Diagnose Preschool Asthma
- like a pro -

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No related conflict of interest
### Diagnose preschool asthma – like a pro

#### Summary

- **Introduction**
- **History**
- **Variable airflow limitation**
- **Steroid responsive inflammation**
- **Consider the mimickers of asthma**
- **Conclude**
**Diagnose preschool asthma – like a pro**

**Summary**

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Introduction

Defining asthma

Asthma = heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary overtime and in intensity, together with variable expiratory airflow limitation.

- GINA. www.ginathma.org. 2018
Introduction

Preschool wheeze: frequent & heterogeneous

- 33% will wheeze before 3 yrs of age
- Few remain symptomatic
- Of those who are eventually correctly diagnosed with asthma:
  - 25% started wheezing at 6 months of age
  - 75% will wheeze by 3 years

- White D et al. ALLSA Handbook of Practical Allergy. 2018
Introduction

Is preschool asthma under or over diagnosed?

- NICE consultation paper:
  - Asthma over diagnosed?
  - Seek objective tests first?
  - Routine FeNO?

Introduction

State of the ‘asthma’ art?

- n=108 Young children with chronic cough:
  - 50% Diagnosed with asthma
  - Asthma diagnosis confirmed in only 5%
    - Marchant JM et al. Chest 2006;129:1132–41

- 60% Asthmatics referred to secondary care have no objective evidence of variable airflow limitation
  - Joyce DP et al.
    http://dx.doi.org/ulib.idm.oclc.org/10.1378/chest.109.3.697
Introduction

Desperate attempts?

- Wheezy phenotypes:
  - Tuscon epidemiologic phenotypes
  - Revised Tuscon phenotypes
  - Avon classification
  - Trousseau wheezing phenotypes
  - ERS symptom based phenotypes

- Asthma predictive indexes & scores:
  - Tuscon stringent & loose API’s
  - Persistent Asthma Predictive Score (PAPS)
  - Clinical Asthma Prediction Score (CAPS)
  - Modified API’s
  - Isle of Wight score
  - Leicestershire tool
  - PIAMA risk score
Introduction

The 4 steps to finding the asthmatic

Build a diagnosis:
1. History
2. Objective evidence of variable airflow limitation?
3. Seek proof of corticosteroid responsive inflammation?
4. Consider the mimickers of asthma?
Diagnose preschool asthma – like a pro

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History

Most valuable tool

1. A story of the inception of asthma?
2. The story of the chest events!
History: the inception of asthma?

Advice on primary prevention of asthma <5yr

1. No exposure to environmental tobacco smoke during pregnancy & after birth
2. Vaginal birth should be encouraged where possible
3. Breast-feeding advised for reasons other than preventing asthma
4. The use of broad spectrum antibiotics during the 1st year of life should be discouraged
History: the inception of asthma?
Early assembly of a diverse microbiome

- Ancillary organ to the innate immune system:
  - Mucosal interface
  - Prerequisite for:
    - Balanced innate & adaptive immune responses
    - Tolerance
  - GIT axes:
    - Immune dysregulation
    - Lung
    - Brain
    - Metabolic illness

- Shanahan F. Inflamm Bowel Dis. 2004;10:S16–S24
**History: the inception of childhood asthma?**

Biome diversity hypothesis & ‘dysbiosis dominos’

- **Phase 1: Intrauterine**
  - 😞 Antibiotics
  - 😞 Prematurity

- **Phase 2: Birth & 1st week**
  - 😞 C-section
  - 😞 Mixed feeds
  - 😞 Antibiotics
  - 😞 NICU

- **Phase 3: 2w-4mth**
  - 😞 Mixed or formula feeds
  - 😞 Antibiotics
  - 😞 Living environment

- **Phase 4: 4mth-1yr**
  - 😞 Incorrect weaning
  - 😞 Living environment
  - 😞 Antibiotics

