Diagnose Preschool Asthma
- like a pro -

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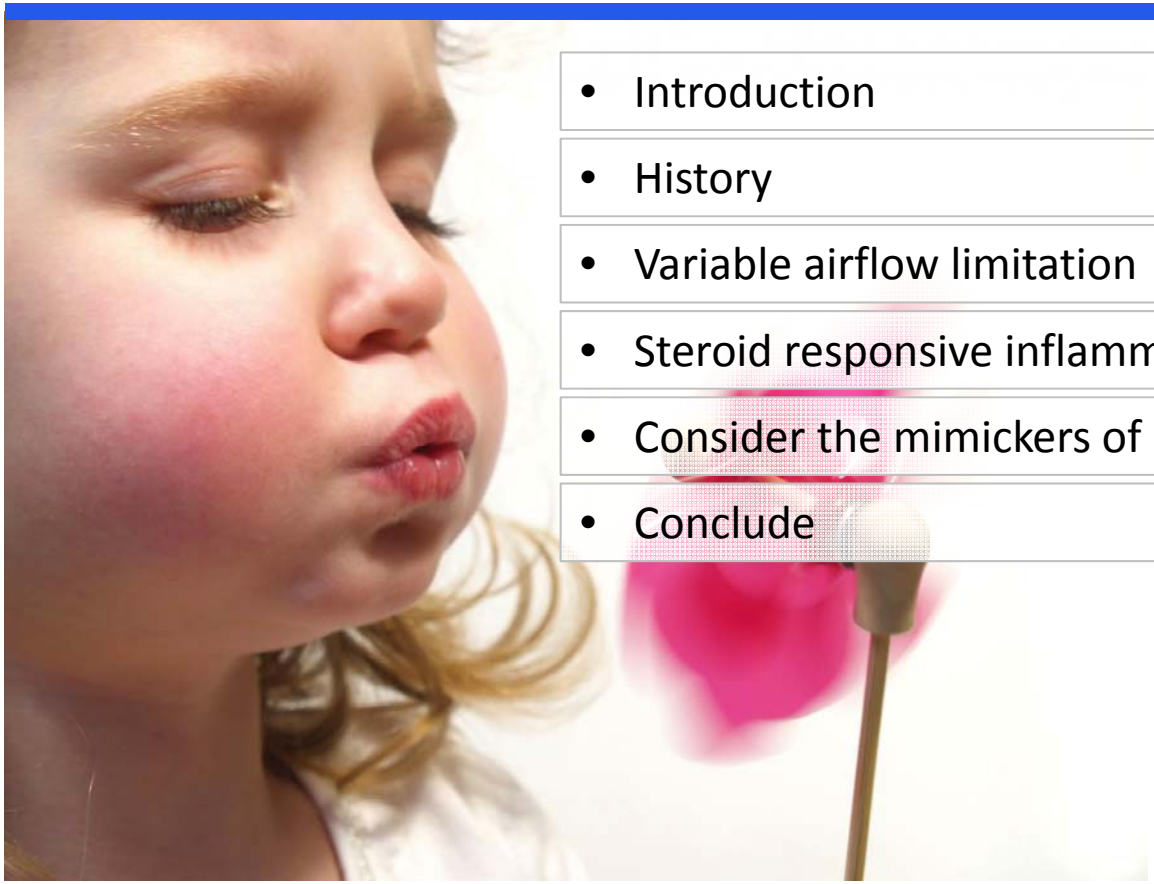
No related conflict of interest

