Houston W’eeze Got a Problem

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SPEAKER DISCLOSURE: NO CONFLICTS OF INTEREST TO DISCLOSE
Colby

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Hasbro Children’s Hospital
Disclosure of having gone to Bowdoin?
Learning Objectives

• Explain common and uncommon etiologies of wheezing in children

• Recognize conditions in wheezing children when systemic corticosteroids are/are not indicated

• Discuss the evidence for the use of an alternative to prednisone in acute asthma exacerbation
Wheeze is a symptom of obstruction of the lower respiratory tract.

- Bronchioles
- Intrathoracic trachea
Wheezing is common in kids

• Children <=1yo

  • Approx 40% have at least one episode of wheezing

  • 8% had recurrent wheezing (>=3 episodes/6months)


All that wheezes is not asthma
Each case is based on patients with wheeze I have taken care of from the past few years

• Common and Uncommon
Case #1

• 4 month old former FT male infant presents with acute respiratory distress

• 3 days of nasal congestion and cough

• Today with increased respiratory distress, poor feeding, less wet diapers
Case #1

On exam:

• Diffuse wheezing and bilateral scattered coarse crackles

• Mild subcostal retractions
What is your next step?

A. Rapid RSV test

B. Albuterol

C. Nasal suctioning

D. Albuterol and oral corticosteroids
Albuterol – language changed

**2006**

**Evidence Profile 2b: Trial of Bronchodilators**
- Aggregate evidence quality: B; RCTs with limitations
- Benefit: some patients with significant symptomatic improvement
- Harm: adverse effects, cost of medications, cost to administer
- Benefits-harms assessment: preponderance of benefit over harm in select patients
- Policy level: option

**2014**

**ALBUTEROL**

**Key Action Statement 2**

Clinicians should not administer albuterol (or salbutamol) to infants and children with a diagnosis of bronchiolitis (Evidence Quality: B; Recommendation Strength: Strong Recommendation).
“Given the greater strength of the evidence demonstrating no benefit, and that there is no well-established way to determine an “objective method of response” to bronchodilators in bronchiolitis, this option has been removed”
No albuterol for you!

2 Cochrane reviews
Chavasse 2002
Gadomski 2014

Chavasse, et al.

- Recurrent wheezers < 2yo
- 8 RCTs
  - 3 studies outpatient
  - 2 hospital setting
  - 3 pulmonology clinic
- Outcome measures: decrease in RR, improved respiratory scores
- No clear benefit of short acting beta-agonist use in bronchiolitis

Gadomski, et al.

Evaluated 30 RCTs from 12 countries

• No benefit in the clinical course

• Adverse effects
  • Tachycardia
  • Tremors
  • Cost

What a minute!: I’ve seen some bronchiolitics get better after albuterol
Some kids respond??....
cough
“Although it is true that a small subset of children with bronchiolitis may have reversible airway obstruction resulting from smooth muscle constriction, attempts to define a subgroup of responders have not been successful to date”

Variability of illness

1. disease process
2. host’s airway
3. subjectivity of respiratory scoring
Some kids respond??....
Think about your own practice for **bronchiolitis**

What influences your decision to give/prescribe bronchodilators?

- Patient factors
- Past medical historical factors
- Family history factors
- Gestalt
- Other objective measures
Defining ‘response’

• I got to get rid of that wheeze (‘sounds better’)

• Looks, feels, acts better
  • More comfortable work of breathing
  • Less tachypneic
  • Resolved hypoxia
Who’s more distressed by Weezy?
What about systemic corticosteroids for bronchiolitis?
CORTICOSTEROIDS

Key Action Statement 5

Clinicians should not administer systemic corticosteroids to infants with a diagnosis of bronchiolitis in any setting (Evidence Quality: A; Recommendation Strength: Strong Recommendation).

Guidelines change management

Bronchiolitis Management Before and After the AAP Guidelines
Kavita Parikh, Matthew Hall and Stephen J. Teach
Pediatrics 2014;133;e1
DOI: 10.1542/peds.2013-2005 originally published online December 2, 2013;

Steroids and bronchodilators trends had $P$ value $< 0.001$.
Antibiotics had $P$ value $= 0.007$

**FIGURE 2**
Diagnostic and treatment utilization over 3 time periods from 41 hospitals ($n = 37,907$).
What’s the big deal with a short course of steroids?

