The Atopic March & The Unified Airway

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The Allergic Rhinitis and Asthma Link: Opportunities for Diagnosis and Treatment

Friday, September 9, 2011
12:15 PM – 2:15 PM

California West, Second Floor
The Westin St. Francis
335 Powell Street
San Francisco, CA 94102
Overview

• Immunology review
• Description of diseases
• Epidemiological considerations
• The Atopic March
• Underlying Mechanisms
• Consequences of Progression
• Interventions
Introduction

• Atopy – genetic predisposition to make IgE in response to allergen exposure

The Atopic March

Atopic dermatitis → Allergic rhinitis → Asthma
Introduction

• Why should we care?
  – Increasing prevalence of atopic disease
  – Huge socioeconomic burden
  – The Unified Airway
  – AD/AR are annoying, but asthma can kill
  – We have a chance to intervene

• These patients are sitting in your waiting area
Immunology

- Type I hypersensitivity
  - IgE-mediated
  - Triggered by an allergen (protein)
  - Early and late phases
Immunology

- Cell types involved in allergic response
  - Antigen presenting cells
  - B cells
  - T cells – Th0, Th1, Th2
  - Mast cells
  - Basophils
  - Neutrophils
  - Eosinophils

[Images of various cell types: lymphocyte, mast cell, dendritic cell, neutrophil, eosinophil, basophil]
Immunology
Immunology

- **Preformed Mediators**
  - Histamine
  - Tryptase
  - Proteoglycans
  - Chemotactic factors

- **Newly Formed Mediators**
  - Arachidonic acid metabolites
    - Leukotrienes
    - COX products
  - Platelet-activating Factor
  - Adenosine
  - Bradykinin

- **Cytokines**
  - IL-4
  - IL-5
  - IL-6
  - IL-13
  - TNF-α
Immunology

• Clinical responses
  – Urticaria/angioedema
  – Atopic dermatitis
  – Allergic rhinitis
  – Allergic asthma
  – Anaphylaxis
Immunology
Immunology

**Crystalloid granule protein**
- Core: MBP
- Matrix: EPO, ECP, EDN
- Respiratory epithelium desquamation
- M2 receptor dysfunction
- Mast cell and basophil degranulation

**Lipid mediators**
- LTC4, LTB4, 5-HETE
- PGE1, PGE2, TxB2, PAF
- Increased mucus secretion
- Increased vascular permeability
- Increased adhesion molecules expression
- Bronchoconstriction
- Eosinophil and Neutrophil chemotaxis

**Cytokines and Chemokines**
- IL-1, IL-2, IL-3, IL-4, IL-5, IL-6,
- IL-8, IL-10, IL-12, IL-16, GM-CSF,
- RANTES, TGF-β, TGF-α, MCP-1, MIP-1α
- Increased Eosinophil survival
- Increased adhesion molecules expression
- Sustained inflammation
- Eosinophil and Neutrophil chemotaxis
- Airway wall remodelling
Atopic Dermatitis

- Intrinsic vs. extrinsic
- Epidemiology
  - 60% present before age 1, 85% by age 5
  - Incidence/Prevalence – increasing worldwide
  - U.S. – up to 20% infants/children, 3% adults
  - International – 2-20% infants/children
  - Highest in developed countries**
  - Estimated direct costs – $1-4 billion
Atopic Dermatitis

- Symptoms = pruritus
  - Itch-scratch cycle
- Findings = eczematous lesions, xerosis, and lichenification
  - Variable location based on age
Atopic Dermatitis

• Diagnosis
  – DDx – contact dermatitis, lichen simplex chronicus, psoriasis, scabies, sebhorreic dermatitis
  – Criteria
    • Pruritus
    • Eczematous changes that vary with age
    • Chronic and relapsing course
    • Atopy (IgE reactivity)
    • Xerosis
    • Personal history of asthma or family history of atopy
    • Onset younger than age 2 years
Atopic Dermatitis

• Prognosis
  – Chronic – intermittent flares/remissions
  – Can be “outgrown”
  • <50% resolution by age 7, 60% resolution by adulthood
  – 30+% develop AR, 30+% asthma
  – Why the variable progression?
Allergic Rhinitis

