The Present and Future of Asthma: Birth Cohorts & Public Health
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Objectives
- Become familiar with the evidence from available long-term studies on the natural history of asthma.
- Discuss the role of health disparities in asthma.
- Discuss current strategies for impacting asthma management.

Disclosures
I have no disclosures.

What is Asthma
- Chronic inflammatory disorder of the airways.
- Many cells play a role in particular: mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells.
- Inflammation causes smooth muscle hypertrophy, bronchial hyperresponsiveness to a variety of stimuli.
- Inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.
- Episodes associated with variable airflow obstruction which is reversible spontaneously or with treatment.

Epidemiology
- Affects 4.8-6 million children.
- About 5% of general population.
- Most children develop asthma before age 8 (1/2 before age 3).
- There’s been an increase of 40% in the past decade.
- Blacks: 5-8% prevalence.
- Roughly 300 children die of asthma each year.

Gender
- Prior to puberty, asthma is more frequent in boys.
- In adolescence, the difference equalizes.
- Adult onset – more frequent in women.
- Hispanic population – adolescent males twice as likely as females.
Asthma Burden

- Asthma accounted for 1.75 million ED visits in 2007.
- One of the most frequent reasons for admission of children to hospitals.
- Accounts for 12-14 million missed school days annually for children.
- About 1/2 of the billions spent annually on asthma is on ED visits and hospitalizations.

Cohort Studies

- **Prospective (concurrent)**
  - Cause
  - Pattern (complete exposure)
  - Consequence (by sex, race, etc.)
  - Outcome: death, disease, remission

- **Retrospective (historical)**
  - Cause (or treatment)
  - Pattern (long before diagnosis)
  - Consequence (by sex, race, etc.)
  - Outcome: death, disease, remission

Natural History of Symptoms in Children

- Tucson Children’s Respiratory Study followed 1,246 unselected subjects from birth until age 6 (66% completed study).
  - 48% of parents reported wheezing at some point, and 3 patterns were recognized.
    - 20% presented with transient wheezing.
    - 15% presented with late-onset wheezing (after age 3).
    - 14% had persistent wheezing.
  - Persistent and late-onset wheezing was associated with atopy.


- British Avon Longitudinal Study of Parents and Children (ALSPAC)
  - 45% of 14,062 unselected children wheezed.
  - 7 time points from birth to 7 years of age assessed.
  - Wheezy phenotypes were analyzed without any specific hypothesis about specific temporal phenotypes.
  - Temporal wheezing patterns and risk factors of Tucson study confirmed, along with an additional “intermediate-onset wheeze” (onset after 18 months of age) and “early prolonged wheeze” (wheezing in first year of life, with remission by 69 months of age).


Asthma Predictive Index was developed as a result of the Tucson Children’s Respiratory Study.

- Children younger than 3 years who have had 4 or more significant wheezing episodes in the past year are much more likely to have persistent (or lifelong) asthma after 5 years if:
  - One major decisive factor
    - Parent with asthma
    - Physician diagnosis of eczema (atopic dermatitis)
    - Sensitivity to Aeroallergens
  - Or two minor decisive factors
    - Food allergies
    - Greater than 4% blood eosinophils
    - Wheezing apart from colds

A positive Asthma Predictive Index in a 2 or 3 year-old child leads to an 80% chance of a child having the diagnosis of asthma when entering first grade.

http://www.healthychildren.org/English/health-issues/conditions/allergies-asthma/Library/Asthma-Predictive-Index.aspx
Natural History of Symptoms in Children

Melbourne Asthma Study

- In 1964, 295 wheezy 7 year-olds and 106 controls were followed.
- 83 children with severe asthma were added at 10 years of age.
- 83% of cohort provided information at 42 years of age.

83% of children with severe asthma at age 7 had persistent symptoms as adults.

50% of severe group added at age 10 had persistent symptoms as adults.

Eczema, hay fever, or allergic sensitization in childhood increased the risk of continued disease later in life.


Other cohort studies have found that 27% of children with wheeze or asthma at 7 years of age continue to wheeze into adulthood.

Dunedin Multidisciplinary Health and Development Study

British 1958 Birth Cohort

Follow-up of the Tucson Children’s Respiratory Study suggested wheezing patterns did not change significantly from 6 to 16 years of age.


Natural History of Lung Function in Children

Asthma at school age is associated with reduced lung function, particularly in patients with severe disease.