Diagnose preschool asthma – like a pro

Summary



- Introduction
- History
- Variable airflow limitation
- Steroid responsive inflammation
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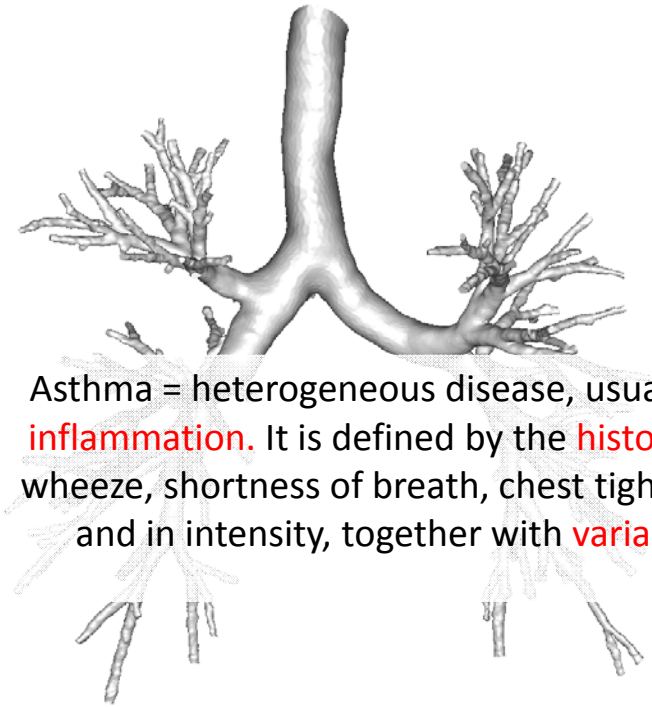
Introduction

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?

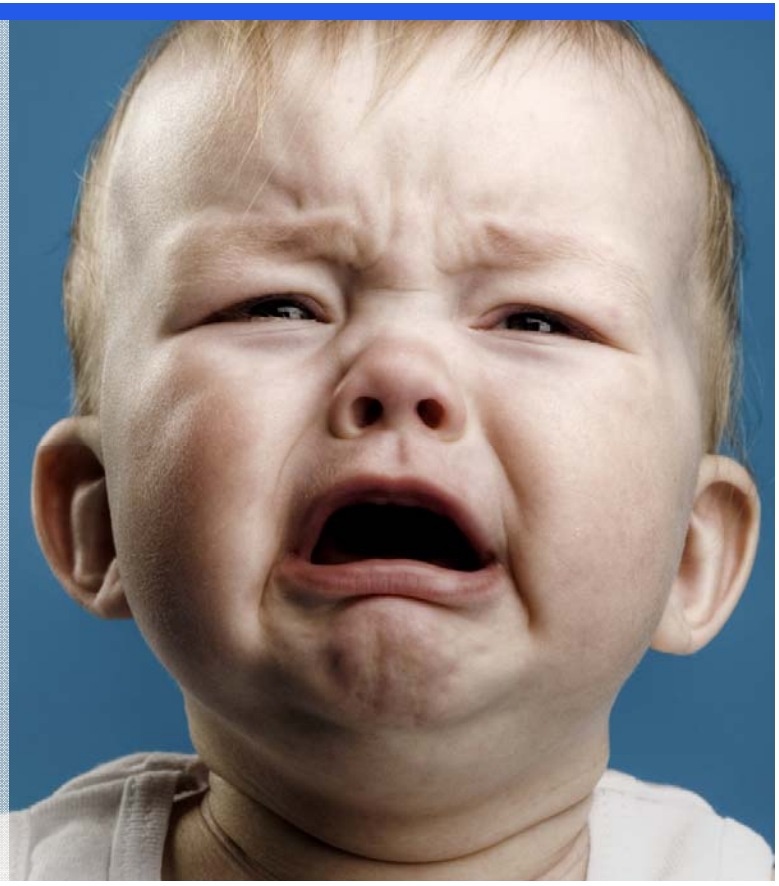
- NICE consultation paper:
  - Asthma over diagnosed?
  - Seek objective tests first?
  - Routine FeNO?
    - http://www.nice.org.uk/guidance/gid-cgwave0640/resources/asthmadiagnosis-andmonitoring-draftniceguideline2

- Bush et al. Arch Dis Child. 2016;101(8):688689

Introduction

State of the 'asthma' art?