• Inflammation of the mucous membranes of the nose, eyes, eustachian tubes, middle ear, sinuses, and pharynx

• Epidemiology
  – 20-25% of US population affected (40+ million people)
  – Costs = $5.3 billion per year
  – Onset age 8-11 y/o
    • 80% develop AR by age 20

• Prognosis
  – Chronic but can be controlled
  – 30+% will develop asthma
Allergic Rhinitis

• Symptoms
  – Sneezing
  – Itching
  – Rhinorrhea/postnasal drip
  – Congestion
  – Anosmia
  – Headache/earache
  – Tearing/red eyes/eye swelling
  – Fatigue/drowsiness/malaise

• Findings
  – Pale/boggy nasal mucosa, polyps, clear rhinorrhea
  – Pharyngeal cobblestoning
  – Injected sclera
  – Allergic shiners, Dennie-Morgan lines, nasal crease
  – Serous OM
Allergic Rhinitis
Asthma

- Episodic reversible airway obstruction, increased bronchial reactivity, and airway inflammation

- Epidemiology
  - Prevalence
    - U.S. – 8.2% (25 million)
    - International – up to 10% (300 million)
  - 1.5 million ED visits, 500K hospital admissions
  - Costs = $30 billion
Asthma

• Symptoms
  – Cough, wheezing, chest tightness, SOB/respiratory distress
  – Daytime vs. nocturnal

• Findings
  – Often none
  – Diffuse expiratory wheezing, prolonged expiration, signs of distress

• Diagnosis
  – Peak flow
  – Pulmonary function tests
  – Bronchoprovocation
## Asthma

- **Classification**

### Components of Severity

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Classification of Asthma Severity (Children 5–11 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>intermittent - mild</td>
</tr>
<tr>
<td>&lt;2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td><strong>Nighttime awakenings</strong></td>
<td>≤2x/month</td>
</tr>
<tr>
<td><strong>Short-acting beta_2-agonist use for symptom control (not prevention of EIB)</strong></td>
<td>≤2 days/week</td>
</tr>
<tr>
<td><strong>Interference with normal activity</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td>Normal FEV&lt;sub&gt;1&lt;/sub&gt; between exacerbations</td>
</tr>
<tr>
<td></td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; = 75–80% predicted</td>
</tr>
<tr>
<td><strong>Exacerbations requiring oral systemic corticosteroids</strong></td>
<td>0–1/year (see note)</td>
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</table>
Asthma

- Classification

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (Youths ≥12 years of age and adults)</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>≤2x/month</td>
</tr>
</tbody>
</table>
| Short-acting 
  beta2-agonist use 
  for symptom control 
  (not prevention of EIB) | ≤2 days/week | >2 days/week but not >1x/day | Daily | Several times per day |
| Interference with 
  normal activity | None | Minor limitation | Some limitation | Extremely limited |
| Lung function          | Normal FEV₁ between exacerbations | FEV₁ >80% predicted | FEV₁ <80% predicted | FEV₁ >60% but <80% predicted | FEV₁ <60% predicted |
|                        | FEV₁/FVC normal | FEV₁/FVC reduced 5% | FEV₁/FVC reduced >5% | |
| Risk                   | Exacerbations requiring oral systemic corticosteroids | 0–1/year (see note) | >2/year (see note) | Relative annual risk of exacerbations may be related to FEV₁ |

Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.
Asthma

• Prognosis
  – Mortality
    • U.S. – 5K deaths/year
    • International – 250K deaths/year
  – Poor control leads to long-term airway remodeling
  – 50% may “outgrow” asthma
    • Less likely with personal/family history of atopy
Why is prevalence increasing?

- Genetic predisposition
  - Significant evidence of heritability
    - Family history
    - Twin studies
    - Gene studies
  - Multiple mutations identified for atopic diseases
    - Many genes on many loci
Why is prevalence increasing?

- Cannot be based on genetics alone
  - Short (20-30 year) period of changes
  - Incomplete penetrance
  - Geographic variability
- Current model – gene dosage effect and environmental dosage effect
Why is prevalence increasing?

• Evidence for the environment – The Hygiene Hypothesis
  – Correlation between ↑ microbial exposure and ↓ allergic sensitization
  – ↓ exposure during infancy results in predisposition to atopic disease
Why is prevalence increasing?

