The Atopic Child

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Disclaimer slide

Honoraria – AAPA
Consultant- Mylan, Merck, TEVA, Sunovion
Speakers Bureau- Aerocrine, Genentech, Mylan, Merck, ThermoFischer Diagnostics, TEVA, Sunovion

Objectives

❖ Describe the prevalence and history of allergic disorders
❖ Explain the importance of inflammation in the upper and lower airway
❖ Describe the diagnostic tools for identification of triggers of allergic disease
❖ Review the updates to the Asthma Guidelines
❖ Discuss the therapeutic options for allergic disease
Patients With AR Can Suffer From Many Comorbid Conditions

Common Childhood Diseases

- The illnesses of the Allergy March
  - Atopic dermatitis (eczema)
  - GI distress (intolerance vs allergy)
  - Recurrent otitis media
  - Allergic rhinitis
  - Allergic asthma
- The symptoms
  - Inflammatory in nature
  - Multiple etiologies
  - Treated empirically


The Allergy March: A Progression of Seemingly Unrelated Diseases
Atopic Dermatitis

- A highly pruritic chronic and relapsing inflammatory skin disease
- Frequently presents during early childhood
- Elevated IgE in majority of AD (may be normal in intrinsic dermatitis)
- Increasing in prevalence (8.7-18%)
- Start of the “allergic march”

Atopic Dermatitis (AD)

- Genetics
  - 81% of the offspring of two parents with AD will develop AD
  - 77% concordance rate in monzygotic twins.
  - Several candidate genes identified
- Current insights into pathophysiology point to both a skin barrier dysfunction and immunoregulatory defects
Atopic dermatitis in school-age children

AD Distribution & Clinical Aspects
- Infantile - face, scalp, trunk, extensor aspects of extremities
- Childhood - neck, flexural surfaces
- Adolescent & Adults - hands, feet, flexural surfaces
- Acute, sub-acute and chronic phases

Triggers
- **Irritants**
  - Wool
  - Soaps / detergents
  - Disinfectants
  - Tobacco smoke
- **Climate**
  - Humidity
  - Temperature
- **Xerosis (Dry skin)**
- **Microbial agents**
  - S. aureus (col&inf)
  - Malassezia furfur
  - Viral Infection
- **Emotional**
  - Stress
  - Anxiety
- **Aeroallergens**
  - Dust mites
  - Animal Dander
  - Tree and Grass Pollen
  - Mold/fungal allergens
- **Foods allergens**
  - IgE mediated reactions
Food Allergy and AD in Children

• Moderate - Severe AD - 33% have a food allergy
• Foods responsible (~ 85% of cases):
  – Outgrown: Milk, egg, soy, wheat
  – Persistent: Peanut, nuts, fish, shellfish

Diagnostic Procedures in AD

• History and physical examination
• Laboratory - (never routine)
  – Serum IgE level
  – Serum test for allergen-specific IgE (Immuno-CAP® System)
  – Skin Biopsy
  – Skin culture (bacterial, viral, fungal)
  – Patch test (corticosteroids, aeroallergens)
• Skin prick test - (never routine)

Evaluation of Food Allergy in AD

• Skin Prick Testing
  – Negative predictive accuracy >95%
  – Positive predictive accuracy <50%
• Specific IgE (Immuno-CAP® System)
  – Data curves for select foods (milk, egg, peanut).
  – *Lower end of probability curve is <0.35. Rarely patients react at very low levels.
  – Helpful in following natural hx
• Diagnostic diet:
  – Elimination diets (up to 6 weeks)
  – Supervised oral food challenges
Skin Infections in AD

 Patients with AD are prone to secondary infection
  a) Bacterial
    • *Staphylococcus aureus* can be isolated in up to 90% of AD skin lesions
    • "super-antigenicity"
  b) Viral
    • localized – verruca, molluscum, herpes
    • systemic – Eczema herpeticum, eczema vaccinatum
  c) Fungal
    • *Malassezia furfur* (present in the seborrheic areas of the skin and the scalp)

Basic Approach to Management

  • Restore skin barrier function
  • Prevent and treat infections
  • Address emotional and psychosocial aspects of the disease

The stepwise management of atopic dermatitis including the use of therapeutic agents

Recalcitrant, severe AD
Step 4
Systemic therapy (e.g. CyA) or UV therapy

Moderate to severe AD
Step 3
Mid-high potency TCS and/or TCI

Mild to moderate AD
Step 2
Low-mid potency TCS and/or TCI

Dry skin only
Step 1
Basic treatment:
Skin hydration, emollients, avoidance of irritants, identification and addressing of specific trigger factors

TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitors, CyA = Cyclosporine A
* Over the age of 2 years

Akdis et al. *J Allergy Clin Immunol* 2006;118:152–69
Topical Anti-inflammatory Agents:
Corticosteroids

- Predominant AD therapy for more than 4 decades.
- Effective flare control through their anti-inflammatory, antiproliferative, immunosuppressive, & vasoconstrictive actions.
- Side effects are directly related to the potency ranking, site of application and length of use. Skin thinning and HPA axis suppression.
- Steroid phobia – some patients may not use or delay use of topical steroids.

