What is the best way to treat recurrent wheeze in pre-school children?
In the beginning...
Lower airway obstruction

Asthma vs bronchiolitis?

- Both cause lower airway obstruction with inflammation and bronchospasm

- The same viruses (RSV, paraflu, rhinoviruses, metapneumovirus, and others) that cause bronchiolitis are the major triggers for acute exacerbations of asthma in pre-school age children (and the most common cold viruses - the rhinoviruses - are the major causes of acute exacerbations in school age children and adults)
What is Bronchiolitis?

Bronchiolitis is a diagnostic term used to describe the initial episode of viral respiratory infection induced lower airway disease in an infant.
Bronchodilators for Bronchiolitis?

- Patel et al, Randomized, controlled trial of neb Rx with epinephrine, albuterol, saline (placebo) in bronchiolitis. *J Pediatr* 2002;141:818-24
  - 149 patients randomized (50 epi, 51 alb, 48 plac)
  - Conclusion: No group differences in effectiveness for hospitalized infants with bronchiolitis.

  - 14 studies, 7 in- 6 out-patient – epi compared with placebo or alb
  - Epi may be favorable compared with placebo and albuterol for short-term benefit in outpatients but effect is transient
  - Insufficient evidence to support routine use of bronchodilators for bronchiolitis in hospital
Corticosteroids for Bronchiolitis


- RDBPC trial in 70 children <24 months (mean age 6.5 months) with 1st episode VRIILAO (i.e. bronchiolitis)
- Initial dose of 1 mg/kg dexamethasone in ETC decreased hospitalization >50% by 4 hours
  - 44% hospitalized in placebo group
  - 19% hospitalized in dexamethasone group
Systemic Corticosteroids for Bronchiolitis


- RDBPC trial in 600 children 2-12 months (mean 5.1) with 1st episode wheezing (bronchiolitis)
- Initial dose of 1 mg/kg dexamethasone in ER
- Hospitalizations after 4 hours
  - 40% for dexamethasone group
  - 41% for placebo
## Comparison of Schuh and Multicenter Studies

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Schuh</th>
<th>Multicenter</th>
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<tbody>
<tr>
<td>No. of children</td>
<td>70</td>
<td>600</td>
</tr>
<tr>
<td>Mean age (months)</td>
<td>6.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Hospitalized after 4 hrs</td>
<td>Dex 19% Plac 44% $p=0.03$</td>
<td>Dex 41% Plac 40% $p=0.74$</td>
</tr>
<tr>
<td>Family history atopy</td>
<td>Dex 83% Plac 53%</td>
<td>Dex 56% Plac 60%</td>
</tr>
<tr>
<td>Prior duration of symptoms (days)</td>
<td>Dex 1.7 Plac 1.8</td>
<td>Dex 3.7 Plac 3.8</td>
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</table>

Differences in the two studies that could have resulted in the conflicting outcomes:

- Schuh study unbalanced regarding family history of atopy
- **Schuh study treated earlier in the clinical course**
Corticosteroids for Bronchiolitis

- Lower doses than in Schuh study produced lesser but significant effect in outpatients
  - Csonka et al, Prednisolone in management of children 7-35 months with VRIILAD: A randomized, placebo-controlled trial. J Pediatr 2003;143:725-30. – Same efficacy in 1st or 2nd time wheezing

- Controlled clinical trials for inpatients all negative even one at doses used by Schuh
Single Dose of Dexamethasone for Hospitalized Children with Bronchiolitis

- RDBPC of 0.6 mg/kg dexamethasone IM
- First episode of wheezing with tachypenia, increased respiratory effort, and a URI
- 1 to 24 months of age
  - Median 9.2 for dexamethasone group
  - Median 10.0 for placebo

Teeratakulpisarn et al, Pediatric Pulmonology 2007;42:433-91

![Bar chart showing duration of distress, O2, and hospitalization with p-values P=0.02, P=0.004, P=0.003]
So Where Are We in the Treatment of Bronchiolitis?

- Bronchodilator may provide transient symptom relief but do not alter clinical course
- Speculation
  - High dose corticosteroid may provide clinical improvement early in the course
  - Perhaps more likely in infants with atopic family history
When an Infant Gets One of the Common Cold Viruses – RSV, PF, RV, etc.