Factors favoring the Th1 phenotype
- Presence of older siblings
- Early exposure to day care
- Tuberculosis, measles, or hepatitis A infection
- Rural environment

Factors favoring the Th2 phenotype
- Widespread use of antibiotics
- Western lifestyle
- Urban environment
- Diet
- Sensitization to house-dust mites and cockroaches

Th1
Protective immunity

Cytokine balance

Th2
Allergic diseases including asthma
Why is prevalence increasing?

• Reidler et al. (2001) – Allergy and Endotoxin Study
  – Cross-sectional survey of 2,618 children (6-13 y/o)
  – Rural environment – farm vs. non-farm
  – Lower frequencies of AD, AR, and asthma in farming children

• Nowak et al. (1996)
  – Children living in West vs. East Germany
    • > exposure to mold/pollution, > # siblings in East
  – Higher incidence of atopic disease in West
Why is prevalence increasing?

- von Hertzen et al. (2007) – compared geographically distinct but genetically related populations (Finland, Russia)
  - Similar climate, large socioeconomic difference
    - GNP per capita in U.S. $ - Finland = 33K, Russia = 4K
    - Poorer hygiene, ↑ infection exposure, ↑ microbial content in water in Russia
    - ↓ allergen-specific IgE levels and ↑ microbial Ab levels in Russia
Tse et al. (2008)
Progression of the Atopic March

- AD is a major risk factor for the development of asthma
- AD is a major risk factor for the development of AR
Progression of the Atopic March

• van der Hulst et al. (2007)
  – 13 prospective cohort studies
  – Odds ratio for risk of asthma w/ or w/o AD = 2.14 (95% CI, 1.67-2.75)
  – ~30% asthma prevalence at age 6

• Kapoor et al. (2008)
  – Cross-sectional study of 2270 children with AD
  – 66% with AR +/- asthma by age 3
  – ↑ risk with poor AD control
Progression of the Atopic March

- Gustafsson et al. (2000)
  - prospective study of 94 children with AD followed to age 7
  - 82/94 showed improved AD
  - 43% developed asthma, 45% developed AR
- ↑ risk with hereditary, early-onset AD
Progression of the Atopic March

• Illi et al. (2004)
  – prospective study of 1314 children with AD followed to age 7
  – ↑ asthma risk w/severe AD, parental h/o atopy and early-onset sensitization
• 70% severe, 30% mild, 8% general pop.
Progression of the Atopic March

• AR is a risk factor for the development of asthma
• Leynaert et al. (2004)
  – Cross-sectional study of young adults
  – Symptom reports, PFTs, skin tests
  – Asthma prevalence 6x higher in subjects with AR
  – Subjects with asthma reported more symptomatic AR
Underlying Mechanisms

• Genetic and environmental factors
  – Changes in adaptive immune system
  – Role of skin
Underlying Mechanisms

• Threshold event – primary epithelial defect
  – Epidermis – occlusive defense barrier
  • Restricts pathogen entry
  • Restricts water loss
  – ↑ transepidermal water loss in AD
Underlying Mechanisms
Underlying Mechanisms

• Genetic predisposition to barrier dysfunction
  – ↑ production of stratum corneum chymotryptic enzyme

• Premature desmosome breakdown, ↑ desquamation
  – ↓ lipid production – “leaky cement”
Underlying Mechanisms

– Filaggrin mutation
  • Filament-associated protein, bind to keratin fibers in epithelial cells
  • Key for barrier function
  • Loss = major risk for extrinsic AD
    – O’Regan et al. (2009) – LOF mutation in >50% of patients with AD
Underlying Mechanisms

• Mareholz et al. (2006) – filaggrin mutation strongly associated with AR and asthma but:
  – Only in patients with AD
  – Not expressed in nasal/bronchial epithelium
  – Support AD as first step in march
• Gene expression down-regulated by IL-4/IL-13 – acquired defect
Underlying Mechanisms

• Environmental factors impacting barrier
  – Trauma to stratum corneum
    • Scratching
    • Repeated washing
    • Soaps/detergents
  – Exogenous proteases
    • House dust mite exposure
    • Staph colonization
AR and Asthma – The Unified Airway