- **Phase 5: 1-3years**
  - 😞 Living environment
  - 😞 Antibiotics

History: the inception of childhood asthma?
Downstream effects of dysbiosis

Decreased gut microbiota diversity, delayed Bacteroides colonisation and reduced Th1 responses in infants delivered by caesarean section

- Characterised intestinal microbiota:
  - n=24 (VB = 15 & C-section = 9)
  - 1 week & 1, 3, 6, 12 & 24 months
  - NGS 16S rRNA genes
  - s-Th1 & Th2 associated chemokines at 6, 12 and 24 months

- C-section associated with:
  - Lower total microbiota diversity during the first 2 years of life
  - Significant decrease in Th1-associated chemokine levels

**History: the inception of childhood asthma?**

C-section birth & deviant immune disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
<th>aIRR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>103 822</td>
<td>1.23</td>
<td>(1.21-1.25)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Asthma &gt; 5 years</td>
<td>48 858</td>
<td>1.16</td>
<td>(1.13-1.19)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Systemic connective tissue disorder</td>
<td>7 498</td>
<td>1.11</td>
<td>(1.04-1.19)</td>
<td>P=0.0021</td>
</tr>
<tr>
<td>Juvenile arthritis</td>
<td>6 946</td>
<td>1.10</td>
<td>(1.02-1.18)</td>
<td>P=0.0117</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>6 136</td>
<td>1.01</td>
<td>(0.93-1.10)</td>
<td>P=0.82</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2 697</td>
<td>1.20</td>
<td>(1.06-1.36)</td>
<td>P=0.004</td>
</tr>
<tr>
<td>Immune deficiencies</td>
<td>2 589</td>
<td>1.46</td>
<td>(1.32-1.62)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>1 944</td>
<td>0.99</td>
<td>(0.87-1.14)</td>
<td>P=0.89</td>
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<tr>
<td>Leukemia</td>
<td>1 631</td>
<td>1.17</td>
<td>(1.00-1.36)</td>
<td>P=0.048</td>
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<tr>
<td>Psoriasis</td>
<td>1 306</td>
<td>0.98</td>
<td>(0.81-1.18)</td>
<td>P=0.81</td>
</tr>
<tr>
<td>Arm fracture</td>
<td>77 490</td>
<td>0.99</td>
<td>(0.96-1.01)</td>
<td>P=0.19</td>
</tr>
</tbody>
</table>

History: the inception of childhood asthma?
C-section delivery & later asthma diagnosis

Meta-analysis on method of delivery & asthma diagnoses up to 18 years of age

• Included 26/76 potential studies on method of delivery & asthma
• No evidence of heterogeneity

• 20% increased risk for asthma after C-section delivery (OR 1.21 CI 1.17-1.25)
History: the inception of childhood asthma?
Dysbiosis: recurrent viral-associated wheeze

- **RSV:**
  - Children born ±120 days before peak RSV season at significant increased risk for bronchiolitis & asthma by 3.5-5.5yr

- **Rhinovirus:**
  - Associated wheezing ±10x higher asthma risk by 6yr
**History: the inception of childhood asthma?**

**Dysbiosis: bacterial infections**

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**Childhood Asthma after Bacterial Colonization of the Airway in Neonates**


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- 2010 COPSAC birth cohort of babies born to asthmatic mothers
- n=321
- Hypopharyngeal aspirates at 1 & 12 months
- Serial eosinophil, IgE, specific IgE & airway resistance measurement
- Endpoints: recurrent wheeze & asthma diagnosis at 5 years
History: the inception of childhood asthma?

Dysbiosis: bacterial infections

Childhood Asthma after Bacterial Colonization of the Airway in Neonates


- 21% Newborns colonised with:
  - *H influenzae*
  - *S pneumoniae*
  - *M catarrhalis*

- Colonisation @ 1 month associated with 2-4x increased risk:
  - Acute severe exacerbation of wheeze (HR 2.99; 95% CI, 1.66-5.39)
  - Persistent wheeze (HR 2.4; 95% CI, 1.45-3.99)
  - Hospitalisation for wheeze (HR 3.85; 95% CI, 1.90-7.79)
  - Eventual airway reversibility & asthma diagnosis at 5 years (33% vs 10%)
History: the inception of childhood asthma?

