Managing the wheezing infant

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Milano, Italy

Asthma and viral infections
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Conflict of interest

Speakers’ Bureau: none

Advisory boards: ALK-Abellò, Pierre Fabre, Stallergènes

Italy

Currently sponsored research: MSD, GSK, Pierre Fabre, Heinz Plada, Paul Ehrlich Institute, Chicco Artsana.
Educational objectives

At the end of this lecture, participants will be able:

• To correctly place a diagnosis of asthma in preschooler
• To help parents with the prediction of asthma
• To take decisions on the actual treatment of wheezing infants
Adrian, clinical history (highlights)

• Adrian G., infant boy, 8-month old
• Family of Albanian origin; exclusively breastfed for 4 months
• Monolateral familiarity for asthma and respiratory allergy (mother)
• 6-months old: mom back at work
Adrian, clinical history (highlights)

- Day-care center since age 6 months
- Now, 10-months old: “always coughing”
- Only sporadic febrile episodes, at most 38.5°C rectal
- Treated with
  a. An antibiotic course (amoxicillin, 50mg/kg/day for 8 days)
  b. Aerosol bronchodilators
  c. Mucolytics
- Once diagnosed with “asthmatic bronchitis”
- Twice diagnosed with “bronchospasm”
- Once diagnosed with asthma attack, oral steroids administered
Adrian, first assessment

- Reported for allergy evaluation
- A flare with cough
- Rectal temperature 38.2
- Reported sleep disturbance

- Objectively:
  - scattered coarse rales
  - expiratory whistles.
1. Should we diagnose Adrian with asthma?

2. Can we predict asthma development?

3. Should we treat Adrian?

4. Conclusions

Managing the wheezing infant
Asthma in preschooler: guidelines

<table>
<thead>
<tr>
<th>Reference</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global strategy for asthma management and prevention in children 5 years and younger.</td>
<td><a href="http://www.ginasthma.com/Guidelineitem.asp??l1=2&amp;l2=1&amp;intId=1689">http://www.ginasthma.com/Guidelineitem.asp??l1=2&amp;l2=1&amp;intId=1689</a> (GINA pediatric reoprt, May 2009)</td>
</tr>
</tbody>
</table>
Making a diagnosis of asthma in children 5 years and younger may be difficult because episodic respiratory symptoms [...] are also common in children who do not have asthma.

Table 1. Is It Asthma?

Consider asthma if any of the following signs or symptoms are present:

- Frequent episodes of wheezing—more than once a month.
- Activity-induced cough or wheeze.
- Cough particularly at night during periods without viral infections.
- Absence of seasonal variation in wheeze.
- Symptoms that persist after age 3.
- Symptoms occur or worsen in the presence of:
  - Aeroallergens (house dust mites, companion animals, cockroach, fungi)
  - Exercise
  - Pollen
  - Respiratory (viral) infections
  - Strong emotional expression
  - Tobacco smoke
- The child’s colds repeatedly “go to the chest” or take more than 10 days to clear up.
- Symptoms improve when asthma medication is given.
If a detailed history suggest the diagnosis of asthma and wheezing episodes are frequent, regular controller therapy should be initiated.

... may also be indicated in a child with less frequent but more severe episodes of viral-induced wheeze.

Where the diagnosis is in doubt ... a diagnostic trial of regular controller therapy should be considered to confirm whether the symptoms are due to asthma.
Case history

In all children, ask about:

- Wheezing, cough
- Specific triggers: e.g. passive smoke, pets, humidity, mold and dampness, respiratory infections, cold air exposure, exercise/activity, cough after laughing/crying
- Altered sleep patterns: awakening, night cough, sleep apnea
- Exacerbations in the past year
- Nasal symptoms: running, itching, sneezing, blocking.

Identification of Asthma Phenotypes Is Critical

Asthma Phenotypes in Children >2 Years of Age

Is the child completely well between symptomatic periods?

Yes

Are colds the most common precipitating factor?

Yes

Virus-induced asthma\(^a\)

No

No

Is exercise the most common or only precipitating factor?