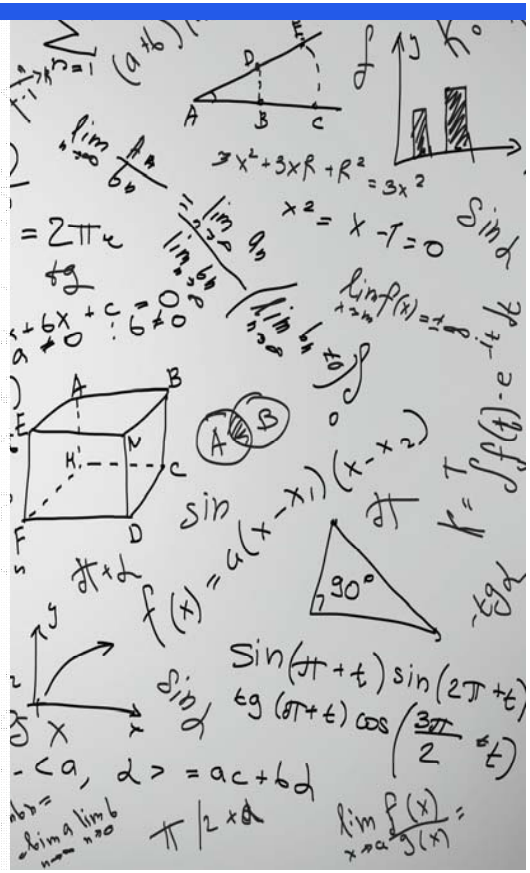
- n=108 Young children with chronic cough:
  - 50% Diagnosed with asthma
  - Asthma diagnosis confirmed in only 5%
    - Marchant JM et al. Chest 2006;129:1132–41
- 60% Asthmatics referred to secondary care have no objective evidence of variable airflow limitation
    - Joyce DP et al. http://dx.doi.org.uplib.idm.oclc.org/10.1378/chest.109.3.697



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

GINA 2018
www.ginasthma.org

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

- Walker W. Pediatr Res. 2017;82(3):387–395. doi:10.1038/pr.2017.111
- 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

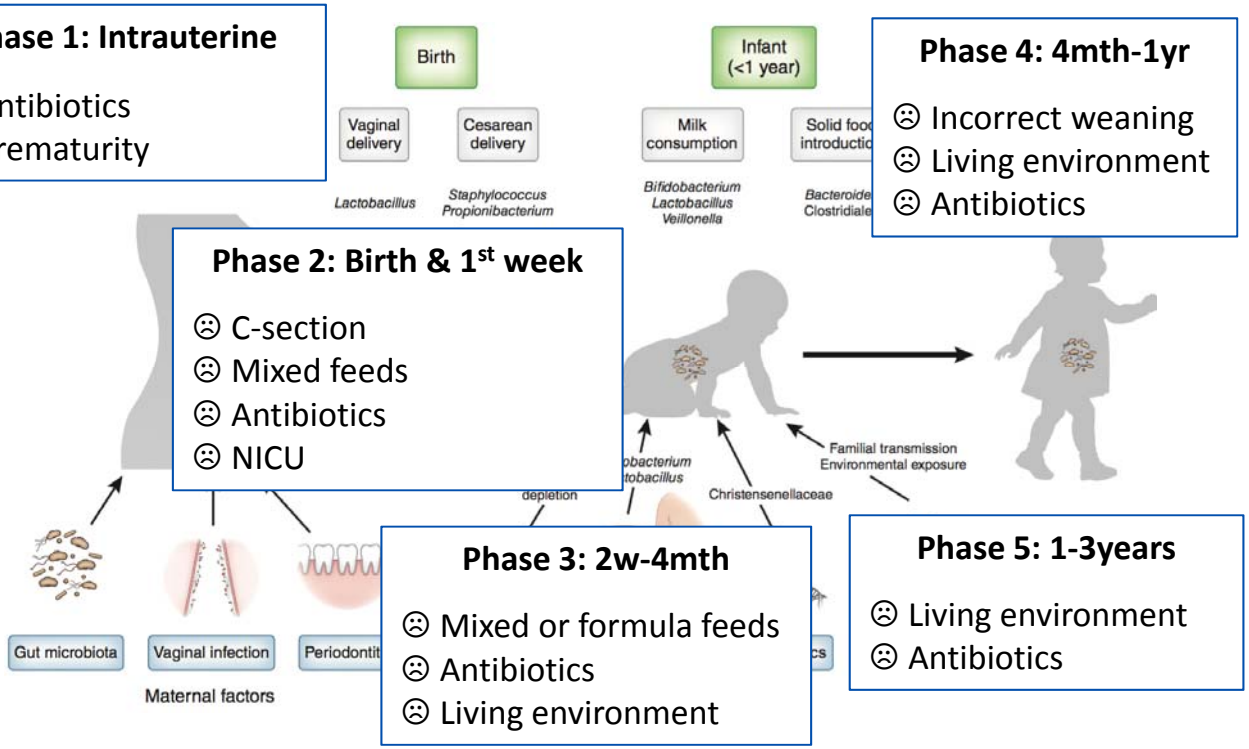
☹ Mixed or formula feeds
☹ Antibiotics
☹ Living environment