Two risk factors

That act alone or in combination during the first few years of life to establish preschool asthma

1. Early development of allergic sensitisation – especially multiple aeroallergens
2. Recurrent wheezing respiratory tract infections - viruses & bacteria

History: the story of the ‘chest events’!
Severity, duration, frequency, between & atopy

Symptoms may vary over time

- Cough, wheeze, heavy breathing < 10d during URTI
  - 2-3 episodes/yr
  - No symptoms between episodes

- Cough, wheeze, heavy breathing > 10d during URTI
  - >3 episodes/yr, severe episodes &/or night worsening
  - Occasional symptoms between episodes

- Cough, wheeze, heavy breathing > 10d during URTI
  - >3 episodes/yr, severe episodes &/or night worsening
  - Symptoms between episodes & play or laughing
  - Atopy

Proportion viral induced wheeze likely to respond to regular ICS / asthma diagnosis

Proportion viral induced wheezing

www.ginasthma.com. 2018
History: the story of the ‘chest events’!

Defining points in the history

- Age at onset
- Atopy
- Hospitalisation because of wheeze
- Symptoms outside of an airway infection
- Quick response to bronchodilators
- Dry nighttime cough
- Specific triggers:
  - Coughing after exercise
  - Cold air
**Diagnose preschool asthma – like a pro**

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**Variable airflow limitation**

Seek objective evidence of variable airflow limitation

Can be difficult in preschool children . . .

But, look for it: again & again . . .

‘Objective testing for asthma must become a reality’
**Variable airflow limitation**

Seek objective evidence of variable airflow limitation

- PEFR fluctuation
- Spirometry
- Exercise provocation
Variable airflow limitation

Modified bronchodilator-response test

Evaluate clinical response (15 minutes after bronchodilator administration) at the time of wheeze
## Diagnose preschool asthma – like a pro

### Summary

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Corticosteroid responsive inflammation
Seek eosinophil mediated inflammation

- Eosinophil vs neutrophil mediated inflammation:
  - Total IgE not indicative
  - Skin prick or RAST testing for specific IgE
  - Peripheral blood eosinophilia
  - FeNO
  - Induced sputum
Corticosteroid responsive inflammation
Pragmatic therapeutic trial

• 3-Step approach:
  – Staged over 8-12 week intervals
  – Low dose ICS
  – Introduce-withdraw-introduce

‘Systemic steroids should be considered only in young children admitted to a hospital with features strongly suggestive of atopic asthma’
- Maria de Benedictus F et al.
  http://ow.ly/XACHS
Diagnose preschool asthma – like a pro

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Consider the mimickers of asthma
Differential diagnosis of preschool wheeze

<table>
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<tr>
<th>Infective</th>
<th>Structural</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis</td>
<td>Trachea / bronchomalacia</td>
<td>Wheezy phenotypes</td>
</tr>
<tr>
<td>Atypical infection</td>
<td>Tracheal stenosis / webs</td>
<td>PCD</td>
</tr>
<tr>
<td>Bacterial airway infection</td>
<td>Tumor / lymphadenopathy</td>
<td>CF</td>
</tr>
<tr>
<td>Laryngotracheobronchitis</td>
<td>Vascular rings</td>
<td>GORD</td>
</tr>
<tr>
<td>PBB</td>
<td>Cystic lesions / masses</td>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td></td>
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<td>Retained foreign body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiolitis obliterans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perceived tight chest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BPD</td>
</tr>
</tbody>
</table>
Consider the mimickers of asthma

Clinical examination

Actively seek clinical features to the mimickers of asthma
Consider the mimickers of asthma
Protracted bacterial bronchitis (PBB)