Yes

Exercise-induced asthma\(^a\)

No

No

Does the child have clinically relevant allergic sensitization?

Yes

Allergen-induced asthma

Yes

Unresolved asthma\(^{a,b}\)

No

\(^a\)Children may also be atopic.

\(^b\)Different etiologies, including irritant exposure and as-yet not evident allergies, may be included here.

Phenotypes according to trigger
Asthma Phenotypes in Children >2 Years of Age

Virus-induced asthma

Exercise-induced asthma

Allergen-induced asthma

Unresolved asthma

- Virus-induced asthma\textsuperscript{a}
- Exercise-induced asthma\textsuperscript{a}
- Allergen-induced asthma
- Unresolved asthma\textsuperscript{a,b}

\textsuperscript{a}Children may also be atopic.
\textsuperscript{b}Different etiologies, including irritant exposure and as-yet not evident allergies, may be included here.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal pattern of wheeze</td>
<td></td>
</tr>
<tr>
<td>Episodic (viral) wheeze</td>
<td>Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes</td>
</tr>
<tr>
<td>Multiple-trigger wheeze</td>
<td>Wheezing that shows discrete exacerbations, but also symptoms between episodes</td>
</tr>
<tr>
<td>Duration of wheeze</td>
<td></td>
</tr>
<tr>
<td>Transient wheeze</td>
<td>Symptoms that commenced before the age of 3 yrs and are found (retrospectively) to have disappeared by the age of 6 yrs; transient wheeze may be episodic or multiple-trigger wheeze</td>
</tr>
<tr>
<td>Persistent wheeze</td>
<td>Symptoms that are found (retrospectively) to have continued until the age of ( \geq 6 ) yrs; persistent wheeze may be episodic or multiple-trigger wheeze</td>
</tr>
<tr>
<td>Late-onset wheeze</td>
<td>Symptoms that start after the age of 3 yrs; late-onset wheeze may be episodic or multiple-trigger wheeze</td>
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Adrian, clinical history (highlights)

When you say "always coughing," what?

- In between episodes, does Adrian have cough…
  …At night?
  …At awakening?
  …After running?
  …After crying?

- Does happen that Adrian is completely well?
Definitions of phenotypes

For clinical purposes, wheeze should be described in terms of its temporal pattern and classified as episodic (viral) or multiple-trigger wheeze.

The term asthma should probably not be used in preschool children because data regarding underlying inflammation are lacking.
Definitions of phenotypes

Use of the terms transient, late-onset and persistent wheeze should probably be limited to population-based cohort studies and should not be used clinically.
Different “Asthma” Phenotypes


There are no data suggesting this phenotype is associated with eosinophilic inflammation or with increased atopic sensitization, the two factors that might be associated with steroid responsiveness.
Viral infection is likely to cause inflammation that primes the airway for enhanced responses to allergen exposure.

It is likely that viral and allergic mechanisms act cooperatively to create an acute, severe asthmatic response.

1. Should be diagnose Adrian with asthma?

2. Can we predict asthma development?

3. Should we treat Adrian?

4. Conclusions
Why is asthma to be predicted?

- High prevalence
- Early childhood is a vulnerable phase
- Pulmonary function in childhood often persists into adulthood \(\Rightarrow\) airway remodeling is an early and irreversible event.
- Prevent or reduce the burden of asthma and its long-term sequelae

Morgan WJ. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med 2005;172:1253-8
Vonk JM. Childhood factors associated with asthma remission after 30 years follow-up. Thorax 2004;59:925-9
Asthma with onset in early adulthood has its origins in early childhood.


Onset of asthma before the sixth year in 80% of cases

Different “Asthma” Phenotypes

Lee Harvey Oswald, JFK’s murder
Early identification of children 5 years and younger at high risk of developing persistent asthma

A number of risk profiles have been evaluated.

Asthma Predictive Index is recommended for children with four or more wheezing episodes in a year

A child with a positive API has a 4- to 10-fold greater chance of developing asthma between the ages of 6 and 13

95% of children with a negative API remain free of asthma.