• Consequences of the March – endpoints of progression
• “One airway, one disease”
• AR is a major risk factor for asthma
• Similar immunologic mechanisms, cellular/tissue changes
• Nasal symptoms, airflow, and markers of inflammation correlate with lower airway involvement
• Poor control of AR = poor control of asthma
AR and Asthma – The Unified Airway

• Epidemiology
  – Settipane et al. (1994) – 23 yr-long study
    • Patients with AR 3x more likely to develop asthma
  – Anderson et al. (1992)
    • Development of asthma 7 years after dx of AR – OR 7.1
  – Burgess et al. (2007) – Tasmanian Asthma Study
    • Childhood AR = 2 to 7-fold ↑ risk for adolescent/ adult-onset asthma
    • 3-fold risk of persistent asthma
AR and Asthma – The Unified Airway

• Nasal-bronchial reflex
  – Common epithelial lining with similar innervation
  – Corren et al. (1992) – nasal provocation ↑ bronchial responsiveness to methacholine
  – Nolte et al. (1983) – acute nasal provocation, acute ↑ airway resistance
  • Blocked by anticholinergic drug
  • Not seen post-laryngectomy
AR and Asthma – The Unified Airway

• Similar immunologic response
  – Large population of mast cells
  – Common associated lymph tissue – MALT
  – Early and late phase allergic response seen in nasal and bronchial tissue
    • Vignola et al. (1993) – ↑ ICAM expression in bronchial brushing of asthmatic patients
    • Ciprandi et al. (1994) – ↑ ICAM expression in nasal secretions of AR patients
    • Braunstahl et al. (2001) – nasal provocation induces ↑ tissue eosinophilia in nasal and bronchial mucosal bx
AR and Asthma – The Unified Airway

• Similar immunologic response
  – Bhimrao et al. (2011) – nasal and bronchial biopsies from 10 patients with AR and asthma
  • Significant and equal levels of eosinophils, neutrophils, and mast cells
AR and Asthma – The Unified Airway

- Similar immunologic response
  - Ciprandi et al. (2004)
    - Upper/lower airway function and nasal inflammation
    - Adults with moderate/severe AR and asthma
    - Functional parameters and immunologic markers
    - ↑ nasal eosinophils/Th2 cytokines, ↑ nasal obstruction, ↓ FEV1
AR and Asthma – The Unified Airway

• AR and asthma control
  – Multiple studies – ↑ hospitalizations/primary care visits with concomitant AR/asthma than asthma alone
  – Valovirta et al. (2006) – 813 adults w/asthma, 806 parents of children w/asthma, w/concominant AR
    • 73% had AR when dx with asthma
    • 79% reported worse asthma symptoms during AR flares
    • 70% reported impaired QOL - ↓ sleep, ↓ concentration, ↓ activity-participation
AR and Asthma – The Unified Airway

• AR and asthma control
  – Stelmach et al. (2005) – DB study of 74 patients with AR and asthma
    • Nasal or inhaled steroid alone or in combo
    • Compared nasal/pulmonary symptoms, pulmonary function, bronchial hyperreactivity
    • Nasal steroid improved symptom control and pulmonary function, ↓ asthma morbidity
  – Watson et al. (2003) – RDBPCT of patients with AR and asthma treated w/intranasal steroids
    • Improved asthma symptoms (nocturnal)
    • ↓ bronchial hyperreactivity
AR and Asthma – The Unified Airway

• AR and asthma control
  – Moller et al. (2001)
  • 205 children, 3 years of immunotherapy
  • 20% with asthma at start of therapy
  • Early recognition of AR in children and tx with allergen-specific immunotherapy ↓ asthma severity and development of asthma
Sinusitis and Asthma – The Unified Airway

- Frequent coexistence of chronic sinusitis and asthma – 20%
  - w/polyps - ↑ to 50%
- Similar effects of chronic inflammation – BM thickening, goblet cell hyperplasia, cellular edema
  - Irreversible remodeling
- Severity of asthma influenced by severity of sinus disease
- Tx of sinus disease via FESS – improves symptoms, QOL, pulmonary function, level of asthma control
Interventions