The ALSPAC birth cohort suggested all wheezy phenotypes were associated with impaired lung function by school age.

Is loss of lung function associated with asthma a cause or a consequence of the disease?


Tucson Children’s Respiratory Study

- 125 unselected infants
- An association exists between early airflow limitation and any wheeze in infancy.
- An association exists between neonatal airflow limitation and development of transient early wheeze.
- Children with persistent wheeze at 6 years of age had normal infant lung function but significantly reduced spirometry at 6 years of age.


Perth Cohort Study

- 243 unselected infants
- An association between early airflow limitation and any wheeze in infancy exists.
- No relationship between early airflow limitation and development of early transient wheeze.
- Persistent wheeze at 4-6 years and 11 years old was associated with lung function deficit in neonates, and did not seem to progress with time.


Copenhagen Study on Asthma in Childhood (COPSAC)

- 411 children born of mothers with history of asthma.
- Exhaled nitric oxide levels were increased in 1 mo symptom-free patients who developed transient wheeze but not persistent wheeze.
- Nitric oxide levels were unrelated to infant lung function, but suggested a premorbid pathology independent of lung function abnormalities and present in asymptomatic neonates.

Natural History of Lung Function in Children

Melbourne Asthma Cohort

- Children originally classified as having asthma had consistently lower FEV₁/FVC ratios vs. controls.
- No progression of lung function decline was observed during 7 year follow-ups until age 42.
- Symptoms did persist throughout the follow-up period.


Risk Factors Associated with Asthma in Cohort Studies

Viruses

- The Childhood Origins of Asthma birth cohort (COAST)
  - 289 children at high risk for asthma focused on viral infections during wheezy episodes in the first year of life.
  - Rhinovirus appeared to be a strong predictor of asthma by age 6.
  - Hospitalization secondary to RSV lower respiratory tract infection has been associated with asthma, atopy, and early wheezing symptoms.
  - Direction of causality remains unknown: do certain viral infections increase the risk of asthma or does the underlying cause of asthma increase the risk of severe response to viral infections?


Bacteria

- Bacterial colonization is a major exposure in a newborn.
- Hygiene Hypothesis?
- Prospective studies have found no association between infant gut microbiota and risk of recurrent wheeze before 2 years of age.
- COPSAC showed a strong association between colonization of the airways with common pathogenic bacteria and development of asthma by 5 years of age.
- Remains unknown whether bacterial colonization acts as the environmental trigger in genetically predisposed persons or whether this colonization is merely a marker of the underlying genetic cause of asthma.


Risk Factors Associated with Asthma in Cohort Studies

Urban Environment and Childhood Asthma (URECA).

- 560 patient birth cohort at high risk for asthma.
- 86% assessed at 3 years of age.
- Factors associated with recurrent wheezing:
  - Annual family income < $15,000
  - Lower birth weight and gestational age
  - Number of smokers in the home

Allergen exposure over the first 3 years of life was associated with recurrent wheezing.

First-year exposure to cockroach, mouse, and cat allergens was found to be protective.

An additive reduction in wheeze was observed with exposure to more than one allergen.

Relative bacterial richness was significantly lower in those children who developed atopy and/or wheezing.

Risk Factors Associated with Asthma in Cohort Studies

Tobacco Exposure
- Strongest known environmental modifier in the natural history of asthma.
- Mother's smoking status was associated with a 7% deficit in lung function among newborns in the COPSAC cohort.
- Prenatal and postnatal smoke exposure has been linked to asthma and wheezing, particularly to disease in the first years of life and less strongly to later in life.


Allergic Sensitization
- The German Multicenter Allergy Study (MAS) cohort showed that early and persistent sensitization was associated with asthma.
- Specifically, this association was noted in children with a family history of atopy, indicating some genetic factor is involved.
- High levels of early allergen exposure combined with sensitization to perennial allergens before 3 years of age were associated with loss of lung function and development of airway hyper-responsiveness at school age.


Air Pollution
- Studies using experimental models suggest particulate matter, including diesel exhaust, has immunologic and epigenetic effects influencing wheezing phenotypes and allergic sensitization.
- Southern California Children's Health Study (CHS) evaluated asthma incidence in 2,057 schoolchildren in 12 communities, measuring traffic-related air pollutants as high or low.
- High lung function testing at the start of the study was associated with low risk for asthma, but this effect was attenuated in children living in areas with high pollution.


