Pediatric chronic wet cough: What are we missing?

Luke Wall, MD
Assistant Clinical Professor of Pediatrics
Section of Allergy/Immunology
LSU HSC New Orleans

Pediatrics Grand Rounds
December 18, 2013
BACKGROUND AND BURDEN OF CHRONIC COUGH
### 2 Definitions of cough for clinical practice

<table>
<thead>
<tr>
<th>Cough type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>A forced expulsive manoeuvre, usually against a closed glottis, that is associated with a characteristic sound</td>
</tr>
<tr>
<td><strong>Acute cough</strong></td>
<td>Cough lasting up to <strong>2 weeks</strong></td>
</tr>
<tr>
<td><strong>Protracted acute cough</strong> (in CHILDREN)</td>
<td>Cough lasting <strong>2–4 weeks</strong></td>
</tr>
<tr>
<td><strong>Chronic cough</strong> (in CHILDREN)</td>
<td>Cough lasting more than <strong>4 weeks</strong></td>
</tr>
<tr>
<td>Chronic persistent cough (in ADULTS)</td>
<td>Cough lasting more than <strong>8 weeks</strong></td>
</tr>
</tbody>
</table>

---

Burden of Chronic Cough

- Survey of 165 school children
  - Australia and Nigeria
  - Average 8% with persistent cough (>3 weeks)

Burden of Chronic Cough

- Children referred for chronic cough
  - 53%: >10 visits
  - 20%: >20 visits
  - Significantly higher parental stress

4 Probability-based diagnosis of chronic cough

If examination, chest x-ray and spirometry are normal, the most common diagnoses or exposures associated with chronic cough are as follows:

**Adults**
- Asthma
- Rhinosinusitis
- Gastro-oesophageal reflux disease

**Children**
- Protracted bacterial bronchitis
- Asthma (if other symptoms are present)

**Exposures**
- Respiratory infection (post-infectious cough)
- Tobacco smoke and other pollutants (active, environmental exposure) •
Cough Due to Asthma

• Features
  – Episodic
  – Expiratory wheeze and/or exertional dyspnea
  – Obstructive pattern on spirometry
    • Reversible
  – May have
    • Exertional cough
    • Atopy

In CHILDREN, chronic cough without the above features is seldom due to asthma, and inhaled corticosteroids are not indicated unless there are positive features to suggest asthma.

Allergic Rhinitis

• Evidence of postnasal drip as cause of cough is weak
  – Coexisting upper airway disease
• Aeroallergen identification and avoidance
• Treatment with intranasal corticosteroid
• No proven benefit of antihistamines in children
• Option of allergen immunotherapy

GERD

• Controversy: Cause vs Effect
• Red flags: Seek GI consultation
  – Choking, vomiting
  – Failure to thrive
• Cease ineffective PPI therapy
• Avoid fundoplication

Protracted Bacterial Bronchitis

- Recognized by multiple thoracic societies
- Clinical Diagnosis of Childhood
  - Chronic wet cough
    - > 4 weeks
  - Complete resolution with antibiotics
  - Absence of other specific cause
- Growth from bronchoalveolar lavage (BAL) makes a definitive diagnosis (not required)

Protracted Bacterial Bronchitis

• Factors to Consider: PBB
  – May masquerade as asthma
    • Cough worse at night
      – Postural
    • Exercise intolerance
    • Exacerbations with viral URI
  – May have concomitant bronchospasm
    • Concurrent wheezing
    • Partial response to inhaled beta-agonist

Protracted Bacterial Bronchitis

• How to differentiate from other conditions?
  – Nature of cough
    • Wet
    • Lasting > 4 weeks
  – Lower airway sounds
    • Wheeze is rare
    • Rattle / rattle is common
      – Coarse, non-musical noise
      – Mucous in larger airways