Anti-inflammatory Agents:
Topical Calcineurin Inhibitors (TCIs)

- Tacrolimus (0.03% and 0.1%) for moderate to severe AD, and pimecrolimus 1% for mild-moderate AD, provide an alternative to topical corticosteroids.
- Not associated with skin atrophy; may be useful for treating eczema on the face.
- Role in treating steroid insensitive or resistant
- A common side effect is transient stinging at the site of application.
- Long-term safety trials including infants are ongoing.

FDA Boxed Warning

- In January 2006, the FDA added a boxed warning to TCI labels noting the lack of long-term safety data.
- Although a casual relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with calcineurin inhibitors.
- AAAAI/ACAAI Calcineurin Inhibitors Task Force concludes that based on current data, the risk-benefit ratio of topical pimecrolimus and tacrolimus are similar to most conventional therapies for the treatment of chronic relapsing eczema.
Role of Antihistamines

- Multiple mediators in addition to histamine
- Sedating antihistamines such as hydroxyzine and diphenhydramine may be useful for improving sleep in patients with flare-ups.
- Second-generation antihistamines are less useful in managing AD; benefit in patients with urticaria.
- Treatment with topical antihistamines should be avoided because of potential sensitization

Common Food Allergies

- Although an individual could be allergic to any food, such as fruits, vegetables, and meats, they are not as common as the following eight foods which account for 90% of all food-allergic reactions:
  - Milk
  - Egg
  - Peanut
  - Tree Nut (walnut, cashew, etc.)
  - Fish
  - Shellfish
  - Soy
  - Wheat
First four more common in Children

Food Urticaria

- Clear-cut patterns
  - <30 to 120 minutes after eating
  - Reproducible
  - Never appears the next day
- Spices
  - Hidden foods (celery, nuts, eggs)
- Dyes, preservatives
  - Rare
Urticaria with Angioedema

Step-up Treatment Plan for Chronic Urticaria

Treatment should be stepped down once control is achieved

1. Standard dose of non-sedating H1 antihistamine
2. Higher dose of H1 antihistamine
3. Add second non-sedating H1 antihistamine (regular or as required)
4. Consider sedating antihistamine at night
5. Consider adding or substituting with second-line agent (ie, anti-leukotriene)
6. Add or substitute other second-line agents (ie, cyclosporin or a low-dose corticosteroid*)

* Low-dose daily corticosteroid (5–10mg/day) or low-dose alternative day corticosteroid (15–20 mg alt day) could be considered.

Common Childhood Diseases

• Recurrent otitis media (OM)
  – 26% prevalence in US1
  – Key risk factors include attendance in daycare, cigarette smoke exposure2
  – 40%–50% involve asymp3,4
  – Common underlying cause = eustachian tube dysfunction
    • Caused by inflammation related to allergy or infection
    • Recurrence = not treating the underlying cause
  – Empirical treatment: antibiotics, surgery

References:
Atopy’s Long-Term Consequences

- Nearly 80% of children with AD go on to develop allergic rhinitis or asthma
- Children with early and long-lasting food sensitization:
  - 3x more likely to develop allergic rhinitis (AR) than those transiently sensitized
  - 5x more likely to develop asthma than those transiently sensitized
- Young wheezers with confirmed atopy are more likely to develop asthma

Most Patients with Asthma Have AR

- Approximately 80% of asthmatics have AR
- Most patients with allergic and non-allergic asthma have AR
- Many patients with AR have asthma
- AR is associated with and also constitutes a risk factor for asthma
- Many patients with AR have increased non-specific bronchial hyperreactivity

Signs of Allergic Rhinitis

- Facial Grimming
- Allergic Salute
- Mouth Breathing
- Allergic Shiner

References:

Allergic Rhinitis + Asthma
Asthma alone
Allergic rhinitis alone


Medical History and Physical Examination Are Essential for Diagnosis of AR

- Detailed and accurate history critical to proper diagnosis and successful treatment
  - Time course: onset, pattern
  - Symptoms
  - Effect of previous treatments (Rx and OTC)
  - Sequelae and comorbidities
  - Family history
- Physical exam: more than the nose


Making the Differential Diagnosis of “Rhinitis”

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
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<tbody>
<tr>
<td>Viral</td>
<td>Seasonal vs. perennial allergic</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Chronic infectious rhinosinusitis</td>
</tr>
<tr>
<td></td>
<td>Nonallergic</td>
</tr>
<tr>
<td></td>
<td>Nonallergic rhinitis with eosinophilia syndrome (NARES)</td>
</tr>
<tr>
<td></td>
<td>Vasomotor</td>
</tr>
<tr>
<td></td>
<td>Gustatory</td>
</tr>
<tr>
<td></td>
<td>Primary atrophic</td>
</tr>
<tr>
<td></td>
<td>Rhinitis medicamentosa</td>
</tr>
<tr>
<td></td>
<td>Associated with systemic disease</td>
</tr>
<tr>
<td></td>
<td>Emotional</td>
</tr>
<tr>
<td></td>
<td>Nasal neoplasm</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
</tbody>
</table>


Physical Examination Should Include an Expanded HEENT Exam

- Skin: eczema, excoriation, shiners, Dennie-Morgan lines
- Eyes: injection, discharge, chemosis
- Ears: air fluid level, retraction
- Nose: transverse crease, turbinates, mucosa, discharge, nasal polyp
- Oropharynx: mouth breathing, palatal arch, post nasal drainage, cobblestoning
- Chest: wheezing

Diagnostic Tests for AR

- General ENT examination
- Allergy tests
  - Skin testing
  - Allergen-specific IgE antibody (RAST vs ImmunoCap®)
- Endoscopy referral
  - Rigid
  - Flexible

RAST = radioallergosorbent testing
RAST and ImmunoCap® are trademarks of PhaDia AB.


Allergy Skin Testing


Predictive Value vs. Skin Prick Testing (SPT)*

<table>
<thead>
<tr>
<th>Performance parameters</th>
<th>In vitro†</th>
<th>SPT</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>87.2</td>
<td>93.8</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>90.5</td>
<td>80.1</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>91.1</td>
<td>90.1</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>86.4</td>
<td>87.1</td>
</tr>
<tr>
<td>Clinical Efficiency (%)</td>
<td>88.8</td>
<td>89.2</td>
</tr>
</tbody>
</table>

* Adapted from Reference 1.
† ImmunoCAP Specific IgE blood test was used in this study.


Authors concluded that ImmunoCAP Specific IgE blood test and SPT values both exhibited excellent efficiency.
Current Treatment Options for AR
For SAR and PAR in adults and children

- Allergen avoidance
- Environmental control
- Oral H<sub>1</sub>-antihistamine
- Intranasal H<sub>1</sub>-antihistamine
- Intranasal corticosteroid
- Intranasal cromolyn sodium
- Subcutaneous specific immunotherapy


US POLLEN SEASONS


Environmental Control Measures:
House Dust Mites

- Vigorous methods necessary
  - Ordinary vacuuming/dusting have little effect
  - wash bedding weekly in water ≥130°F
- Simple furnishings without carpeting
  - Especially bedroom, family room, etc.
  - Plastic, leather, wood are best

Measures for Reducing Animal Allergens

• The ideal solution: remove pets from house
• If not possible:
  – Keep pet out of bedroom
  – Use HEPA air filtering system
  – Remove carpet and other reservoirs for allergens from bedroom
  – Encasing on mattress, box springs, and pillow
  – Wash pet weekly


Shaving the Cat?

Courtesy of Dr David Kahn UT Southwestern Dallas

Courtesy of Dr David Kahn UT Southwestern Dallas
Pharmacologic Options in the Management of AR

- **Antihistamines**
  - Oral
  - Nasal
- **Decongestants**
  - Oral
  - Topical
- **Anticholinergics**
  - Oral
  - Intranasal
- **Antihistamine/Decongestant Combinations**
- **Corticosteroids**
  - Intranasal
  - Systemic
- **Cromolyn sodium**
- **Leukotriene antagonists**
- **Immunotherapy**