Antibiotics
- Longitudinal cohort study in British Columbia consists of all live births from Jan 1997 through Dec 2013 (n = 251,817).
- Antibiotic exposure in the first year of life was associated with a small risk of developing asthma in early childhood.
- Increased number of antibiotic exposures was associated with increased asthma risk, with the highest risk in those children with > 4 courses of antibiotics.
- All antibiotics were associated with increased risk of developing asthma, with the exception of sulfonamides.


Traffic congestion may have a greater impact on asthma than traffic flow.
- In this study, evidence of higher socioeconomic status was associated with increased ED visits for asthma.


Antibiotic Exposure Variable | n | 2-yr | 3-yr | 4-yr | 5-yr
---|---|---|---|---|---
Antibiotic exposure | 108,918 | 43.1 | 1.49-1.54 < 0.0001 | 1.45 | 1.39-1.52 < 0.0001 | 1.31 | 1.29-1.44 < 0.0001
No of antibiotic prescriptions | 108,918 | 0-2 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050
| 3-5 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050
| 6+ | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050 | 0.75 | 0.6-1.0 > 0.050

Risk Factors Associated with Asthma in Cohort Studies

- Acetaminophen
  - Acetaminophen is thought to interfere with the antioxidant glutathione, which can result in endothelial damage in the lungs, particularly during viral infections.
  - Acetaminophen has been associated with wheezing and asthma.
  - Multiple studies have not statistically accounted for viral infections.
  - According to Wickens et al., increasing doses of acetaminophen appeared to increase risk for wheeze, recurrent asthma, and atopy.

- Genetics
  - It is likely that genetics contributes to the different clinical phenotypes of asthma
  - Genes associated with asthma:
    - Filaggrin (FLG): a skin barrier protein.
    - Strongly associated with development of atopic dermatitis.
    - Chromosome 17q21 locus (ORMDL3).
    - Associated with nonatopic asthma phenotype characterized by bronchial hyperresponsiveness in newborns and early onset acute asthma exacerbations.
    - DENND1B: involved in adaptive immune response.
  - Risk factor in both white and African-American populations.

Advantages and Limitations of Cohort Studies

- Advantages
  - Suitable for studying rare exposures.
  - Allow for studying more than one outcome.
  - No temporal ambiguity between exposure and outcome.
  - Less prone to bias than case-control and cross-sectional studies.

- Limitations
  - Expensive
  - Time-consuming
  - Not appropriate for studying rare outcomes
  - Observational studies can only suggest associations.
  - Confounding of associations in observational long-term studies remains a risk, despite extensive attempts to adjust for covariates, because underlying variables are either unknown or unavailable.
  - Loss to follow-up, in which adherence might relate to symptoms or risk, is critical in long-term studies
  - Some follow-up studies include only a fraction of the original cohort with a potential bias from overrepresentation of symptomatic subjects and loss of external validity.
Health Disparities and Asthma

Health Disparity: a chain of events signified by a difference in:
- environment
- access to, utilization of, and quality of care
- health status
- a particular health outcome that deserves scrutiny
- If a health outcome is seen in a greater or lesser extent between populations, there is disparity

http://healthypeople.gov/2020/about/disparitiesAbout.aspx

Effective asthma management depends on factors such as:
- Access to care
- Education
- Understanding of therapies
- Adherence to prescribed regimens
- Affordability of treatments/care
- Treatment efficacy
- Many of these factors are linked to socioeconomic status


Asthma Capitals 2009

<table>
<thead>
<tr>
<th>2009 Rank</th>
<th>Metropolitan Area</th>
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<tbody>
<tr>
<td>1</td>
<td>St. Louis, MO</td>
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<tr>
<td>2</td>
<td>Milwaukee, WI</td>
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<tr>
<td>3</td>
<td>Birmingham, AL</td>
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<td>4</td>
<td>Chattanooga, TN</td>
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<td>Charlotte, VA</td>
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<td>4</td>
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<td>Chattanooga, TN</td>
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<tr>
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<tr>
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<td>Augusta, GA</td>
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<td>Virginia Beach, VA</td>
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Asthma Capitals 2012

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<td>New Haven, CT</td>
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<td>Knoxville, TN</td>
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<td>4</td>
<td>Pittsburgh, PA</td>
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<td>Chattanooga, TN</td>
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<tr>
<td>6</td>
<td>Hartford, CT</td>
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<td>7</td>
<td>St. Louis, MO</td>
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Asthma Capitals 2013