CHRONIC BRONCHITIS

The applicability of this definition to children is unclear. The existence of chronic bronchitis as a distinct entity in children is controversial. Like adults, however, children with chronic inflammatory diseases or those with toxic exposures can develop damaged pulmonary epithelium. Thus, chronic or recurring cough in children should lead the clinician to search for underlying pulmonary or systemic disorders (see Table 383-3). One proposed entity is persistent or protracted bacterial bronchitis, which may be mistaken for asthma and shares some characteristics with other forms of suppurative lung disease.
HOW COMMON IS PROTRACTED BACTERIAL BRONCHITIS?
• Large Pulmonary group in Australia
• 108 children over 2 year period
  – Referred by primary care
  – Chronic wet cough > 3 weeks duration
• Applied diagnostic algorithm to determine cause
Findings: Wet cough > 3 weeks
- ≤ 10% Asthma
- ≤ 10% Upper airway cough syndrome (UACS)
- 15% GERD
- 33% Airway malacia
- 40% Protracted Bacterial Bronchitis (PBB)
  • 22% Definite PBB
  • 18% Probable PBB
<table>
<thead>
<tr>
<th>Working Diagnosis prior to evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Working Diagnosis prior to evaluation</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
</tbody>
</table>
CAUSES OF PROTRACTED BACTERIAL BRONCHITIS?
• Retrospective review
  – University of Iowa Pulmonary 1999-2009
  – Children <5 yrs old
    • Cough, wheeze, noisy breathing
      – ≥ 1 month
    • Positive bacterial growth from BAL
    • Excluded asthma, other known causes
Results

• Organisms
  – *S. pneumoniae*
  – *M. catarrhalis*
  – *H. influenzae*

• Cause
  – Airway malacia in 74%
  – No cause reported in 26%

Boiling Down the Problem

We did not routinely examine for a defect in immunity in these children. However, other symptoms of immune deficiency were not apparent. Specifically, none of the children had sepsis, bacterial pneumonia, meningitis, or evidence of other serious bacterial infections. In a few of our first experiences identifying patients with PBB, we had examined for abnormalities of antibody function without finding any.

- On the contrary, a child with PIDD might not develop a life threatening infection for many years, in this era of vaccination and antibiotic usage in developed countries.

NATURAL PROGRESSION?
Fig. 2. Using the pathophysiologic model, protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSDL) and radiological bronchiectasis likely represents different ends of a spectrum. This is however speculative and yet to be confirmed. Untreated it is likely that some (but not all) children with PBB will progress to develop CSLD.
Natural Progression
SIGNIFICANCE OF BRONCHIECTASIS
Bronchiectasis

- Radiographic diagnosis
- Irreversible bronchial dilatation
- Key features
  - One or more “dilated” bronchi
    - Diameter of airway exceeding that of adjacent vessel
    - Non-tapering of bronchi
    - Visible bronchi in distal lung fields
- Primary Immunodeficiency accounts for 25% of non-CF bronchiectasis.

Bronchiectasis

- 25% Primary Immunodeficiency
- 50% Idiopathic

- What do we mean by “Idiopathic?”
  - There is no underlying cause?
  - Current medical knowledge falls short of determining a cause?
Chronic Suppurative Lung Disease

- Precursor to bronchiectasis
- Identical symptoms (no dilated bronchi)
  - Prolonged productive cough
  - Exertional dyspnea
  - Growth failure
  - Recurrent chest infections
  - Clubbing
  - Chest wall deformity / hyperinflation

Vicious Circle Hypothesis

- Impaired Host Defense
- Bacterial Infection/Colonization
- Airway Inflammation
- Impaired Mucociliary Clearance
- Host Defect
- Impaired Mucociliary Clearance
- Progressive Lung Damage

Wall, Luke MD
Bronchiectasis: Diagnostic Dilemma

• CT criteria for bronchiectasis based on adult data
  – Bronchial lumen : artery ratio (>1)
  – Used by radiologists despite age
• Ratio influenced by age
• Infant normal ratio is 0.4-0.5
• May explain CSLD in children

Phenotypes of Adult Bronchiectasis: Onset of Productive Cough in Childhood and Adulthood

Paul T. King¹,² (paul.king@med.monash.edu.au), Stephen R. Holdsworth² (stephen.holdsworth@med.monash.edu.au), Michael Farmer¹ (mwfarming@netspace.net.au), Nicholas Freezer¹ (nicholas.freezer@southernhealth.org.au), Elmer Villanueva³ (elmer.villanueva@med.monash.edu.au), and Peter W. Holmes¹ (peter.holmes@southernhealth.org.au)

¹Respiratory and Sleep Medicine, Monash Medical Centre/Southern Health, Melbourne, Australia
²Monash University Department of Medicine, Monash Medical Centre, Melbourne, Australia
³Gippsland Medical School, Monash University, Melbourne, Australia
When does chronic cough of bronchiectasis begin?

