Outcome, classification and management of wheezing in preschool children

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Valle de la Luna, San Pedro de Atacama, Lunes 10 Octubre
1050 beds 2-location facility
Largest non-university teaching hospital in the country
275 medical specialists
100 registrars, 90 house officers
At the end of this presentation...

You will be able to:
- counsel parents on long-term outcome of their preschool child with wheeze
- discuss the pros and cons of distinguishing episodic viral wheeze and multiple trigger wheeze
- provide evidence-based treatment to a preschool child with recurrent troublesome wheeze
Guidelines for young children

“Asthma is defined as a chronic inflammatory disorder of the airways and is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing”

“Making a diagnosis of asthma in children 5 years and younger may be difficult because episodic respiratory symptoms such as wheezing and cough are also common in children who do not have asthma, particularly in those younger than 3 years”

Pediatr Pulmonol 2011;46:1-17
One of the main findings of the present Task Force was that the evidence on which to base recommendations is limited in this age group.

The present recommendations are likely to change when more evidence becomes available.
Outcome of preschool wheeze
Disagreement

“the simplicity and reasonably good likelihood ratios of the stringent API should encourage its use for early asthma diagnosis among young children with recurrent wheeze in clinical practice in many health care settings”

“the API is not useful in predicting the long-term prognosis of preschool children with more severe or recurrent wheeze in clinical practice.”

J AllergyClin Immunol 2011;127:293-4 and 1082-3
In other birth cohort studies:
More phenotypes (cluster analysis):
prolonged early wheeze
intermediate onset wheeze
Related to severity & pattern of atopy

Tucson population study

Other population studies: Wheeze ever

What you see in your office Recurrent wheeze
Frequency of wheeze episodes

Majority of wheezy preschool children wheeze only once or twice

Visser, Pediatric Pulmonol 2010;45:149-56
Prediction of outcome of preschool wheeze

Tucson study: “asthma predictive index”

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental MD asthma (^2) MD eczema (^3)</td>
<td>MD allergic rinitis (^4) Wheezing apart from colds Eosinophilia (≥4%)</td>
</tr>
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</table>

Strict index = early frequent wheezer + 1 or more major criteria or 2 or more minor criteria

Am J Respir Crit Care Med 2000;162:1403-6
Prediction of outcome of preschool wheeze in a population study (Tucson)

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1000 preschool children with wheeze ever during preschool years
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**Sensitivity:** \( \frac{49}{222} = 22\% \)
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<td>23</td>
<td>72</td>
</tr>
<tr>
<td>API -ve</td>
<td>173</td>
<td>755</td>
<td>928</td>
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Specificity: \( \frac{755}{778} = 97\% \)
Prediction of outcome of preschool wheeze in a population study (Tucson)

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Positive (or negative) predictive value

Is dependent on prevalence of the disease (in this case, asthma at the age of 6 years) in your population.
Prediction of outcome of preschool wheeze in a population study (Tucson)

Sensitivity and specificity are constant characteristics of a test (stringent API)

Predictive value of a test depends on the likelihood (prevalence) of asthma in your population

You can work with this in practice using the likelihood ratio and the Fagan nomogram
Likelihood ratio of a positive API (LR+) = sensitivity/(1-specificity), or the true positives divided by the false positives

• LR+ API = 7.3
Tucson study:

Likelihood of asthma at age 6 in children who had ever wheezed during first three years of life: 22.2%
Tucson study:

Likelihood of asthma at age 6 in children who had ever wheezed during first three years of life: 22.2%

Is the likelihood of asthma at age 6 in your population higher, lower, or the same of that of the Tucson population?
Likelihood of asthma at age 6 in children who had ever wheezed during first three years of life: 40%
**Prediction of outcome of preschool wheeze in a clinical population (your office)**

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Positive predictive value is better (77% → 83%)

But the negative predictive value is worse (90% → 65%)
# Prediction of outcome of preschool wheeze in a clinical population (your office)

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Large majority of children in your office will have –ve API

Children with –ve API: 1 in 3 will have asthma at age 6: Could it be used to withhold treatment?

Children with +ve API: 1 in 5 will not have asthma at age 6: could it be used to provide treatment?
Prediction of outcome of preschool wheeze in Bogotá

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<td>API +ve</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>API -ve</td>
<td>12</td>
<td>57</td>
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Large majority of children in Bogotá had −ve API

Children with −ve API: 1 in 5 had asthma at age 6:
Could it be used to withhold treatment?

Children with +ve API: 6 in 10 did not have asthma at age 6:
could it be used to provide treatment?

Prediction of wheeze outcome

API:
- Tucson study: SENS 22%, SPEC 97%, prev 22%
- Bogotá study: SENS 43%, SPEC 79%, prev 23%

Other predictive indices:
- PIAMA study: SENS 20%, SPEC 95%, prev 11%
- Frank study: SENS 48%, SPEC 90%, prev 9%

Different populations → different results

Can we use Tucson’s API in a different population?
It’s up to you to decide

“API useful in clinical practice”

“API not useful in clinical practice”
Classification of preschool wheeze
Classification of preschool wheeze

Episodic (viral) wheeze: wheezing during discrete time periods, often in association with clinical evidence of a viral cold

Multiple trigger wheeze: wheezing that shows discrete exacerbations but also symptoms between episodes

“The present recommendations are likely to change when more evidence becomes available.”

