoriasis

**MAJOR CLINICAL FEATURES**

- Itching/pruritus
  - Typical distribution and age-specific patterns
    - Infants: cheeks, scalp, trunk and extremities
    - Early childhood: flexural areas
    - Adolescents/Adults: hands and feet
  - Typical dermatitis with a chronic or relapsing history
  - Patient or family member with atopy
MINOR CLINICAL FEATURES

- Early age of onset
- Dry skin
- Keratosis pilaris
- Ichthyosis vulgaris
- Lip dermatitis
- Hand eczema
- Lichenification
- Elevated IgE level
- Itching on sweating
- Recurrent infections
- Pityriasis alba
- Dermatographism
- Eye symptoms
- Cataracts, keratoconus, inflammation

JT IS DIAGNOSED WITH ECZEMA. WHICH OF THE FOLLOWING IS THE BEST TREATMENT PLAN FOR JT?

A. Moisturizers and a topical calcineurin inhibitor
B. Warm baths and an oral antihistamine
C. Use mild soaps and a topical corticosteroid
D. Cut fingernails short and use a topical antihistamine

MAIN THERAPIES

1. Maintenance skin care
2. Topical anti-inflammatory medications
3. Itch control
4. Managing infectious triggers, recognition and treatment of infection related flares

- Exacerbating Factors: soaps, detergents, fragrances, chemicals, temperature changes, dust, pollens, stress, foods (unclear)
SKIN THERAPIES

- Maintain hydration, avoid irritants and triggers
- Use mild cleansers, soap and detergents
- Avoid hot or long showers/baths
- Only bathe 3-5 minutes (optimal frequency??), pat dry and use emollient immediately
- Fingernails should be short, smooth and clean
- Long, loose pajamas/gloves/socks may be worn
- Wet-wrap therapy for acute flares

MOISTURIZERS

- Use moisturizers twice daily
- Fragrance-free, least number of preservatives
- All moisturizers are mixture of lipids and water
  - Ointments have higher lipid content (petroleum jelly = 100% lipids)
  - Greatest moisturizing effect
  - Creams are emulsions of water in liquid (more oil than water)
  - Contains preservatives and ingredients to help it not separate, can be irritating to skin
  - Lotions are emulsions of water in liquid (more water than oil)
  - Need frequent applications

WHICH OF THE FOLLOWING IS THE BEST REGIMEN FOR THE STEROID?

A. Apply once a day on affected areas every day
B. Apply four times a day on affected areas every day
C. Apply two times a day on affected areas for 2 weeks
D. Apply three times a day on affected areas for 4 weeks
### TOPICAL CORTICOSTEROIDS

- **Topical corticosteroids** are the first line agent used to treat an eczema flare.
- Use first on skin and then moisturizers.
- Use once or twice a day on affected areas until skin is smooth or no longer red or irritated.
- Not for continued use (no daily use), avoid if skin is open, weeping or cracked!
- Typically use low to moderate potency steroids, higher potency generally not needed.
- Moderate potency can only be used on trunk and extremities.
- Vehicle is important:
  - Ointments are better tolerated and more effective than creams or lotions; occlusive effect increases potency.
- **Adverse Effects**
  - Atrophy, striae, telangiectasia, and adrenal suppression.

### TOPICAL CALCINEURIN INHIBITORS (TCI)

- Second line agents for moderate to severe eczema.
- Topical immunosuppressive agents which inhibit T-cell function (little to no systemic absorption).
  - Tacrolimus ointment (0.03% and 0.1%)
  - Pimecrolimus cream (1%)
- Both are effective in reducing inflammation and pruritus.
  - Tacrolimus is more effective than pimecrolimus.
  - Excellent for the face or sensitive skin areas.
  - Higher cost than steroids.
- Can cause burning or stinging of skin (tacrolimus > pimecrolimus).