60-80% of adults with newly diagnosed bronchiectasis have had chronic wet cough since childhood.

When does chronic cough of bronchiectasis begin?

RESPIRATORY INFECTIONS: THE CONTROVERSY
Principles of Judicious Antibiotic Prescribing for Bacterial Upper Respiratory Tract Infections in Pediatrics
Adam L. Hersh, Mary Anne Jackson, Lauri A. Hicks and the COMMITTEE ON INFECTIOUS DISEASES
*Pediatrics*; originally published online November 18, 2013;
DOI: 10.1542/peds.2013-3260
• Highlights risks of antibiotic use
  – Antimicrobial resistance
  – *C. difficile* diarrhea
  – Side effects and reactions
• Focused on three most common URI’s
  – Acute otitis media
  – Acute bacterial sinusitis
  – Group A streptococcal (GAS) pharyngitis
• Principles
  – Applying stringent clinical criteria for diagnosis
  – Weighing benefits and harms of antibiotics
  – Implementing judicious prescribing strategies

• In summary: Reduce overuse and ensure appropriate agents are prescribed
Doctors told to use antibiotics for children wisely

The American Academy of Pediatrics (AAP) Committee on Infectious Diseases has issued an update to a previous clinical report on the prescribing of antibiotics for bacterial upper respiratory tract infections (RTIs) in children. The organization’s report suggests strategies for these infections, including acute otitis media, acute bacterial sinusitis, and streptococcal pharyngitis.

AAP: Judicious Use of Antibiotics Advised

A report from the American Academy of Pediatrics (AAP), in collaboration with the CDC, focuses on reducing unnecessary antibiotic prescribing in the treatment of three common pediatric upper respiratory infections.

Principles of judicious antibiotic prescribing for bacterial upper respiratory tract infections in pediatrics

This clinical report focuses on antibiotic prescribing strategies for bacterial upper respiratory tract infections, including acute otitis media, acute bacterial sinusitis, and streptococcal pharyngitis. The principles for judicious antibiotic prescribing that are outlined focus on applying stringent diagnostic criteria, weighing the benefits and harms of antibiotic therapy, and understanding situations when antibiotics may not be indicated.
Why’s and how’s of judicious antibiotic prescribing for URIs

by Mary Anne Jackson, M.D., FAAP, and Adam L. Hersh, M.D., Ph.D., FAAP

A new AAP clinical report released Nov. 18 outlines three principles of judicious antibiotic prescribing for pediatric upper respiratory tract infections (URIs). The document also identifies situations in which antibiotic overuse is significant (common cold and bronchitis) and highlights risks associated with antibiotic use, including the growing threat of antimicrobial resistance and increasing rates of Clostridium difficile diarrhea.


For the three most common bacterial URIs — acute otitis media, acute bacterial sinusitis and group A streptococcal (GAS) pharyngitis — the principles focus on:
1. using stringent clinical criteria to establish the diagnosis;
2. understanding the benefits and harms of antibiotic therapy; and
3. implementing judicious prescribing strategies, including use of narrow-spectrum agents as first-line therapy for most children, minimizing therapy duration and initial observation in place of antibiotics in certain cases.

Acute otitis media

The clinical report highlights the diagnostic and treatment recommendations from the AAP clinical practice guideline for acute otitis media (Pediatrics. 2013;131:e964-e999). Criteria for diagnosis of acute otitis media include identification of middle ear effusion with signs of inflammation (e.g., bulging). Watchful waiting without antibiotics should be considered.

Pediatricians and the Law

What to do if your patients’ health information is breached

from the AAP Department of Practice

A stolen laptop, a missing thumb drive, lab results faxed to the wrong number or a medical chart recycled intact instead of shredded. What must you do if unauthorized people access your patients’ health information?

These instances are potential breaches of protected health information (PHI) under the Health Insurance Portability and Accountability Act (HIPAA) Omnibus Final Rule that took effect on Sept. 23. As such, a provider may be required to notify the affected patients, the secretary of the U.S. Department of Health and Human Services.