Eur Respir J 2008;32:1096-1110
Usefulness of clinical phenotypes of wheeze

The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze

A Schultz (andre.schultz@health.wa.gov.au), SG Devadason, OEM Savenije, PD Shy, PN Le Souëf, PLP Brand

132 2-6 yr old children with asthma treated with ICS
Classified as EVW or MTW at start of study
Follow-up 1 yr (4 visits)
Wheeze during colds only or also apart from colds? classification as EVW or MTW

Acta Paediatr 2010;99:56-60
Start of study

EVW 38

MTW 71

End of study (1 year later)

EVW 12

no wheeze 22

MTW 11

13 13

38

Acta Paediatr 2010;99:56-60
There’s more to preschool wheeze than just EVW/MTW

**EVW-MTW:** does not allow for differentiation by severity/ frequency of wheezing episodes

There’s more to preschool wheeze than just the wheeze

Dimensions of Respiratory Symptoms in Preschool Children
Population-based Birth Cohort Study

Jaclyn A. Smith¹, Richard Drake², Angela Simpson¹, Ashley Woodcock¹, Andrew Pickles³, and Adnan Custovic¹

• Birth cohort n=942 followed up to 5 yrs
• Principal components analysis: five variables (wheeze, wheeze with irritants, wheeze with allergens, cough, chest congestion) explained half of variance age 5
• atopy only related to symptoms when treated as continuous trait

Smith, AJRCCM 2008; 177:1358-63
Wheeze & allergic sensitization

2612 Swedish 4-yr olds

Similar results in Manchester cohort: risk of symptoms and poor LF ↑ with number and severity of sensitizations

Wickman, Allergy 2005;60:650-7; Simpson, JACI 2005;116:744-9
Size matters!

Difference between EVW and MTW is not clear-cut

There’s more to preschool respiratory problems than just wheeze

Effect of atopy on preschool wheeze depends on the extent and severity of sensitization
Treatment of preschool wheeze
Classification of preschool wheeze

Episodic (viral) wheeze: wheezing during discrete time periods, often in association with clinical evidence of a viral cold.

Multiple trigger exacerbation: wheezing that shows discrete exacerbations but also symptoms between episodes.

Thought at the time to be useful as a guide to therapy.

“The present recommendations are likely to change when more evidence becomes available.”

Eur Respir J 2008;32:1096-1110
Treatment of multiple trigger wheeze

- Dose response relationship unclear
- Evidence not demonstrated < 1 yr age
- Effect smaller than in older children
- **ICS more effective than montelukast** *(J Allergy Clin Immunol 2007;120:1043-50)*
- **Effect ICS can not be predicted by FeNO or other exhaled breath markers** *(Clin Exp Allergy 2011;41:1076-83)*
Treatment of episodic (viral) wheeze

NNT to prevent one symptomatic episode = 9
NNT to prevent one unscheduled doctor visit = 19
No effect on exacerbations requiring oral steroids

Montelukast effective in reducing wheeze when started at first signs of URTI
In 2-14 yr old children with recurrent viral wheeze
(Robertson, AJRCCM 2007;175:323-9)

Bisgaard,
AJRCCM 2005; 171:315-22
Treatment of recurrent wheeze

- MTW: inhaled corticosteroids as first choice therapy
- EVW: montelukast as first choice therapy

“The present recommendations are likely to change when more evidence becomes available.”

Brand, Eur Respir J 2008;32:1096-1110
Treatment of recurrent wheeze
- New evidence (SR)

ICS are effective in recurrent wheeze in preschool children, irrespective of wheeze pattern

Treatment of recurrent wheeze
- New evidence (BALLOON Study)

992 2-6 yr old children with recurrent wheeze + +ve API or +ve Phadiatop

Baseline Period (2 - 4 weeks)

Double-blind Treatment period (24 weeks)

Placebo PM

Ciclesonide 160 µg/d PM

Ciclesonide 80 µg/d PM

Ciclesonide 40 µg/d PM

Placebo PM

Brand et al, Respir Med 2011; 105:1588-95
Exacerbations more likely in placebo group than in pooled ciclesonide groups (p=0.03)

Brand et al,
Respir Med 2011;
105:1588-95
Lung function in 4-6 yr olds

All patients

Non-Asians

Patient selection issues have major impact on study results

Aim at including children with high risk of asthma persistence → end up with mixed bag of phenotypes

• less severe illness in Asians (40 vs 60% severe asthma)
• less history of eczema (8 vs 50%)
Treatment: methodological issues

- Phenotypes & inclusion criteria unclear (heterogeneity)
- Phenotypes unstable
- Large differences between studies
- Most studies: small numbers
- Adherence and inhalation technique not assessed
- Age important effect modifier: the younger, the poorer the response
Conclusions I

- Preschool wheeze complex and poorly understood group of syndromes
- Outcome can (not) be reliably predicted
- There’s more to preschool wheeze than just the pattern of wheeze
  - Need to take other symptoms into account
  - Need to take allergic sensitization into account (not just presence, but also pattern and severity)
Conclusions II

- ICS and montelukast may both be given on a trial basis in almost any patient
- At group level, ICS more effective than montelukast
- Discontinue treatment if no clear benefit
- Need more, large RCTs with clear description of patients on a range of clinical characteristics (at least symptoms & atopic sensitization, preferably also lung function)
¡Muchas gracias!

San Pedro de Atacama, October 2011

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