Clinical predictors of asthma from epidemiologic studies

- Parental history of asthma and atopy;
- History of wheeze;
- Presence of other atopic conditions, such as eczema, rhinoconjunctivitis, or food allergy;
- Increased serum concentrations of IgE;
- Cytokines…

# Modified Asthma Predictive Index

In past 12 months, ≥4 wheezing episodes (>24h), with at least 1 physician-confirmed,

**PLUS**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>Parental history of asthma (MD)</td>
<td>Allergic sensitisation to milk, egg or peanut</td>
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<tr>
<td>Atopic dermatitis (MD)</td>
<td>Wheezing apart from colds</td>
</tr>
<tr>
<td>Sensitisation to &gt; 1 aeroallergen*</td>
<td>Eosinophilia &gt;5%</td>
</tr>
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* House dust mite, cockroach, dog, cat, mold, grass, tree, and weed.

Guilbert TW. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 2004; 1282-7
Clinical predictors of asthma from epidemiologic studies

- Negative predictive values are higher than positive

- These models are better at excluding than at predicting

- These models are not suitable for identifying the children at high risk who are likely to benefit from prevention strategies.

Adrian, a mother’s question

Doctor, will Adrian be an asthmatic?

• Is there anyone in your family with asthma?
• Did he have atopic dermatitis?
• When it goes well, has the baby whistle or cough?....

... Then let’s go an do a skin prick test.
Skin prick test can identify eczematous infants at risk of asthma

- Egg allergy $\Rightarrow$ high risk of asthma [OR = 3.52]
- Risk of asthma greater if large SPT with egg [OR = 4.61]

Lowe AJ. Skin prick test can identify eczematous infants at risk of asthma and allergic rhinitis. Clin Exp Allergy 2007; 37:1624–31
Adrian: Asthma Predictive Index

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Guilbert TW. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 2004; 1282-7
Values from the API, Isle of Wight and PIAMA indices

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<thead>
<tr>
<th>Risk of asthma</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>API*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6-8 y</td>
<td>22</td>
<td>97</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>At 11-13 y</td>
<td>15</td>
<td>97</td>
<td>47</td>
<td>85</td>
</tr>
<tr>
<td>At 6-13 y</td>
<td>16</td>
<td>97</td>
<td>77</td>
<td>68</td>
</tr>
<tr>
<td>Isle of Wight† at 10-11 y</td>
<td>10</td>
<td>98</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>PIAMA‡ at 7-8 y</td>
<td>60</td>
<td>76</td>
<td>23</td>
<td>94</td>
</tr>
</tbody>
</table>

+ LR, Positive likelihood ratio (sensitivity/1-specificity); − LR, negative likelihood ratio (1-sensitivity/specificity).

*Positive stringent index.
†Risk score strata = 4.
‡Cutoff ≥20.

Early identification of children 5 years and younger at high risk of developing persistent asthma

The applicability and validation of the API in other countries and clinical situations is awaited

1. Should be diagnose Adrian with asthma?

2. Can we predict asthma development?

3. Should we treat Adrian?
   a. Controller medications
   b. Reliever medications

4. Conclusions
Management of asthma in children 5 years and younger.

Asthma education should be provided to family members and caregivers of wheezy children 5 years and younger when wheeze is suspected to be caused by asthma.

For all patients with a confirmed diagnosis of asthma, the goal of treatment is to achieve control of the clinical manifestations of the disease and maintain this control for prolonged periods, with appropriate regard to the safety and cost of the treatment required to achieve this goal.

Management of asthma in children 5 years and younger.

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   a. Controller medications
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4. Conclusions

Managing the wheezing infant
**Need for answers**

**Figure 4.3-2: Management Approach Based on Control For Children 5 Years and Younger**

The available literature on treatment of asthma in children 5 years and younger precludes detailed treatment recommendations. The best documented treatment to control asthma in these age groups is inhaled glucocorticosteroids and at Step 2, a low-dose inhaled glucocorticosteroid is recommended as the initial controller treatment. Equivalent doses of inhaled glucocorticosteroids, some of which may be given as a single daily dose, are provided in Chapter 3 (Figure 3-4).