See Breach, page 7

Reading, media exposure tackled at Peds 21 symposium

See Antibiotic, page 4
Why’s and how’s of judicious antibiotic prescribing for URIs

by Mary Anne Jackson, M.D., FAAP, and James Margolis, M.D., FAAP

Ampicillin (GAS) pharyngitis — the principles
1. Using appropriate clinical criteria to establish the diagnosis.
2. Understanding the benefits and harms of antibiotic therapy.
3. Implementing judicious prescribing strategies, including use of narrow-spectrum agents as first-line therapy for most children, minimizing therapy duration and initial observation in place of antibiotics in certain cases.

State of the art
The clinical report highlights the diagnostic and treatment recommendations from the AAP clinical practice guideline for acute otitis media. Pediatrics, 2013;131(6):e564.e599. Criteria for diagnosis of acute otitis media include identification of middle ear signs and symptoms of inflammation (e.g., bulging) and containing without antibiotics should be common practice.

Reading, media exposure tackled at Ped’s 21 symposium

A new AAP clinical report released Nov. 18 outlines three principles of judicious antibiotic prescribing for pediatric upper respiratory tract infections (URIs). The document also identifies situations in which antibiotic overuse is significant (common cold and bronchitis) and highlights risks associated with antibiotic use, including the growing threat of antimicrobial resistance and increasing rates of Clostridium difficile diarrhea.
• judicious

– having, exercising, or characterized by sound judgment
WHY DO WE CARE?
Figure 8
Patient Age at PIDD Diagnosis

Q9. At what age (in years) was that person first diagnosed with a primary immunodeficiency disease? (N=1,330 – excludes missing data)
Q9. At what age was that person first diagnosed with a primary immunodeficiency disease? Q8. At what age (in years) did these repeated, serious or unusual infections begin? (N=1,137 – excludes those with missing information)
Figure 15
Type of Permanent Functional Impairment Prior to Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Permanent Loss</td>
<td>51%</td>
</tr>
<tr>
<td>Other</td>
<td>9%</td>
</tr>
<tr>
<td>Neurological</td>
<td>8%</td>
</tr>
<tr>
<td>Mobility</td>
<td>7%</td>
</tr>
<tr>
<td>Digestive Function</td>
<td>16%</td>
</tr>
<tr>
<td>Hearing</td>
<td>13%</td>
</tr>
<tr>
<td>Vision</td>
<td>6%</td>
</tr>
<tr>
<td>Lung Function</td>
<td>32%</td>
</tr>
</tbody>
</table>

Q10. By the time of initial diagnosis as immune deficient, had the patient suffered any permanent loss of...? (N=1,327 – excludes missing data)
Recent Case

- 11 year old boy
- Ill from September- March annually
- Frequent asthma exacerbations
  - Cough is predominant symptom
  - Antibiotics given >75% of episodes
    - Resolution of symptoms
  - Oral steroids 2-3x annually
- Wheeze with exercise
- Recurrent otitis media and sinusitis
Recent Case

- IgG 493 mg/dL [595-1275] L
- IgA 22.3 mg/dL [43.2-207.5] L
- IgM 69.9 mg/dL [28.1-184.3]
- IgE 90.1 IU/mL [0-195]

- Previous evaluation:
  - Normal immunoglobulins
ROLE OF IMMUNITY
The Lungs: Basic Defense

- Surface area of tennis court
- Air volume: 10,000 L/day
- Extremely thin membrane
- Barrier defense mechanisms
  - Filtration: nasopharynx, conducting airways
  - Sneezing and coughing
  - Mucociliary clearance

Pulmonary Immunity

• Innate Immunity
  – Toll-like receptors
    • TLR2: *S. pneumoniae*
  – Adapter molecules
    • IRAK4, MyD88:
      • *S. pneumoniae, S. aureus*
  – Transcription factors
    • NF-κB: *E. coli, S. pneumoniae*, multiple others
      – Central mediator of multiple immune mechanisms

Pulmonary Immunity

- Innate Immunity
  - Mannose-binding lectin (MBL)
    - Collectin protein family
    - Activation of lectin complement pathway
    - Most substantiated clinical role:
      - Coexistent primary or secondary immune deficiency

Pulmonary Immunity

• Innate Immunity
  – Surfactant proteins
    • SP-A and SP-D
      – Collectin protein family
      – Opsonize bacterial pathogens
      – Activate signaling cascades (TLR2, TLR4)
  • Absent SP-D in BAL (limited data)
    – Associated with PBB
    – Increased frequency of pneumonia

