Pre-School Wheeze: The ERS Task Force, and other new and old insights

Andrew Bush MD FRCP FRCPCH
Imperial College & Royal Brompton Hospital

a.bush@imperial.ac.uk
Aims of the Talk

• Describe the basics of the management of pre-school wheeze

• Discuss new insights into phenotyping (ERS Task Force)

• Consider how we treat the condition in light of new clinical trials
Pre-School Wheeze

- Clinical Approach – Diagnosis
  - Wheeze phenotypes – Relevant?
  - Pathophysiology – Relevance
  - Implications for Treatment
  - Summary and Conclusions
Is it true wheeze?

- < 50% agreement between parents and clinicians on whether child wheezed; only 11% parents mentioned ‘whistling’
  - *Arch Dis Child* 2000; 82: 327-32

- Only 32% agreement between parents and physicians
- Objective recording correlated with physician report
- Nurses and parents were not reliable
  - *J Asthma* 2004; 41: 845-53

- Video-questionnaire: 30% parents used words other than wheeze to describe wheeze, or wheeze to describe non-wheeze sounds
  - *Arch Dis Child* 2001; 84: 31-4

- Video-questionnaire helps identify UA abnormalities
  - *Arch Dis Child* 2005; 90: 961-4
Where does the asthma label take us?

• Is it a clinical and/or physiological description?

• Does it imply pathology (inflammation)?

• Does it mean the child has local airway steroid deficiency, requiring urgent replacement therapy?
All that wheezes is not asthma!

- Take a good history, detailed physical examination

- Targeted investigations
  - Many need none
  - Selective approach

- THEN, consider phenotypes
Coughs and Wheezes...

Fall into one of five categories!

- Normal child (hardest diagnosis)
- Serious illness - eg CF, TB (rare, but essential to get right)
- An ‘asthma syndrome’
- Minor problems +/- asthma (rhinitis, reflux)
- Overanxious, psychological
Mimics of Asthma: Normal Child

- “Nursery School Syndrome”
- Post-viral/bronchioliotic cough
- Pertussis and its relatives
Nursery School Syndrome

• Usually 1\textsuperscript{st} Child

• Early placement in child care facility

• Repeated viral infections, one viral cold merging into another

• No response to antibiotics, bronchodilators, ICS, etc.
What caused the Symptoms?

• 15/12 old girl with 4 months of cough intermittently

• Admitted centrally cyanosed on one occasion, never ventilated

• Poor response to therapy

• CXR, CT scan, bronchoscopy:
What caused the Symptoms?

Foreign Body

- Very sudden onset of symptoms
- Ask specifically about the possibility of choking or aspiration
- Listen for abnormal signs – asymmetric, fixed monophonic wheeze; Signs MAY be bilateral, or absent
- CXR may be normal
  - Bronchoscope on history alone
  - World Record – 25 years delay?
Points in the History - 1

• Is it really wheeze?

• Upper airway symptoms prominent?

• Symptoms from first day of life

• Sudden onset symptoms

• Chronic moist cough/sputum – *reliable!*
Points in the History - 2

- Worse after meals, irritable feeder, arches back, vomits
- Systemic illness or immunodeficiency
- Continuous, unremitting symptoms
- What happens during sleep?
Points in the Physical Examination -1

• Clubbing, weight loss, failure to thrive

• Upper airway disease – tonsils, rhinitis

• Unusually severe chest deformity
Points in the Physical Examination -2

- Fixed monophonic wheeze
- Stridor (monophasic or biphasic)
- Asymmetrical signs
- Signs of cardiac or systemic disease
Pre-School Wheeze

• Clinical Approach – Diagnosis

—who Wheeze phenotypes – Relevant?

• Pathophysiology – Relevance

• Implications for Treatment

• Summary and Conclusions
Epidemiological Classification of Infant Wheezing Phenotypes

- Never (51%)
- Transient (20%)
  - Wheeze 0-3, not at age 6
- Persistent (14%)
  - Wheeze 0-3 still present age 6
- Late onset (15%)
  - Wheeze after age 3
Epidemiological Classification of Infant Wheezing Phenotypes-2

![Graph showing the probability of wheezing across different age groups for various phenotypes.](image-url)
Epidemiology: Problems

- GREAT for disease mechanisms and understanding
- Tell us nothing about treatment
- Can only be applied retrospectively

Therefore, clinically completely useless!
What about Atopy?