What’s the big deal with a short course of steroids?

Systematic review of the toxicity of short-course oral corticosteroids in children

Fahad Aljebab, Imti Choonara, Sharon Conroy

• ’roid rage – other behavior changes
• Vomiting
• Sleep disturbances

Downside to steroids?

• Infants getting steroids for lung disease of prematurity may be associated with long term lower IQ scores and neuromotor function.
  • Yeh TF, et al.
  • Wilson-Costello et al.

• Increased steroids in adults with rheumatologic disease and asthma associated with worse cognition.
  • Frol AB, et al.

Case #2: ‘Emma’
It’s late summer 2014

6 yo female presents with cough, respiratory distress, fever and wheezing

No history of asthma, wheezing or eczema

No family history of wheezing
• Kansas City, MO: “Lots of admissions for respiratory symptoms, particularly wheezing and hypoxia even in children who were not known to be asthmatic, It's like Winter already!”

• Chicago, IL: “There have been a series of patients admitted to the PICU at Comer Children's Hospital at University of Chicago with new onset wheezing”
What respiratory virus was responsible?

A. Rhinovirus
B. Enterovirus
C. Coronavirus
D. Influenza virus
E. Human Metapneumovirus
FIGURE 2. Percentage of enterovirus reports, by month of specimen collection — United States, 1983–2005
Some viruses are more wheeze-inducing

Chatter on Listserv of Enterovirus D68 preceded MMWR by 3 weeks
What is Enterovirus EV-D68, the disease causing alarm in the Midwest?

By Jethro Mullen, CNN

Updated 3:33 PM ET, Tue September 9, 2014
EV D68 caused a lot of first time wheeze

15% first time wheeze
EV D68 caused first time wheeze in older kids

Average age of first time wheezers 6 years old
EV D68 is caused more severe symptoms than rhinovirus.

Viral PCR on Nasal swabs
Rhinovirus/Enterovirus

EV D68

EV D68 = more febrile, more wheezy, more bronchodilator use, more PICU admission

Rhinovirus

Viral PCR on Nasal swabs
Rhinovirus/Enterovirus

EV D68
Rhinovirus

Despite initial worse severity
NO DIFFERENCE in length of stay

Why are some viruses more wheeze inducing?

Virulence Factors  Host Responses
“Question- are you managing this like asthma in the > 2 year old crowd without history of wheeze/asthma ...or more like bronchiolitis (supportive care without albuterol or steroids)?”

“I have been treating them like asthma even if its first time wheezing just because they seem to respond to albuterol like asthmatics.”

“some appear responsive at first....and then less so as time goes on in which case we’re moving to PRN albuterol and doing more supportive care.
CLEAR AS MUD
To steroid or not to steroid?

- **South Carolina**: “I've seen a lot of 4 year olds and haven't treated them with steroids... I’m not having any initial asthma conversations with families during an epidemic of a virus that makes everyone wheeze..I try albuterol and objectively evaluate if it works, but I would not be giving a lot of steroids”

- **Kansas City, MO**: “the amount of corticosteroid use has been painfully high, to the point that we are paying through the nose to get it from other regions of the country. The lack of evidence on what effect it has in the non-asthmatic kids makes this strategy particularly frustrating. I keep hearing the mantra "do less, do less" in my head, and then I sign the order anyway”
Case #3: Emma’s cousin ‘Beth’

• Has recently spent time around Emma

• PMH: mild persistent asthma

• Has been having persistent wheezing, intermittent fevers and malaise for the past few weeks.

• On exam: some pallor, shotty cervical lymphadenopathy, diffuse wheeze, no crackles
What do you want to do for Beth?

A. Get a nasopharyngeal PCR swab to confirm EV-D68

B. Get CXR

C. Trial bronchodilator

D. She has a history of asthma: Treat with oral corticosteroids and bronchodilator
Why would steroids be a bad idea in this case?
• Adverse affects on pathological accuracy

• Cause a delay in definitive diagnosis
Case #4

2 year old visiting grandparents house found to be eating peanuts

Started gagging, coughing, sputtering

Now with wheezing and vomiting

No rash or lip swelling
What is a next step in management?