Pulmonary Immunity

• Adaptive Immunity
  – Immunoglobulins
    • Hypogammaglobulinemia and bronchiectasis
      – XLA, CVID, others
  – IgG Subclasses
    • Concomitant role with other defects
      – SAD, Selective IgA Deficiency

Pulmonary Immunity

• Adaptive Immunity
  – Specific Antibody Deficiency (SAD)
    • Associated with recurrent respiratory infections
    • Documented in bronchiectasis (4% of cases)
    • Never investigated in PBB
  – Memory B Cells
    • Deficiency associated with CVID, SAD
    • Associated with recurrent respiratory infections
    • Never investigated in PBB

BACK TO THE BASICS
Potential Pitfalls: Every Child Coughs

Referral
Antibiotic Use
Diagnostic Testing
Don’t Miss the Forest

• Wet cough responding to antibiotics
  – Common:
    • Sinusitis
    • Pneumonia
  – Zebras:
    • Primary Immunodeficiency (1:1000)
    • Tuberculosis or atypical infection
    • Cystic fibrosis
    • Primary ciliary dyskinesia
    • Structural anomaly
    • Aspirated foreign body
Diagnosing PBB: Old Methods

• **History:**
  – Young child, **wet** cough >4 weeks
    • Parental report of “wet cough” is accurate
  – Complete resolution with antibiotics
    • Poor response to other therapies

• **Physical Exam:**
  – Chest rattle (rattle) in most
  – Wheeze may be present
    • Not the primary symptom

Recommendations

• Approach to PBB
  – Antibiotics
    • 2 week course
    • Cover common respiratory pathogens
    • Amoxicillin / clavulanic acid
  – Two-thirds: recurrence
  – Half: symptom free following 2 courses

Recommendations

• Referral and evaluation:
  – Other concomitant infections
  – ≥ 2 episodes PBB in one year
• Allergy/Immunology and Pulmonology

Recommendations

• Suggested Immunologic Workup
  – Complete Blood Count with differential
  – IgG, IgA, IgM, and IgE
  – Pneumococcal antibody titers

Pediatric Wet Cough

Rhinitis

Viral LRTI +/- RAD

Wet Cough >4 weeks Resolved with antibiotics (PBB)

Recurrence OR Other RedFlags

GERD

ZEBRA ZONE

Wall, Luke MD
FINAL THOUGHTS
# 10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

Arrows: indicators which may represent permanent morbidity or late findings
**Indicators of Serious Chronic Lower Respiratory Tract Disease in Children**

- Persistent fever
- Ongoing limitation of activity
- Failure to grow
- Failure to gain weight appropriately
- Clubbing of the digits
- Persistent tachypnea and labored ventilation
- Chronic purulent sputum
- Persistent hyperinflation
- Substantial and sustained hypoxemia
- Refractory infiltrates on chest x-ray
- Persistent pulmonary function abnormalities
- Family history of heritable lung disease
- Cyanosis and hypercarbia

*Arrows: indicators which may represent permanent morbidity or late findings*
3 Alarm symptoms and findings in chronic cough
In CHILDREN
  • Prominent dyspnoea, especially at rest or at night
  • Recurrent episodes of chronic, wet or productive cough
  • Systemic symptoms: fever, weight loss, failure to thrive
  • Feeding difficulties (including choking or vomiting)
  • Recurrent pneumonia
  • Stridor and other respiratory noises
  • Abnormal clinical respiratory examination
  • Abnormal chest x-ray
Final Thoughts

- 12 year delay in diagnosis of PIDD
- 32% with PIDD have permanent lung impairment at time of diagnosis
- 60-80% of adults with newly diagnosed bronchiectasis: Wet cough since childhood
Special Thanks

- LSU Faculty and Children’s Staff
  - Teaching me all things Pediatrics
- Section of Allergy Immunology
  - Teaching me all things A/I
- A/I Fellows
  - Showing me what I don’t know
- Dr. Ricardo Sorensen
  - Teaching me how to chase zebras
- Dr. Derek Pepiak
  - Keeping me from getting lost on the zebra chase
- Wife and children, for their love, support and patience
Thank You!

Luke Wall, MD
lwall@lsuhsc.edu
504-896-9589