The clinical benefits of intermittent systemic or inhaled glucocorticosteroids for children with intermittent, viral-induced wheeze remain controversial. While some studies in older children have found small benefits, a study in young children found no effects on wheezing symptoms. There is no evidence to support the use of maintenance low-dose inhaled glucocorticosteroids for preventing transient early wheezing.

**Leukotriene modifiers:** Clinical benefits of monotherapy with leukotriene modifiers have been shown in children older than age 2. Leukotriene modifiers reduce viral-induced asthma exacerbations in children ages 2-5 with a history of intermittent asthma. No safety concerns have been demonstrated from the use of leukotriene modifiers in children.
Inhaled steroids in infants

This meta-analysis shows that ICSs are useful in infants and preschoolers with persistent wheeze/asthma in reducing exacerbations and withdrawals caused by exacerbations as compared with placebo.

ICS control but do not cure the disease

285 preschool kids with wheeze and high asthma risk

Does early inhaled steroids influence long term prognosis of asthma?

- ICS control asthma symptoms and lung function, but does ICS influence long term prognosis?

The early use of inhaled fluticasone propionate for wheezing in preschool children had no effect on the natural history of asthma or wheeze later in childhood, and did not prevent lung function decline or reduce airway reactivity.

Intermittent inhaled corticosteroid therapy had no effect on the progression from episodic to persistent wheezing and no short-term benefit during episodes of wheezing in the first three years of life.
Steroid improvement only in atopic children

- 61 children with intermittent wheeze
- Fluticasone or placebo for 16 weeks
- Measurement of airway resistance (Rint), bronchodilator responsiveness (BDR)

Pao CS, McKenzie SA. Randomized controlled trial of fluticasone in preschool children with intermittent wheeze. Am J Respir Crit Care Med. 2002; 166:945-9
PREventing Virus-Induced Asthma

- 549 children
- Aged 2 to 5 years
- Intermittent asthma symptoms from common cold
- 1-week screening period
- 2-week, single-blind, placebo run-in period
- 48-week, double-blind active treatment period
- Montelukast 4-mg chewable tablet or placebo

Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma

Different response profiles


<table>
<thead>
<tr>
<th>Baseline Characteristic (N, %)</th>
<th>Fluticasone Propionate</th>
<th>Montelukast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilator use &gt; 4 puffs/week (65, 52%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma-free days ≤ 2 days/week (68, 54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-bronchodilator FEV₁ % predicted &lt; 90% (41, 33%)</td>
<td></td>
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</tr>
<tr>
<td>Pre-bronchodilator FEV₁/FVC &lt; 80% (51, 40%)</td>
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<td></td>
</tr>
<tr>
<td>Methacholine PC₂₀ ≤ 1 mg/ml (54, 45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum bronchodilator response &gt; 15% (58, 46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled nitric oxide &gt; 25 ppb (61, 55%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood total eosinophil count &gt; 350 cells/mm³ (51, 41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum eosinophilic cationic protein &gt; 15 mcg/L (68, 54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum IgE &gt; 200 kU/L (55, 44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary leukotriene E4 &gt; 100 pg/mg creatinine (59, 50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender (52, 41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minority (60, 48%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 10 (84, 67%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lemanske RL. Step-up Therapy for Children with Uncontrolled Asthma while Receiving Inhaled Corticosteroids. NEJM 2010, e-pubbl in ahead of print

ICS step-up, 250 µg fluticasone twice daily
LABA step-up, 100 µg fluticasone plus 50 µg LABA twice daily
LTRA step-up, 100 µg fluticasone twice daily plus 5 or 10 mg MK

157 children 6-12, asthma not controlled despite FP100 µg/die:
Step-up Therapy for Children with Uncontrolled Asthma