A. Get R and L lateral decubitus chest Xrays

B. Give IM epinephrine 1:1,000 concentration

C. AP/Lateral CXR

D. Go right to bronchoscopy

E. Give albuterol
Anaphylaxis can go unrecognized

**TABLE I. Clinical criteria for diagnosing anaphylaxis**

Anaphylaxis is highly likely when **any one of the following 3 criteria** are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **AND AT LEAST ONE OF THE FOLLOWING**
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure **to a likely allergen for that patient** (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure **to known allergen for that patient** (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Anaphylaxis can go unrecognized

**TABLE I. Clinical criteria for diagnosing anaphylaxis**

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In **up to 20 percent** of all anaphylaxis episodes:

Skin symptoms and signs (such as hives, itching, flushing, and angioedema) are **absent or unrecognized**.

Under recognition = delayed delivery of Epinephrine

• Increase risk of death (very rare)
  • US rate 0.7 per 1,000,000 population/yr
  • 4-40 US children/year
    • Turner, P. *Current opinion in allergy and clinical immunology* 2016.

• Increase rate of hospitalization
Looked at Epinephrine use before ER (early vs. late)

- 384 cases of anaphylaxis
  - 70% had prior to ER

- Rate of Hospitalization
  - Early (17%) vs. Late (43%)

Can steroids help prevent Biphasic Reaction?

• Biphasic reaction: return of allergy symptoms/anaphylaxis without continued or re-exposure to allergen

• Timing of biphasic reaction varies:
  • Up to 76 hrs after initial event (Average 10hrs)
2 ERs over a 5 years period

473 cases of anaphylaxis
  • 75% got steroids (initial +/- 5 day course of prednisone)
  • 25% no steroids

• No difference in biphasic reactions or allergy related-return visits to ER (NNT 176 to prevent 1 return visit)

Outcomes:
Mortality
Biphasic Reaction

No evidence for or against steroids

Case #5

• 8 month old with a history of laryngomalacia and GERD (treated with ranitidine due to frequent vomiting with poor weight gain)

• Parents have been reluctant to start many solid foods since he seemed to vomit more when introduced

• He seems to ‘always be sick’ for the past few months during bronchiolitis season, and has been wheezing.

• Albuterol is not helping
What workup combination is most likely to give the diagnosis at this time?

A. bronchoscopy and impedance study

B. Flexible laryngoscopy and EKG

C. CXR and barium esophagram

D. Fecal occult blood and partially hydrolyzed formula trial
Vascular Ring

Congenital anomalies
  • Complete or Partial

Symptoms often respiratory and feeding issues

Diagnosis challenging for physicians
95% of vascular rings

Start with CXR and esophagram.

**Fig. 6. Diagnostic Algorithm for Symptomatic Vascular Rings.**

Case #6

• You’re seeing in follow-up in the office a 12 yo with moderate persistent asthma who was recently admitted overnight for an acute asthma exacerbation. Family has had issues with adherence with her daily inhaled corticosteroid (ICS).

• You ask what oral medicine she was discharged home with in addition to her ICS and albuterol......She says none.
No PO meds on discharge with asthma exacerbation?

A. Inpatient prescriber oversite

B. Family misunderstood – unfilled med at pharmacy

C. Took last med for exacerbation at hospital

D. She’ll increase her ICS dosing for few days
Evidence for use of dexamethasone in acute asthma exacerbations
Dexamethasone lasts longer

• Half life Prednisone 12-36hrs

• Half life Dexamethasone 36-72hrs
Dexamethasone for Acute Asthma Exacerbations in Children: A Meta-analysis
Grant E. Keeney, Matthew P. Gray, Andrea K. Morrison, Michael N. Levas, Elizabeth A. Kessler, Garick D. Hill, Marc H. Gorelick and Jeffrey L. Jackson
Pediatrics 2014;133;493
PEDIATRICS: Meta-analysis