### ITCHING RELIEF

- **Itching typically worse at night**
- Oral antihistamines can help itch (but not underlying pathogenesis).
- Reduces sensation of itch.
- Decreased scratching and trauma to skin.
- **Sedating Antihistamines**
  - Diphenhydramine
  - Hydroxyzine
- **Nonsedating Antihistamines**
  - Cetirizine
  - Loratadine
- Topical antihistamines not effective—also contain potential irritants and allergens.
- **Other**—Colloidal oatmeal baths.
COMPLICATIONS

- Secondary Bacterial Infections
  - Pustules, crusting, cellulitis
    - Antibiotics warranted only with infection
    - Bleach baths can be helpful for those with recurrent infections
  - Viral skin infections
    - Molluscum contagiosum, eczema herpetica, eczema coxsackie
    - Antivirals may be warranted depending on infection

3 YEARS LATER

JT is now almost 4 years old. It is early fall and he keeps sneezing and rubbing his nose and eyes constantly. He has a runny nose often as well. Mom noticed he was like this last year but it went away after a few weeks. Mom thinks JT is showing similar symptoms as his sister, who has allergies.

ALLERGIC RHINITIS
Allergic Rhinitis (Hay Fever)

If you sneeze a lot, if your nose is often runny or stuffy, or if your eyes, mouth or skin often feels itchy, you may have allergic rhinitis, a condition that affects 40 million to 60 million Americans.

ALLERGIC RHINITIS

- IgE mediated disorder triggered from allergen exposure to the nasal mucosa
- 20-40% of children suffer from allergic rhinitis

Pathogenesis
- Genetic
- Environmental factors

Risk Factors
- Family history of atopy
- IgE level of >100 IU/mL before 6 years of age
- Clinical diagnosis
- Usually diagnosed by 6 years of age
- Allergy testing when necessary

Comorbid diseases/Complications
- Sinusitis, conjunctivitis, urticaria, urticarial hives, hyperreactive cough, and asthma

CLINICAL FEATURES

- Types
  - Inter歇性 (20%): Symptoms occur in spring, summer and early fall, usually caused from allergies to airborne mold spores or grass, tree or weed pollens
  - Persistent (40%): Symptoms occur year round, usually caused by dust mites, pet dander or hair, cockroaches or mold.
  - Underlying food allergies rarely cause persistent nasal symptoms

- Symptoms
  - Nasal congestion
  - Rhinorrhea (nasal drainage)
  - Itching
  - Sneezing
  - Conjunctival irritation
  - Fatigue (due to poor sleep quality from nasal obstruction)
JT is diagnosed with intermittent allergies. Which of the following is the best treatment plan?

A. Saline drops PRN
B. Fluticasone furoate 1 spray in each nostril daily
C. Cetirizine 2.5 mg po daily
D. Montelukast 4 mg po daily

TREATMENT OF ALLERGIC RHINITIS

- Allergen avoidance
  - Reduce exposure to allergens, if known
  - Can be beneficial for patients with asthma

- Nasal Irrigation
  - Saline mist or drops
  - Improves mucociliary function, reduces mucosal edema and decreases inflammatory mediators
  - Good adjunct agent

INTRANASAL GLUCOCORTICOIDS

- Intranasal glucocorticoids are most effective class for controlling symptoms of allergic rhinitis
- Use first line in children with intermittent and persistent allergic rhinitis
- Should be recommended over oral and intranasal H1-antihistamine use
- Benefits from studies demonstrate:
  + Improved symptom control
  + Improved quality of life
  + Improved sleep
  + Potential cost savings due to monotherapy
  + Targets local effect
INTRANASAL GLUCOCORTICOIDs

Adverse Effects
- Nasal and throat irritation
- Epistaxis
- Headaches
- Disturbances with smell and taste
- Headache

Intranasal glucocorticoids have low bioavailability and have not been found to impair growth.

Weaning not necessary as hypothalamic-pituitary-adrenal axis not affected.