Role of Medications in AR: Antihistamines

<table>
<thead>
<tr>
<th>Sedating</th>
<th>Non sedating / low sedating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpheniramine, diphenhydramine</td>
<td>Azelastine, cetirizine, desloratadine, fexofenadine, loratadine, levocetirizine, olapalidine</td>
</tr>
<tr>
<td>Competitive antagonists of H1-mediated effects</td>
<td>Equally efficacious compared with sedating antihistamines</td>
</tr>
<tr>
<td>Relieve rhinorrhea, pruritus, sneezing, and ocular symptoms</td>
<td>Lack prominent CNS and anticholinergic effects</td>
</tr>
<tr>
<td>Use limited by sedation, performance impairment, and anticholinergic effects</td>
<td>Non sedating: desloratadine, fexofenadine, loratadine</td>
</tr>
<tr>
<td>Mildly sedating: cetirizine, azelastine (intranasal)</td>
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Currently Available Intranasal Corticosteroids

<table>
<thead>
<tr>
<th>Currently Available Intranasal Corticosteroids</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate (BDP)</td>
<td>Beconase®, Beconase AQ, © Qnasl</td>
</tr>
<tr>
<td>Budesonide (BUD)</td>
<td>Rhinocort Aqua®</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Omnaris, Zetonna</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Nasalide®</td>
</tr>
<tr>
<td>Fluticasone furoate (FF)</td>
<td>Veramyst™</td>
</tr>
<tr>
<td>Fluticasone propionate (FP)</td>
<td>Flonase®</td>
</tr>
<tr>
<td>Mometasone furoate (MF)</td>
<td>Nasonex®</td>
</tr>
<tr>
<td>Triamcinolone acetonide (TAA)</td>
<td>Nasacort® AQ</td>
</tr>
</tbody>
</table>
What Do We Know About Intranasal Corticosteroids?

- Most effective pharmacotherapy for AR
- Control all four major symptoms
  - Sneezing
  - Rhinorrhea
  - Itching
  - Nasal blockage
- Similar in terms of efficacy, safety, and effect on QOL vs. placebo
- Important differences can influence patient preference, compliance, and outcomes
  - Onset and duration of action
  - Magnitude of effect

QOL = Quality of Life


Safety of Intranasal Corticosteroids

- Potential concerns
  - Local adverse effects on nasal mucosa
  - Systemic activity
- Low risk of localized changes in nasal mucosal biopsy studies
  - Mometasone furoate
  - Fluticasone propionate
  - Budesonide
- Low systemic bioavailability = low risk of adverse systemic effects
  - Mometasone furoate
  - Fluticasone propionate


Onset of Symptoms in Children With Asthma

- 20% 1-2 years
- 30% <1 year
- 20% 2-3 years
- 30% >3 years

Natural History of Childhood Asthma

Age (Years) vs Wheezing Prevalence

- Transient early wheezers
- Non-atopic wheezers
- IgE-associated wheeze/asthma


Asthma Predictive Index

H/O ≥4 wheezing episodes in the past year (at least one must be provider diagnosed)

**PLUS**
- One major criteria
  - Parent with asthma
  - Atopic dermatitis
  - Aeroallergen sensitivity

**OR**
- Two minor criteria
  - Food sensitivity
  - Peripheral eosinophilia (≥4%)
  - Wheezing not related to infection

If +, then 65% likelihood of developing persistent asthma
If -, then 95% likelihood of not developing persistent asthma


Wheezing Phenotypes: Risk Factors for the Development of Asthma

- Male gender
- Prematurity
- Lung function
- Family history of asthma
- Passive smoke exposure
- Airway hyperresponsiveness
- Eczema
- Socioeconomic status
- Western life style
  - Diet
  - Sedentary life style
- **Viral infections**
- **Atopy**
**Asthma: Pathophysiologic Features and Changes in Airway Morphology**

- Epithelial damage
- Inflammatory cell infiltration
- Vascular dilation
- Mucous gland hypertrophy and hyperplasia
- Edema
- Mucus hypersecretion
- Thickening of basement membrane
- Airway smooth muscle hypertrophy, hyperplasia, and bronchoconstriction
- Inflammatory cell infiltration
- Goblet cell hyperplasia


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**Asthma Triggers**

- Allergen exposure
- Respiratory infections
- Strong expressions of emotion (laughing, crying)
- Vigorous exercise
- Cold air
- Dust
- Air pollution
- Cigarette smoke
- Household products
- Drugs
- Pets


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**Asthma Differential Diagnosis**

- COPD
- GERD
- Anxiety
- Bronchitis (acute or chronic)
- Upper airway dysfunction – croup
  – excessive post nasal drip
  – vocal cord dysfunction
- Sinusitis
- Cystic fibrosis
- Bronchopulmonary aspergillosis
- Other infectious respiratory diseases including pertussis, TB
- Habit cough