- Transient wheeze
- Non-atopic (viral induced) wheeze
- Atopic wheeze

Thorax 1997; 52:946-52

Problems with Atopy

- Atopy may not be apparent at the time

- Does: +

= atopic digitopathy??
RESULTS. Of eighty-nine studies identified, 29 (N = 3592 subjects) met the criteria for inclusion. Patients who received inhaled corticosteroids had significantly less wheezing/asthma exacerbations than those on placebo (18.0% vs 32.1%); posthoc subgroup analysis suggests that this effect was higher in those with a diagnosis of asthma than wheeze but was independent of age (infants versus preschoolers), atopic condition, type of inhaled corticosteroid (budesonide metered-dose inhaler versus fluticasone propionate metered-dose inhaler), gender of subject, or methodological quality of study.
Atopy and Multi-trigger wheeze

Am J Respir Crit Care Med 2008; 178: 476-82
Symptom Patterns

• Episodic (viral) wheeze
  – Wheeze in association with (usually) clinically diagnosed viral URTI

• Multi-trigger wheeze
  – Wheeze both with viral URTI and with other triggers between URTIs
Multi-trigger vs. Episodic
Pre-School Wheeze

- Clinical Approach – Diagnosis
- Wheeze phenotypes – Relevant?
  - Pathophysiology – Relevance
- Implications for Treatment
- Summary and Conclusions
Maternal Factors Affecting Airway development

- Maternal smoking
  - Maternal and fetal glutathione metabolism
- Maternal Atopy
- Maternal HT/PET
- Maternal antibiotic use
- Maternal Diabetes
  - *BlueJ 2007; 175: 16-21*
- Maternal diet
- Antenatal air pollution
- EPIGENETICS
ADAM33 & Lung Development

ADAM33 Expression in Human embryonic Lung tissue

BlueJ 2005; 173: 55
ADAM33 & Early lung function

ADAM33 polymorphisms associated with worse early lung function

BlueJ 2005; 172: 55
Control vs. Nicotine

Collagen α1(I) mRNA

Type 1 Collagen protein

Type 111 Collagen protein

RedJ 2002; 26: 31-41
Alveolar Attachments

Reduced by exposure to maternal smoke

BlueJ 2003; 167: 45-9
Smoking & Pregnancy Immunology

- Cord blood cells from 223 women
- Proliferation to HDM
- Proliferation increased in infants of smoking mothers
Multiple Pregnancies: Implications for the hygiene hypothesis?

Multiple pregnancies may have effects on the mother, before viral infections supervene!

*CEA* 2002; 32: 43-50
Relevance of Epigenetics?
What is Epigenetics?

- Epigenetics is the study of heritable changes in gene expression which occur without directly altering the DNA sequence.
  - May be multi-generation
  - May be cell type specific (T-cell vs. dendritic)
Trans-generational Risk

• **If Grandmother smoked:**
  – OR for *maternal* asthma = 1.3; 95% CI, 0.9 to 2.0
  – OR for *grandchild* asthma, even if mother did not smoke = 1.8; 95% CI, 1.0 to 3.3
  – OR for *grandchild* asthma, if mother and grandmother smoked = 2.6; 95% CI, 1.6 to 4.5

*Chest 2005; 127: 1232-41*
Epigenetics and ETS

- Buccal scrapes from 348 children
- Gene methylation, GST polymorphisms, and maternal smoking
- Global DNA methylation, illumina analyses
- Detailed quality control

1031 illumina CpG Clustering
Epigenetic and ETS

- Maternal smoking in pregnancy affected DNA methylation

- There was an interaction with GSTP haplotypes (biologically plausible)

*Am J Respir Crit Care Med 2009; 180: 462-7*
Pieces in the Puzzle: Early sensitization

- MAS study data
- 1314 children from birth to 13 years
- Measurements
  - Allergen exposure assessed at 0.5, 1.5, 3, 4, 5 years of age
  - Lung function 7, 10, 13 years
  - BDR 10, 13 years
  - Histamine challenge 7 years
Prevalence of wheeze by age
(All children with any wheezing episode age 5-7 years)