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<td>Memphis, TN</td>
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<tr>
<td>4</td>
<td>Philadelphia, PA</td>
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<tr>
<td>5</td>
<td>Oklahoma City, OK</td>
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<tr>
<td>6</td>
<td>Detroit, MI</td>
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<tr>
<td>7</td>
<td>Dayton, OH</td>
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Asthma Capitals 2014

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<tr>
<td>2</td>
<td>Memphis, TN</td>
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<tr>
<td>3</td>
<td>McAllen, TX</td>
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<tr>
<td>4</td>
<td>Oklahoma City, OK</td>
</tr>
<tr>
<td>5</td>
<td>Philadelphia, PA</td>
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<tr>
<td>6</td>
<td>Chattanooga, TN</td>
</tr>
<tr>
<td>7</td>
<td>Fresno, CA</td>
</tr>
</tbody>
</table>

Health Disparities, Asthma, and Tennessee


Over 750,000 Tennesseans are estimated to have asthma.

Among children in Tennessee schools reporting a chronic disease, 42.1% identify that disease as asthma.

In 2006, the death rate due to asthma was 13.1 per 1,000,000 in Tennessee.

Rates were similar for males (12.6) and females (13.7), though mortality was significantly higher for African-Americans (33.1) than for Caucasians (9.4).

Health Disparities and Asthma

Asthma provides an example of the relationships that exist between environmental risk factors, socioeconomic vulnerability, and poor health.

A variety of outdoor and indoor triggers may impact severity and control of asthma.

Many triggers are linked to low socioeconomic status.

Children from low-income homes are more likely to have asthma; they are also more likely to be exposed to environmental triggers in their homes, schools, and communities.

Classifying Asthma Severity in Patients Not Taking Long-term Controller Medication (Children 5-11 Years)

<table>
<thead>
<tr>
<th>Component(s) of Severity</th>
<th>Intermittent (step 1)</th>
<th>Mild (step 2)</th>
<th>Moderate (step 3)</th>
<th>Severe (step 5 or 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom(s)</td>
<td>3 days/week</td>
<td>1 day/week</td>
<td>1 day/week</td>
<td>1 day/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>2/night</td>
<td>Major</td>
<td>Minor</td>
<td>Major</td>
</tr>
<tr>
<td>SABA use for symptom(s)</td>
<td>3/week</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Long function impairment</td>
<td>Normal/FVC &gt;80%</td>
<td>≤20%</td>
<td>≤50%</td>
<td>≤50%</td>
</tr>
<tr>
<td>Risk</td>
<td>Exacerbations requiring hospitalization 0/year</td>
<td>≤3/year</td>
<td>≤1/year</td>
<td>≥2/year</td>
</tr>
</tbody>
</table>

CIB-Exercise-induced bronchoconstriction, FVC-forced vital capacity.


Assessing Asthma Control in Children 5 to 11 Years of Age

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>FEV/FVC &gt;80%</td>
<td>FEV/FVC &lt;60%</td>
<td>FEV/FVC &lt;50%</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>No</td>
<td>1/night</td>
<td>2/night</td>
</tr>
<tr>
<td>SABA use for symptom(s)</td>
<td>3/week</td>
<td>2/night</td>
<td>2/night</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal/FVC &gt;80%</td>
<td>Normal/FVC &lt;60%</td>
<td>Normal/FVC &lt;50%</td>
</tr>
<tr>
<td>Risk</td>
<td>Consider severity and interval since last exacerbation.</td>
<td>Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FVC/FVC.</td>
<td></td>
</tr>
</tbody>
</table>
Asthma Management: Step Up/Step Down

- Step 1: SABA (Albuterol) as needed
- Step 2: Low-dose ICS
  - Alternatives may include cromolyn, Leukotriene Antagonist (LTRA), or theophylline
- Step 3: Medium-dose ICS or Low-dose ICS + LABA, LTRA, or theophylline
- Step 4: Medium-dose ICS + LABA or Medium-dose ICS + LTRA, theophylline
- Step 5: High-dose ICS + LABA, possibly in association with oral systemic corticosteroids

- With all steps, provide education on self-management and controlling environmental factors, management of co-morbidities

"Asthma, the word which properly signifies difficulty of breathing, has been as much misused, and has been made the cognomen of as many different diseases as any word in medicine."

- Laennec, 1819

Questions?