- Symptom management – AD
  - Environmental control
  - Moisturizers
  - Topical steroids
  - Antihistamines
  - Immunomodulators

All studied, minimal effect on progression of March
Interventions

• Symptom Management – AR
  – Environmental control
  – Pharmacotherapy
    • Antihistamines – oral/intranasal
    • **Steroids – oral/intranasal**
    • Decongestants – oral/intranasal
    • Anticholinergics
    • And others
Interventions

ARIA (2008)

Step 1
Preferred: SABA PRN
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2
Preferred: Low-dose ICS
Alternative: Medium-dose ICS + LABA

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: High-dose ICS + either LTRA or Theophylline

Step 4
Preferred: High-dose ICS + LABA
Alternative: High-dose ICS + either LTRA or Theophylline

Step 5
Preferred: High-dose ICS + LABA + oral systemic corticosteroid
Alternative: High-dose ICS + either LTRA or Theophylline + oral systemic corticosteroid

Step 6
Step up if needed
(first, check adherence, inhaler technique, environmental control, and comorbid conditions)
Assess control
Step down if possible
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes)

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Caution: Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
## Interventions

### Components of Severity

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Persistent</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>3–4x/month</td>
<td>&gt;1x/week but not nightly</td>
<td>Often 7x/week</td>
</tr>
<tr>
<td>Short-acting beta₂ agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Several times per day</td>
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<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
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### Lung Function

- Normal FEV₁ between exacerbations
- FEV₁ >80% predicted
- FEV₁/FVC >85%

### Exacerbations requiring oral systemic corticosteroids

<table>
<thead>
<tr>
<th>Risk</th>
<th>0–1/year (see note)</th>
<th>&gt;2/year (see note)</th>
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<tr>
<td>Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV₁.</td>
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<td></td>
</tr>
</tbody>
</table>

### Recommended Step for Initiating Therapy

- **Step 1:**
  - In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.

- **Step 2:**
  - Step 3, medium-dose ICS option, or Step 4, and consider short course of oral systemic corticosteroids.

### Classification of Asthma Severity (5–11 years of age)

- **Persistent**
  - Moderate
  - Severe

ARIA (2008)
Immunotherapy

• Administration of increasing concentrations of antigen-specific extracts to produce changes in the immune system
• Goal – alleviate/reduce symptoms in response to natural exposure
• Utilizes adaptability of immune system
• Changes in immune system down-regulate immunologic response to allergen
• The key to stopping the Atopic March
Immunotherapy

- Efficacy for AR symptoms
- Efficacy for AD symptoms
  - Bussman et al. (2007) – 25 children with severe AD
    - SCIT x 6 months
    - Significant ↓ in symptom scores
Immunotherapy

• Efficacy for asthma symptoms
  – Niu et al. (2006) – DBRCT 24 weeks SLIT vs. placebo
    • 97 children w/DM allergy and mild/mod asthma
    • ↓ symptoms scores, improved PFTs
  – Ozdemir et al. (2007) – DBRCT SLIT/ICS vs. ICS
    • 62 children w/DM allergy and mild/mod asthma
    • q3 month symptom eval and PFTs
    • ↓ dose/duration of ICS usage
    • ↑ rate of ICS discontinuation
Immunotherapy

• Marogna et al. (2008) – RCT
  – 216 children w/AR +/- intermittent asthma
  – AR meds vs. SLIT/AR meds x 3 years
  – Followed PFTs, methacholine challenge, skin testing
  – Results
    • SLIT ↓ onset of persistent asthma
    • SLIT ↓ bronchial hyperreactivity
    • SLIT ↓ onset of new sensitizations
Immunotherapy

- Ozdemir et al. (2007) – retrospective study
  - 39 children w/AR and asthma – SLIT x 3 years
  - ↓ number of acute attacks
  - 95% with clinical remission of asthma
Conclusions

• Atopic diseases are common and have a huge socioeconomic burden
• Atopic diseases affect QOL, but asthma alone can be deadly
  – Prevalence is increasing
• AD is considered the 1st step – may not be a linear progression
• The upper and lower airways are intimately related and immunologically similar
• Halting the Atopic March is paramount, and immunotherapy is the key