- Atopic (n=94)
- Non-Atopic (n=59)

Aeroallergen sensitization also associated with loss of lung function & AHR

1-5 years, atopy = non-atopy

MAS Study: Lancet 2006; 368: 763-70
* P < 0.001
Neutrophils, not eosinophils, are mainly activated in preschool wheeze

Arch Dis Child 2003; 88: 529-31
The neutrophil is the key cell in preschool wheeze

*Am J Respir Crit Care Med 1999; 159: 1533-40*
Note that the chronic coughers have normal cellularity

Am J Respir Crit Care Med 1999; 159: 1533-40
Episodic (Viral) Wheeze and BAL Cytology

- Blind non-FOB BAL
- Children anaesthetised for routine surgery
- No evidence of airway eosinophilia in episodic (viral) wheeze

Clin Exp Allergy 1997; 27: 1027-1035
Established Asthma:
Inflammation and structural airway changes

RBM

Eosinophils
Biopsy from 4 month old infant

Biopsy from 15 year old child
Bronchoscopy in Infant and Preschool Wheezers

**Helsinki Cohort**

- Infants 3-26 months
- sGAW and BDR
- Clinically indicated rigid bronchoscopy
- A (reduced sGAW, BDR, n=16); B (reduced sGAW, no BDR, n=22); C (normal sGAW, n=15)

**RBH Cohort**

- Children age 7-58 months
- Video-questionnaire (confirmed vs. reported vs. none)
- Clinically indicated FOB
- Confirmed wheeze (n=16), reported (unconfirmed) wheeze (n=14), control (n=10)
RBM thickness in preschool wheezers compared to asthmatic school-aged children
Pathology: Summary

- Episodic: neutrophil dominates (c.f. eosinophil in multi-trigger asthma)

- Preschool years are critical
  - Atopic sensitisation
  - Immigration studies

- Age one year – no inflammation or structural wall changes

- Age three years – these are starting to appear
Pre-School Wheeze

• Clinical Approach – Diagnosis

• Wheeze phenotypes – Relevant?

• Pathophysiology – Relevance

➢ Implications for Treatment

• Summary and Conclusions
Environmental Smoke exposure?

- I never smoke in front of the children, Dr!

- Their dad smokes, but only outside!

- Worse symptoms if passive smoke exposure (all phenotypes)

- Smokers have less eosinophilia and are steroid resistant; also childhood multiple-trigger wheezers exposed to passive smoke?
Allergen Effects:

Multiple trigger wheezers

• He is no worse when the cat is around, Dr!

• I took the cat away for 2 weeks, and he was no better!

• Honey the kids are allergic to the cat; we had better get rid of the kids!
Is the drug going to the right place?
Indications for Treatment

• Prevention of disease progression
  – (anti-histamines)
  – Intermittent ICS
  – Continuous ICS

• Treatment of symptoms
  – LTRAs
  – Inhaled corticosteroids
  – Oral Corticosteroids
Steroids help symptoms and exacerbations, but are not disease modifying.

*NEJM 2006; 354: 1985-7*
Intermittent ICS in low dose are not disease-modifying

NEJM 2006; 354: 1998-2005
Disease Modifying Therapies
Urinary cys-LTs are raised in preschool wheeze
Intermittent Montelukast?

- Cys-LTs only raised acutely
- Parents probably will not medicate well children

PREEMPT study
- Robertson C, Am J Respir Crit Care Med 2007; 175: 323-9
### TABLE 5. IMPACT OF ASTHMA EPISODES ON CHILDREN AND PARENTS