Healthy baby

URI only

No recurrent LRI with VRI

Bronchiolitis

Recurrent LRI with VRI (intermittent asthma)

Chronic (persistent) asthma

Genetic and prenatal factors

Atopy
Just What is Asthma?

- Asthma is a physiologic abnormality of the airways characterized by hyper-responsiveness to various stimuli resulting in airway obstruction that is reversible either spontaneously or as a result of treatment.

- The airway obstruction is a result of various degrees of bronchial smooth muscle spasm and inflammation.
Clinical Patterns (phenotypes) of Asthma

- Intermittent
- Chronic
- Seasonal allergic
- Chronic with seasonal allergic exacerbations

Severity can range from trivial to life-threatening for all patterns
But What About Reactive Airway Disease

"Reactive Airway Disease"

A Lazy Term of Uncertain Meaning That Should Be Abandoned

Recurrent wheeze in pre-school age children is a common asthma phenotype!
When Does Asthma Begin?

Asthma Incidence Rates in Rochester MN by Age

80% of asthma has onset by age 5!

Hospital Discharge Rates for Asthma by Age Group

Source: National Hospital Discharge Survey, National Center for Health Statistics, Centers for Disease control & Prevention

Akinbami & Schoendorf, Pediatrics 2002;110:315-322
Why the high hospitalization rate for asthma under age 5?

- >80% of children with exacerbations had evidence of viral respiratory infection (Johnston et al. BMJ 1995;310:1225)
- Rhinovirus predominates (Minor et al. JAMA 1974;227:292)
- RSV (recurrent) common in pre-school age (McIntosh et al. J Pediatr 1973;82:578)
- Metapneumovirus and others also contribute to recurrent wheeze
Infection and Asthma

- Bacterial infections do not exacerbate asthma
- Role of Mycoplasma and Chlamydia pneumoniae are controversial
- Respiratory viral infections (common cold viruses) have repeatedly been shown to be major exacerbants of asthma
Mean Annual Incidence of Colds

Monto & Ulman, JAMA 1974;227:164

Figure from “The common cold” Lancet 2003;361,53
Epidemiology of Viral Respiratory Infections (common cold viruses)


- Most pre-school age children get 3-8 per year
- 10-15% get ≥ 12 per year
Autumnal Increase in Asthma

Johnston et al. JACI 2006;117:557-62
Why Do Common Cold Viruses that Usually Just Cause Upper Respiratory Symptoms Cause Lower Respiratory Inflammatory Disease in Some?
Deficient Innate Immunity to Rhinovirus in Asthma

Asthmatic and normal epithelial cells infected with rhinovirus

- Asthmatic epithelial cells produce less interferon-β than normal
- Greater replication of virus occurs in asthmatic epithelial cells

Deficient Innate Immunity to Rhinovirus

Stimulation of PBMC* by Rhinovirus

*Peripheral Blood Mononuclear Cells

Adapted from Papadopoulos et al, Thorax 2002;57:328-32
Contoli et al. Role of deficient type III interferon-\(\lambda\) production in asthma exacerbations.

- Infection with rhinovirus associated with increased respiratory epithelial cells interferon-\(\lambda\)
- Comparing asthmatics and normals infected with rhinovirus
  - Greater interferon-\(\lambda\) from BAL cells from asthmatics
  - Greater viral production in BAL cells from asthmatics
  - Greater cold symptoms in asthmatics
  - Greater decrease in FEV\(_1\) in asthmatics
What happens to the pre-school asthmatic? Do they *outgrow* it?
Prevalence of Symptoms by Age in Atopic and Non-Atopic Asthma

Illi et al. Lancet 2006;368:763-770
Allergy in Asthma

11 month old with CA pollen season rhinoconjunctivitis and asthma

- Bioassay for specific IgE
- No age limitation
- 10% of asthmatic infants with positive skin tests
- Prognostic value even if not correlating with symptoms at initial evaluation
Implications from Epidemiology and Natural History Data

- Asthma is common
- Asthma typically begins in early childhood
- The highest hospitalization rate for asthma is those under 5 years of age
- An intermittent pattern (*not necessarily mild*) is the most prevalent clinical pattern for asthma
- The long term outlook for remission of intermittent (*but not chronic*) asthma is most commonly good despite early morbidity
How should children with viral respiratory infection induced asthma be treated?
Medication Use for Asthma