INTRANASAL GLUCOCORTICOIDs FDA-LABELED INDICATIONS BY AGE

<table>
<thead>
<tr>
<th>Beclomethasone</th>
<th>Fluticasone</th>
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<tbody>
<tr>
<td>AR ≥ 6 years</td>
<td>Furoate: AR ≥ 2 years</td>
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<tr>
<td>Budesonide</td>
<td>Triamcinolone</td>
</tr>
<tr>
<td>AR ≥ 6 years</td>
<td>AR ≥ 2 years</td>
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<tr>
<td>Ciclesonide</td>
<td>Mometasone furoate</td>
</tr>
<tr>
<td>Nasal aerosol: AR ≥ 12 years</td>
<td>AR ≥ 2 years</td>
</tr>
<tr>
<td>Nasal spray: seasonal AR ≥ 6 years, persistent AR ≥ 12 years</td>
<td></td>
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<tr>
<td>Flunisolide</td>
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<td>AR ≥ 6 years</td>
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<td>AR ≥ 2 years</td>
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<tr>
<td>Mometasone furoate</td>
<td>AR ≥ 2 years</td>
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<td>AR ≥ 2 years</td>
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</tbody>
</table>

2Zetonna prescribing information. Marlborough, MA: Sunovion; Jan 2012
3Omnaris prescribing information. Marlborough, MA: Sunovion; Oct 2011
4Nasacort AQ prescribing information. Bridgewater, NJ: Sanofi-Aventis; Nov 2010

ANTIHISTAMINES

Relieve sneezing and rhinorrhea.

May be used first line for mild, intermittent symptoms.

Recommend 2nd generation oral H1-antihistamines over 1st generation oral H1-antihistamines.

Less sedating, longer duration of action and faster acting.

Suggest use of oral over intranasal H1-antihistamines in children with intermittent or persistent allergic rhinitis.

Some data suggest equally effective.

Use oral if patients have ocular symptoms or may use intraocular.

Suggest use of intranasal H1-antihistamines in children with intermittent allergic rhinitis, but not persistent allergic rhinitis.

Intranasal has faster onset than oral.

Suggest use of intranasal H1-antihistamines over intranasal cromolyn in patients with allergic rhinitis.

Barr JG. BMJ 2014;349:4153.
ANTIHISTAMINES

- Benefits from studies show:
  - Rapid onset of action
  - Oral administration
  - Relief of symptoms
  - Nonprescription availability
  - Relief of eye symptoms

- Adverse Effects
  - Headache, GI upset
  - Intranasal: bitter taste

H1-ANTIHISTAMINES FDA-LABELED INDICATIONS BY AGE

2nd generation oral
- Cetirizine
  - Seasonal AR ≥ 2 years
  - Perennial AR ≥ 6 months
- Desloratadine
  - Seasonal AR ≥ 2 years
  - Perennial AR ≥ 6 months
- Fexofenadine
  - Seasonal AR ≥ 2 years
  - Persistent AR ≥ 6 months
- Levocetirizine
  - Seasonal AR ≥ 2 years
  - Perennial AR ≥ 6 months
- Loratadine
  - Seasonal AR ≥ 2 years

Intranasal
- Azelastine
  - Seasonal AR ≥ 5 years (≥ 6 years Astepro spray)
  - Seasonal AR ≥ 12 years in combination with fluticasone propionate
- Desloratadine
  - Seasonal AR ≥ 6 months
- Clemastine fumarate
  - Seasonal AR ≥ 5 years
- Diphenhydramine
  - Seasonal AR ≥ 6 years
- Mequitazine
  - Seasonal AR ≥ 6 years
- Olopatadine
  - Seasonal AR ≥ 6 years

OTHER OPTIONS

- Leukotriene receptor antagonists
  - Third line treatment option (may be helpful for patients with asthma); not to be used as primary therapy for allergic rhinitis
  - Montelukast (Singulair) is an example of a leukotriene receptor antagonist used in adults with allergic rhinitis and is prescribed in combination with an inhaled corticosteroid drug
  - Montelukast can be used in children ≥ 6 years of age

- Decongestants
  - Relieve stuffiness and pressure from swollen nasal tissue
  - Do not help with any other symptoms
  - Nasal forms: rebound congestion