<table>
<thead>
<tr>
<th>Time off School/Childcare for Patient</th>
<th>Montelukast (n = 329 episodes)</th>
<th>Placebo (n = 325 episodes)</th>
<th>p Value(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) days absent per episode</td>
<td>0 (0–2)</td>
<td>1 (0–2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Proportion of days absent per days at risk*</td>
<td>349/29,816</td>
<td>552/29,840</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Days absent per year at risk for whole population</td>
<td>4.27</td>
<td>6.75</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time off Work for Parent/Caregiver</th>
<th>Montelukast (n = 329 episodes)</th>
<th>Placebo (n = 325 episodes)</th>
<th>p Value(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) days absent per episode</td>
<td>0 (0–2)</td>
<td>1 (0–3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Proportion of days absent per days at risk*</td>
<td>416/29,816</td>
<td>622/29,840</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Days absent per year at risk for whole population</td>
<td>5.09</td>
<td>7.61</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nights disturbed for Child</th>
<th>Montelukast (n = 329 episodes)</th>
<th>Placebo (n = 325 episodes)</th>
<th>p Value(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) nights disturbed per episode</td>
<td>2 (1–4)</td>
<td>3 (2–4)</td>
<td>0.013</td>
</tr>
<tr>
<td>Proportion of nights disturbed per days at risk*</td>
<td>1,010/29,816</td>
<td>1,105/29,840</td>
<td>0.043</td>
</tr>
<tr>
<td>Nights disturbed per year at risk for whole population</td>
<td>12.4</td>
<td>13.5</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviation: IQR = interquartile range.

*Days at risk are the total number of days in the study for all 202 patients who had at least one treated episode.

\(^*\) p value from the chi-square or Mann-Whitney test.
Intermittent ICS

- 129 children age 1-6 years
- FP 750 mcg bd vs. placebo with acute episodic (viral) wheeze
- In 40 weeks, 8% FP vs. 18% placebo were given prednisolone (43 vs. 93; OR 0.49, 0.30-0.83)
- **BUT: SAFETY**
  - 10% children have > 10 colds/year
  - There was a growth effect (-0.24 Z score)
  - Adrenal function only crudely assessed

*NEJM 2009; 360: 339-53*
Episodic BUD vs. LTRA

- 238 children aged 2-14 years, episodic viral wheeze
- Minor changes in severity for both BUD, LTRA
- More benefit if +ve API

JACI 2008;122: 1127-35
Episodic Treatment

• **FIRST CHOICE:** Intermittent LTRA
  – Potentially safer

• **NEXT:** Intermittent high dose ICS
  – Dose and duration unknown
  – MONITOR carefully

• **COUNCIL OF DESPAIR:** Intermittent combination therapy
  – Evidence base = zero
Oral Prednisolone

Parent-initiated
- 217 children, already one admission
- Parent initiated treatment at next exacerbation
- No benefit seen

Hospital-initiated
- 687 children (atopy NOT an exclusion)
- Clinically diagnosed acute viral wheeze
- Time to hospital discharge

Lancet 2003; 362: 1433-8
NEJM 2009; 360: 329-38
Prednisolone: Ineffective

[Graph showing the percentage of children in hospital over hours after admission for Prednisolone and Placebo groups, with corresponding numbers of children at risk listed in a table.]
Episodic (viral) Wheeze: The role of Prednisolone

• NOT a community medication

• NOT a routine 2\textsuperscript{ry} care medication

• (Possibly) multi-trigger wheeze with a severe exacerbation

• (Possibly) any severe episodic (viral) wheeze heading for PICU
Preschool Wheeze - Trial of Prophylactic Medication

- **USUALLY ONLY IN MULTI-TRIGGER WHEEZE**
  
  - **Step 1**
    - Inhaled BUD 400 mcg bd
    - OR, montelukast 4 mg od

  - **Step 2**
    - Stop treatment after c. 8 weeks

  - **Step 3 (Only if “response” to Step 1)**
    - Restart BUD, titrate to lowest dose
    - OR, restart montelukast
Pre-School Wheeze

• Clinical Approach – Diagnosis

• Wheeze phenotypes – Relevant?

• Pathophysiology – Relevance

• Implications for Treatment

➢ Summary and Conclusions
Take Home Messages

• Make sure it is wheeze; make sure you are not missing a diagnosis (history and examination)

• Classify wheeze as ‘episodic (viral)’ and ‘multi-trigger’

• The pathology is of fixed airflow obstruction and neutrophilic airway inflammation, not ICS responsive eosinophilia

• There are no disease-modifying therapies

• So, treat episodic symptoms episodically
  – Bronchodilators first line
  – Then Montelukast
  – Consider high dose ICS burst (BUT, numbers of URTIs)
  – Finally, combine all three (Bronchodilator, montelukast, high dose ICS)

• Do NOT use oral corticosteroids for episodic (viral) wheeze
Has Grampa stopped talking yet?