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157 children 6-12, asthma not controlled despite FP100 µg/die:

Although LABA step-up was significantly more likely to provide the best response than either ICS or LTRA step-up, many children had a best response to ICS or LTRA step-up, highlighting the need to regularly monitor and appropriately adjust each child’s asthma therapy within this level of care before further step-up.
Options for children < 5 years

Steroids

LTRA

Association

Options for children 0 to 2 Years

- Asthma ~ >3 episodes in the previous 6 months
- Start with $\beta_2$ agonists as first choice
- LTRA daily controller therapy for virus induced asthma symptoms
- Inhaled steroids for persistent wheezing, especially if severe or requiring frequent oral corticosteroid therapy
- Oral steroids (e.g. 1–2 mg/kg prednisone) for 3–5 days during acute and frequently recurrent obstructive episodes
- Evidence of atopy lowers the threshold for use of ICS and they may be used as first-line treatment in such cases

1. Should be diagnose Adrian with asthma?

2. Can we predict asthma development?

3. Should we treat Adrian?
   a. Controller medications
   b. Reliever medications

4. Conclusions

Managing the wheezing infant
Preemptive use of high-dose fluticasone for virus-induced wheezing in young children

- 129 children 1 to 6 yrs
- to receive 750 µg of fluticasone propionate or placebo x2
- beginning at the onset of an upper respiratory tract infection
- Continuing for 10 days, over a period of 6 to 12 months

In FP treated children:
- symptoms milder and of shorter duration;
- fewer days of albuterol use
- less negative effect on their parents’ quality of life.

OR 0.49
8%


Courtesy of Attilio Boner
Preemptive use of high-dose fluticasone for virus-induced wheezing in young children

- 129 children 1 to 6 yrs
- to receive 750 µg of fluticasone propionate or placebo x2
- beginning at the onset of an upper respiratory tract infection
- Continuing for 10 days, over a period of 6 to 12 months

Given the potential for overuse, this preventive approach should not be adopted in clinical practice until long-term adverse effects are clarified.

No justification for the administration of prednisolone to preschoolers without atopy who have episodic (viral) wheezing in either a community or hospital setting unless a severe clinical course is anticipated.
What treatment can be recommended for acute episodic wheezing in preschool children?

**β2-Agonists** that are inhaled through an appropriate spacer, with a mask if age appropriate, should be given.

Intermittent use of **leukotriene receptor antagonists** may be beneficial, but comparisons with intermittent inhaled corticosteroids are needed.

**Prednisolone** should be administered to preschoolers only when they are severely ill in the hospital.

Intermittent, **high-dose inhaled corticosteroids** should not be used.

Managing the wheezing infant

1. Should be diagnose Adrian with asthma?
2. Can we predict asthma development?
3. Should we treat Adrian?
   a. Controller medications
   b. Reliever medications
4. Conclusions
Adrian, the diagnosis and the future

Multitrigger, persistent wheezing

Virus-induced exacerbations

Egg allergy

Positive API
Conclusions

1. Control of asthma in pre-schoolers is a realistic goal
2. Ban maternal & environmental smoking
3. A diagnosis of asthma in children 5 years and younger may be difficult – label as wheezing
4. It can be based on symptom patterns and on a careful clinical assessment of family history and physical findings.
5. Asthma education should be provided
6. For patients with asthma, the goal of treatment is to control the clinical manifestations of the disease for prolonged periods

Conclusions

7. The prolonged use of high doses of inhaled or systemic glucocorticosteroids must be avoided
8. Use a pressurized MDI with a valved spacer
9. **Inhaled steroids** in children 5 years and younger are effective
10. **Rapid-acting inhaled β2-agonists** are the preferred reliever treatment
11. **Oral glucocorticosteroids only in acute severe exacerbations**
12. A low-dose inhaled glucocorticosteroid is recommended as the preferred initial treatment to control asthma
13. If it does not control symptoms (check technique & adherence!), double the initial dose of glucocorticosteroid
14. Asthma treatment should be **re-assessed** every 3–6 months.