- Intranasal cromolyn
  - OTC formulation only, requires frequent administration

- Intranasal ipratropium bromide
  - Effective for severe rhinorrhea

Seidman MD. Otolaryngology- Head and Neck Surgery 2015;152(2);197-206.
OTHER OPTIONS

- Immunotherapy
  - Used in patients with poorly controlled symptoms despite maximum drug therapy and avoidance.
  - Only treatment with disease modifying effects.
  - May reduce the risk of asthma.
- Subcutaneous
  - Weekly injections for 2-3 years.
- Sublingually
  - Optimal length is unknown, but typically 3 years.
  - Reduce symptoms in children as young as 3 years of age, more effective if used more than 18 months.
  - Reduce medication use.

COUNSELING POINTS

Intranasal
- Blow nose first.
- Head tilted forward.
- Nozzle pointed along hard palate and slightly laterally to avoid contact with septum.
- Shake suspensions prior to use.
- Prime as directed for each form.
- Start therapy two weeks prior to symptoms onset (intermittent).

3 YEARS LATER

JT is now almost 7 years of age. He is playing soccer and has evening practice with early morning games on the weekend. His father and mother notice him wheezing sometimes after practice and he tends to cough a lot at night those evenings. This last weekend he had to sit out of the game for a while to catch his breath. Dad recalls he had similar symptoms when he was a child.

The pediatrician diagnoses JT with mild persistent asthma and prescribes a ProAir® (albuterol) HFA inhaler and Flovent® (fluticasone) HFA 44mcg 1 puff twice daily.
ASTHMA

- Chronic inflammatory condition of the airway that results in episodic airflow obstruction
- Affects 7 million children who are <18 years of age (2010 Statistic)
- Chronic management aimed to reduce inflammation with medications
  - Inhaled corticosteroids
  - Long-acting beta agonists
  - Leukotriene modifiers

The father asks if the steroid will affect JT’s height in the future. What is the best response regarding the inhaled corticosteroid?

A. It will not affect JT’s future height
B. It may slow his growth for a few years but he will still reach his ‘planned’ height
C. It can likely decrease his height by only about 1 cm shorter
INHALED CORTICOSTEROIDS

- Temporary reduction in growth velocity known (0.5-3 cm, avg 1 cm) during first few years of therapy
- Returns to normal

Effect of Inhaled Glucocorticoids in Childhood on Adult Height
- 943 adult participants in the Childhood Asthma Management Program (mean age 24.9±2.7 years)
- Between 5-13 years of age participants randomized to one of the following for 4 to 6 years:
  - 200 mcg of budesonide BID (low dose)
  - 8 mg of nedocromil BID
  - Placebo
- 4.8 years of follow-up after study end (9.1 total years)

Results
- Adult height was 1.2 cm lower in budesonide group than placebo, (Confidence Interval (CI): -1.9 to -0.5, p=0.001)
  - -1.8 cm for women (p=0.001) and -0.8 cm for men (p=0.10) versus placebo
  - No difference in gender, race, age at entry or duration of asthma
  - Large daily dose in first 2 years associated with lower adult height (-0.1 cm for each mcg per kg of body weight, p=0.007)
  - Decrease was not progressive or cumulative
- Adult height was 0.2 cm lower in the nedocromil group than placebo, (CI: -0.9 to 0.5, p=0.61)
- Confirmed growth velocity decreases in the budesonide group in prepubertal participants
- Determined duration of asthma and history of atopy were independent factors of reduced height

Key Points
- Growth reduction seen in the first few years of inhaled corticosteroid use in prepubertal children exist into adulthood
- Inhaled corticosteroids benefits in asthma still outweigh this risk
- Use the lowest effective dose for symptom control in all patients
INHALED CORTICOSTEROIDS + LONG-ACTING $\beta_2$-AGONISTS

<table>
<thead>
<tr>
<th>Combination Product</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone + Salmeterol</td>
<td>HFA MDI, DPI</td>
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<tr>
<td>Budesonide + Formoterol</td>
<td>HFA MDI</td>
</tr>
<tr>
<td>Mometasone + Formoterol</td>
<td>HFA MDI</td>
</tr>
</tbody>
</table>

Long-acting $\beta_2$-agonists should not be utilized as monotherapy for control.