- **Maintenance** - daily scheduled medication to prevent asthma
- **Intervention** - as needed medication to stop acute symptoms of asthma
Limitation of Maintenance Therapy

Effect of inhaled corticosteroids on episodes of viral induced exacerbations of asthma

- 104 Children (7-9 yrs)
- Only wheezed with URIs
- RDBPC - BDP 400 mcg/d
- Followed 6 months

Outcome

- No significant differences in frequency, severity, or duration of symptoms
- Small but significant difference in airway reactivity during intercurrent periods

Doull et al, BMJ 1997
Limitation of Maintenance Therapy

Effect of inhaled corticosteroids on episodes of viral induced exacerbations of asthma

- 4 month DBPC 400 mcg/day in 41 children (0.7-6 years) with acute asthma with colds
  (Wilson et al, Arch Dis Child 1995)
  - No difference in number of episodes
  - No difference in mean symptoms score

- Cochrane review: “There is no current evidence to favour maintenance low dose inhaled corticosteroids in the prevention and management of episodic viral induced wheeze.”
Medication Use for Asthma

- **Maintenance** - daily scheduled medication to prevent asthma

- **Intervention** - as needed medication to stop acute symptoms of asthma
$\beta_2$ Bronchodilator Aerosol
Hand Position for VHC with Mask for Infant or Toddler
Limitation of Inhaled Bronchodilators in Asthma
Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children


- 238 children aged 12 to 59 months with intermittent asthma
- RDBPC to budesonide, montelukast, placebo
- Monitored for 12 months
- Severity reduced in those that were atopic
- No difference in episode-free days
- No difference in use oral corticosteroids
What About Higher Doses of Inhaled Corticosteroids During an Exacerbation?

- Four studies in children not receiving maintenance meds compared effect of high dose inhaled corticosteroid (1600-3200 µg/day) with placebo for VRI induced asthma

  - Conclusion: some clinical effect but no overall significant decrease in need for intervention with oral corticosteroids or hospitalization

What can be done for the pre-school wheezer?


These investigators say oral corticosteroids are of no value!

- 708 admitted with acute lower respiratory tract symptoms
  - 345 excluded following review
  - 130 refused consent
  - 217 randomized to 20 mg qd or placebo

- Outcome – of 217 children, mean age 25 months
  - ~30% with no further symptoms
  - ~15% with no symptom diary
  - 121 remaining – mean symptom scores <1 on scale of 0-3 (*no sleep disturbance & treatment not given*) for prednisolone and placebo group
What can be done for the pre-school wheezer?

My interpretation of their data: Children with symptoms as mild and self limited as those don’t need oral corticosteroids
No Benefit from Oral Corticosteroid?

- 700 children, mean age 26 months, placebo or prednisolone
- Dosage used
  - 10 mg once daily for 10 to 24 months
  - 20 mg once daily for 2-6 years of age
- Outcome
  - Rapid improvement in placebo and treated
  - Symptom scores ~1.5 on scale of 12 by 24 hrs

Consequence of Patient Selection

- Primary outcome: Decision to discharge
  - Median 12 hours for placebo
  - Median 10.1 hours for prednisolone

- Logical conclusion: for children with acute wheezing (presumably asthma) who will rapidly improve spontaneously within 12 hours, a low dose of prednisolone doesn’t significantly shorten the course.

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

**Question:** If they are effective in preschoolers when they are severely ill in the hospital, why wouldn’t they be effective if an adequate dose was given prior to entering the hospital?

**Answer:** Logic and data indicate they are!
Issues: Dosage

Haskell et al. Arch Intern Med 1983;143:1324-7

Percent Change of FEV1 after Starting Different Doses of 6 hourly MPR

Time from Starting Methylprednisolone

n=8 for each
Value of Early Corticosteroid Use in the Emergency Room

from Tal et al, Pediatrics 1990.

- Randomized DBPC trial (age 0.5 - 5 yrs)
- Methylprednisolone, 4 mg/kg, or normal saline
- Decision to admit made 3 hours after IM blinded study medication
- Significantly more admissions among placebo treated
Value of Early Corticosteroid Use in the Hospitalized Child

- Randomized DBPC trial (mean age = 5 yrs)
- Prednisolone, 30 mg PO for < 5 yr old; 60 mg for ≥ 5 or matched placebo
- Significantly more rapid improvement for patients receiving prednisolone
- Significantly earlier discharge for patients receiving prednisolone

Number of patients discharged at 5 hr exam from Storr et al, Lancet 1987.