• Meta-analysis included 6 studies in children comparing dexamethasone to prednisone/prednisolone

• All 6 studies investigated patients discharged from the ER

• Primary outcomes were return visits (ER/PMD) or hospital admission

Measurement of time until return visit varied between studies

- 5 days
- 10-14 days
- 30 days
5 Days

- Altamini, Canada, 2006: RR (95% CI) = 3.67 (0.42–31.88) 4/61 1/56
- Gordon, USA, 2007: RR (95% CI) = 0.76 (0.36–1.59) 10/69 14/73
- Gries, USA, 2000: RR (95% CI) = 1.20 (0.03–56.93) 0/15 14/73
- Klig, USA, 1997: RR (95% CI) = 1.00 (0.02–48.19) 0/22 0/22

Subtotal (I²= 0.0%)
RR (95% CI) = 0.90 (0.46–1.78) 14/167 15/169

10-14 Days

- Gordon, USA, 2007: RR (95% CI) = 1.07 (0.62–1.85) 19/68 19/73
- Greenberg, USA, 2008: RR (95% CI) = 1.99 (0.56–7.00) 8/51 3/38
- Qureshi, USA, 2001: RR (95% CI) = 1.07 (0.58–1.97) 20/272 18/261

Subtotal (I²= 0.0%)
RR (95% CI) = 1.13 (0.77–1.67) 47/391 40/372

30 Days

- Gries, USA, 2000: RR (95% CI) = 1.20 (0.03–56.93) 0/15 0/18

Overall (I²= 0.0%)
RR (95% CI) = 1.07 (0.77–1.50) 62/571 55/558

Relapse Rate (Relative Risk)
More recent evidence supports using dex outpatient

Randomized Trial of Dexamethasone Versus Prednisone for Children with Acute Asthma Exacerbations

• 2 doses of dexamethasone versus 5 days of prednisolone/prednisone
• Follow-up phone interviews at 7 and 15 days
• Primary outcomes = % patients with asthma sx, and quality of life
• Secondary outcomes = ED visits and admission within 15 days.

• No difference between the dex and prednisone groups for any outcome

Paniagua et al 2017
Dexamethasone

Considerations with route and administration
Considerations with route and administration

Dexamethasone (10mg dose)

Tablet
No 10mg tablet
4mg + 6mg
Considerations with route and administration

Dexamethasone (10mg dose)

Intramuscular

10mg/mL
Considerations with route and administration

Dexamethasone (10mg dose)

Solution

0.5mg/5mL

100mL
No significant asthma relapses or increase in ER return visits at 30 day follow-up
1 dose or 2?

**1 Dose**
- Gries 2000
- Gordon 2007
- Klig 1997
- Altamimi 2006
- Cronin 2016
- McCallister 2017

**2 Doses**
- Qureshi 2001
- Greenberg 2008
- Paniagua 2017
Head to head on the horizon

<table>
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<th>Trial of One Versus Two Doses of Dexamethasone for Pediatric Asthma Exacerbation (R2D2)</th>
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One-time dexamethasone has benefits

No need for prescription

• 25% of patients were noncompliant with med as prescribed

Butler et al. Pediatric Emergency Care (2004): 730-735
• 64% of patients had complete adherence to 5 day course of prednisone for asthma
Personal Practice

Give 2nd dose of dexamethasone if still hospitalized 24hrs after first dose

If well enough to be discharged. I don’t send with Rx
Caregivers and patients like dexamethasone
Patient experience less vomiting with dexamethasone compared to prednisone

If given a choice, caregivers want shorter courses
Final point: All hands on dex!!

- Equivalent to prednisone in outpatient asthma exacerbations
- Less vomiting
- Better adherence
- Caregivers prefer
Final Questions
Studies have shown that a systemic corticosteroid course after anaphylaxis reduces the risk of biphasic reaction?

A. True

B. False
Which medication regimen is an option to prescribe in the setting of an acute asthma exacerbation?

A. 5 days course of prednisone/prednisolone

B. 1 dose of dexamethasone

C. 2 doses of dexamethasone

D. Answers A, B

E. Answers A, B, C
References:


References (cont):


References (cont):