SALMETEROL MULTICENTER ASTHMA RESEARCH TRIAL (SMART)

- Large, multicenter, randomized, double-blind study adding long-acting $\beta_2$-agonist versus placebo to asthma therapies
- Started in 1996, halted in 2003 after planned interim analyses
- 28 week study
- Patients $\geq$ 12 years of age included
- Patients with prior use of long acting beta-agonist were excluded

Endpoints
- Primary: Respiratory-related deaths + life threatening events (LTE)
- Secondary: Asthma-related deaths, LTE

Midpoint analysis (n=26,355)
- No difference in primary endpoint (50 vs 36; relative risk [RR] = 1.40; CI: 0.91 to 2.14)
- Asthma-related deaths (13 versus 3, RR 4.37; CI: 1.25 to 15.34) and asthma-related deaths + LTE (37 versus 22, RR 1.71; CI: 1.01 to 2.89)
- Asthma-related deaths seen more in patients who did not have inhaled corticosteroids initiated
- African-Americans experienced a significantly great number of respiratory-related deaths + LTE (20 vs 5, RR 4.1; CI: 1.54 to 10.9) and asthma-related deaths or LTE (19 vs 4, RR 4.92; CI: 1.68 to 14.45)
- However, AA had more severe asthma versus Caucasians
SALMETEROL MULTICENTER ASTHMA RESEARCH TRIAL (SMART)

• Outcomes
  • Black box warnings added to labeling
  • Long acting β₂-agonists should not be the 1st medicine used to treat asthma
  • Long acting β₂-agonists does not replace inhaled corticosteroids for treatment
  • Do not use long acting β₂-agonists to treat wheezing or asthma that is getting worse
  • Long acting β₂-agonists do not stop sudden wheezing, a short acting beta-agonist must be used in all patients for acute symptoms

LEUKOTRIENE MODIFIERS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Leukotriene-receptor antagonist</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast (Singulair®)</td>
<td>Leukotriene-receptor antagonist</td>
<td>Oral granules, tablets, chewable tablets</td>
</tr>
<tr>
<td>Zafirlukast (Accolate®)</td>
<td>Leukotriene-receptor antagonist</td>
<td>Tablet</td>
</tr>
<tr>
<td>Zileuton (Zyflo®)</td>
<td>Leukotriene-receptor antagonist</td>
<td>Tablet</td>
</tr>
</tbody>
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LEUKOTRIENE MODIFIERS CONCERNS

• Montelukast and Zafirlukast
  • Rare idiosyncratic syndrome similar to Churg-Strauss syndrome
  • Systemic eosinophilia, heart failure, clinical features of vasculitis
  • Post-marketing reports of behavioral changes in children and adults
  • Agitation, anxiety, depression, hallucinations, insomnia, irritability, memory impairment, suicidal thinking and behavior

• Zafirlukast
  • Hepatic adverse effects (hepatitis, hepatic failure and hyperbilirubinemia)

• Zileuton
  • Limited use due to increased in liver enzymes, especially in first 3 months and drug interactions (CYP3A4, 1A2 substrate)
THE PEDIATRICIAN CALLS YOU, SAYING HE HAS THE FOLLOWING REFERENCES AND ASKS WHICH IS THE BEST FOR PEDIATRIC DOSING OF DRUGS. WHAT IS YOUR RECOMMENDATION OF THOSE LISTED BELOW?

A. Micromedex
B. Pediatric and Neonatal Dosage Handbook
C. Pediatric Injectable Drugs
D. Harriet Lane Handbook

PEDIATRIC REFERENCES

- Neofax®, Part of Micromedex, Truven Health.

COMMON PEDIATRIC REFERENCES

- Micromedex, Truven Health