![Graph showing number of patients discharged at 5 hr exam](image)
Value of Early Corticosteroid Use in the Emergency Room

- Randomized DBPC trial (mean age = 5 yrs)
- Prednisone, 2 mg/kg PO, or placebo
- Repeated albuterol nebulizations
- No difference at 2 hrs
- Significant decrease in decision to hospitalize at 4 hrs

*from Scarfone et al, Pediatrics 1993*

% of pts hospitalized

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Most Sick</th>
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<tbody>
<tr>
<td>Prednisone (n=36)</td>
<td>70%</td>
<td>80%</td>
</tr>
<tr>
<td>Placebo (n=39)</td>
<td>80%</td>
<td>90%</td>
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</table>
High Inhaled vs Oral Steroids for Acute Asthma in the ER

- 100 children
- RDBPC trial in ER
  - 2 gm fluticasone (8 puffs of Flovent MDI via AeroChamber)
  - 2 mg/kg oral prednisone
- Albuterol and ipratropium nebs for all
- Substantially better lung function in prednisone treated

Value of Early Corticosteroid Use to Prevent Progression of Acute Asthma

- RDBPC trial of 1 week PO prednisone, 30-40 mg bid, or placebo in 41 pts with chronic asthma (median age 12 yrs)
- Prednisone or placebo started for bronchodilator subresponsive symptoms
- All prednisone pts improved; 8/19 placebo pts worsened while 11 improved at a slower rate

From Harris et al, J Pediatr 1987
Prevention of Acute Asthma With Oral Corticosteroids in High Risk Patients

- 32 children < 6 yrs old requiring repeated hospitalization from asthma triggered by URI
- After 1 year, 16 received 1 mg/kg/day prednisone at beginning of URI
- Prednisone treated group had 90% reduction in hospitalization

Signs and Symptoms that Precede Wheezing Children with Intermittent Asthma


Which most important? Which resulted in treatment?

Most important

Initiation of therapy
When Should Oral Corticosteroids Be Started?

Signs and Symptoms that Precede Wheezing Children with Intermittent Asthma


- 238 children 12 to 59 months
- History of recurrent wheezing but well between
- Monitored for 12 months
- Survey captured signs and symptoms at start of a respiratory illness that led to wheezing and onset of treatment
Signs and Symptoms that Precede Wheezing
Children with Intermittent Asthma


- Symptoms preceding wheezing requiring intervention
  - Nasal
  - Cough, minor
  - Cough, troublesome
    - Sleep disturbance
    - Activity interference
    - “Asthma cough”

- Troublesome cough most important predictor
Contrary Data


- **Dosage used**
  - 10 mg once daily for 10 to 24 months
  - 20 mg once daily for 2-6 years of age

- **Outcome**
  - Rapid improvement in placebo and treated
  - Primary outcome – duration of hospitalization
    - 12 hours for placebo group
    - 10.1 hours for prednisolone group
  - Symptom scores ~1.5 on scale of 12 by 24 hrs
Contrary Data

Dosage used – 20 mg once daily

Outcome

- High dropout rate
- Mean symptom scores low for prednisolone and placebo group

Our Experience with Intermittent Viral Induced Asthma in Young Children

Prednisolone started at onset of requiring repeated albuterol
- 20 mg bid for ages 1-3
- 30 mg bid for ages >3

Outcome
- 93% reduction in acute care
- 90% reduction in hospitalizations

Najada et al. Ann Allergy Asthma Immunol 2001;87:335-43
High dose systemic corticosteroids may be of clinical value early in the course of bronchiolitis.

Systemic corticosteroids are indicated early in the course of acute exacerbations of asthma at any age, most of which are induced by viral respiratory infections.

Bronchodilators provide transient symptomatic relief but do not alter the course of VRI induced asthma or bronchiolitis.
Conclusion

- Parents can generally identify in advance when a viral respiratory infections will be followed by wheezing and respiratory distress warranting intervention.
- Inhaled corticosteroids don’t significantly alter the course.
- Prednisone in adequate dose favorably alters the clinical course.
- Limit maintenance Rx to persistent Sx.