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Goal of Asthma Therapy: Achieve Control

- Prevent chronic and troublesome symptoms
- Require infrequent use of inhaled SABA (≤2 days/week)
- Maintain (near) “normal” pulmonary function
- Maintain normal activity levels
- Meet patients' expectations of, and satisfaction with, asthma care

Reduce Risk
- Prevent recurrent exacerbations
- Minimize need for emergency department visits or hospitalizations
- Prevent progressive loss of lung function
- Provide optimal pharmacotherapy, with minimal or no adverse effects

Classifying Asthma Severity and Assessing Asthma Control

- In patients not on controller medications
  - Severity based upon domains of impairment and risk
  - Level of severity based upon most severe category in which any feature appears
- In patients on controller medication
  - Severity based upon lowest step required to maintain clinical control
  - Control of asthma based upon domains of impairment and risk
    - Level of control based upon most severe impairment or risk category
    - Validated questionnaires may be used in patients aged ≥12 years

Severity, Control and Responsiveness

- Severity
  - Intrinsic intensity of the disease process
  - Severity is most easily and directly measured in patients not receiving long-term therapy
- Control
  - Degree to which asthma-related symptoms, functional impairment, and risk of untoward events are minimized and the goals of therapy are met
- Responsiveness
  - Ease with which asthma control is achieved by therapy
  - Responsiveness to asthma treatment is highly variable
Current Impairment and Future Risk

- Both severity and control include the domains of current impairment and future risk
- **Impairment**
  - Frequency and intensity of symptoms and functional limitations the patient is currently experiencing or has recently experienced
- **Risk**
  - Likelihood of asthma exacerbations, progressive decline in lung function, or risk of adverse effects from medications

STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE
Overview of Asthma Medications

Long-Term Control
• Corticosteroids
• Cromolyn/nedocromil
• Long-acting beta₂-agonists
• Methylxanthines
• Leukotriene modifiers

Quick Relief
• Short-acting inhaled beta₂-agonists
• Anticholinergics
• Systemic corticosteroids


Metered Dose Inhalers-MDI

Dry Powder Inhalers-DPI
ICS + LABA Combinations

- Greater efficacy in combination products versus ICS alone:
  - Improved daytime and nighttime symptoms
  - Improved lung function
  - Decreased SABA need
  - Reduced frequency of exacerbations
  - Improved asthma control
  - Reduced ICS dose
- Increased convenience
- May improve adherence
- U.S. combinations:
  1. Budesonide + formoterol (HFA) Approved 2007
  2. Fluticasone + salmeterol (DPI & HFA)
  3. Mometasone + formoterol (HFA)

What Is Allergen Immunotherapy?

- Desensitization process
  - Includes administration of increasing doses of a specific allergen, over time, to a sensitive individual
  - Increases tolerance for the particular allergen
  - Decreases symptoms when patient comes in contact with particular allergen
  - Effective when optimally administered
- May be useful in patients unresponsive or intolerant to conventional therapy
- Not generally recommended for children <5 yrs
- Should be performed by a specialist

Consider Referral to a Specialist

- Symptoms are prolonged
- Symptoms interfere with daily activities, sleep (QOL)
- Patient has a suboptimal response to medications
- Comorbid conditions (asthma, sinusitis, otitis media) are present
- Structural abnormalities exist
- Allergic triggers need to be identified
- Immunotherapy is to be considered
- Oral corticosteroids are required

QOL = Quality of life.
A/R Summary

• AR may be associated with a substantial economic burden and is a major cause of presenteeism
• AR may have a negative impact on quality of life, resulting in impairments in sleep, cognition, daily activity, work productivity, and learning abilities
• Patients with AR often do not seek adequate treatment for their symptoms
• Despite treatment, many patients with AR experience moderate/severe symptoms
• Future therapies for AR should address both nasal and ocular symptoms, produce minimal side effects, and possess favorable sensory attributes

Asthma Summary

• Severity, control, and responsiveness to treatment are key elements of asthma assessment and monitoring
• The goal of asthma therapy is to achieve control based on NAEPP draft guidelines
• Clinical assessment and patient self-assessment are primary methods for monitoring asthma control
• ICS is preferred monotherapy to achieve asthma control in patients with persistent asthma, across all ages
• LABAs are preferred adjunctive agents in patients aged ≥12 years who cannot be controlled with ICS monotherapy

QUESTIONS?