- Usually young children <5 yr
- Persistent cough (>4 weeks):
  - 'Wet' cough on reclining & early morning.
  - May last the whole night
  - 'Out of breath' during cough
  - Worse during exercise
  - Coloured sputum
- Response to antibiotic therapy
- Associated:
  - 'Noisy chest' with chest ruttles
  - Other airway biofilm disease

Consider the mimickers of asthma
Diagnostic criteria for PBB

- Chronic, daily wet cough > 4 weeks
- No evidence of an alternative diagnosis:
  - Normal spirometry
  - Normal CXR other than bilateral peribronchial accentuation
- No symptoms or signs of other causes
- Must confirm resolution after appropriate treatment

Consider the mimickers of asthma

Cystic fibrosis (CF)

Time for a different approach!
Consider the mimickers of asthma

Population distribution

- Not limited to Caucasians:
  - Global increase in non-Caucasian diagnosis
- Epidemiology:
  - 1:3,000 Caucasians
  - 1:9,200 Hispanics
  - 1:15,000 African Americans
- CFTR mutation carriers:
  - 1/25 Caucasians
  - 1/46 Hispanics
  - 1/61 African Americans

**Consider the mimickers of asthma**

CF class mutations & phenotype modifiers

<table>
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<tr>
<th>Class of mutation</th>
<th>Basic defect</th>
<th>Example of mutation</th>
</tr>
</thead>
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<tr>
<td>Class I</td>
<td>Absence of gene synthesis, nonsense mutations and large deletions</td>
<td>621+1G→T, 3659delC, 1717-1G→A</td>
</tr>
<tr>
<td>Class II</td>
<td>Premature stop degradation or incomplete maturation</td>
<td>p.Phe508del, G85E, R506T, N1303K</td>
</tr>
<tr>
<td>Class III</td>
<td>Disordered regulation such as diminished ATP binding and adenosine hydrolysis</td>
<td>G551D, S1251N, S1255P, G551S, G970R, G178R</td>
</tr>
<tr>
<td>Class IV</td>
<td>Defective chloride conductance or channel gating</td>
<td>R117H, R334W, R347P</td>
</tr>
<tr>
<td>Class V</td>
<td>Reduced number of CFTR transcripts due to promoter or splicing abnormality</td>
<td>2789+5G→A, 3849+10KcC→T, A455E</td>
</tr>
<tr>
<td>Class VI</td>
<td>Accelerated cell turnover from cell surface</td>
<td></td>
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Many CF patients present with mild and ‘atypical’ symptoms

Consider the mimickers of asthma

Sweat the sweat test

- 3d – 6months:
  - CF unlikely ≤29mmol/l
  - Intermediate 30-59mmol/l
  - CF ≥60mmol/l

- > 6months:
  - CF unlikely ≤39mmol/l
  - Intermediate 40-59mmol/l
  - CF ≥60mmol/l
Common mimickers of asthma
Ciliary function disorders (PCD)

- Prevalence 1:10,000-20,000
- Early onset
- Upper & lower airway symptoms
- Mirror organs in only 50%

Prolonged offensive otorrhoea & hearing loss should warn of PCD
Consider the mimickers of asthma
Think PID

Severe, persistent, unusual & recurrent infections
Consider the mimickers of asthma

PID-asthma overlap

### Diagnose preschool asthma – like a pro

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Conclude
Do not trivialise childhood asthma

Increasing concern about the over-diagnosis & trivialising of asthma with easy prescription of inhalers?
**Conclude**

Get the diagnosis right

‘Key to diagnosing asthma correctly is being confident in making that most difficult diagnosis of all: normal child.’

**Conclude**

The 4 steps to finding the asthmatic

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Think again

Oliver Cromwell: ‘I beseech you, in the bowels of Christ, think it possible (especially when dealing with the unwell airway) that you may be mistaken'
• Prof Robin Green
• UP Paediatric Pulmonology Team