Phase 4: 4mth-1yr

☹ Incorrect weaning
☹ Living environment
☹ Antibiotics

Phase 5: 1-3years

☹ Living environment
☹ Antibiotics



Adapted from Walker WA. Pediatr Res. 2017;82(3): 387–395. doi:10.1038/pr.2017.111 7 & Tamburini S, et al. Nature Medicine. 2016;22:713–722 I doi:10.1038/nm.4142

History: the inception of childhood asthma?

Downstream effects of dysbiosis

Jakobsson HE, et al. Gut (2014) 63:559–66. doi:10.1136/gutjnl-2012-30

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

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

Sevelsted et al. Pediatrics 2015;135:e92-8.

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

- Huang et a. J Asthma 2015;52(1):16-25

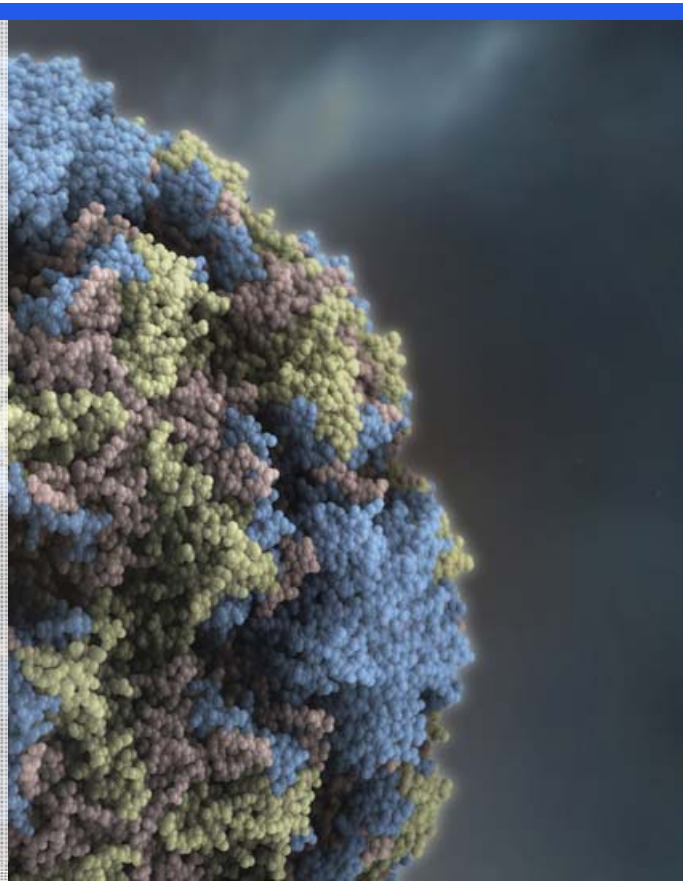
- Included $^{26}/_{76}$ potential studies on method of delivery & asthma
- No evidence of heterogeneity

- 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
    - Wu P et al. Am J Respir Crit Care Med 2008;178:1123-9.
- Rhinovirus:
  - Associated wheezing ±10x higher asthma risk by 6yr
    - Jackson DJ et al. Am J Respir Crit Care Med 2008;178:667-72.



History: the inception of childhood asthma?

Dysbiosis: bacterial infections

Childhood Asthma after Bacterial Colonization of the Airway in Neonates

- Bisgaard et al. N Eng J Med 2007;357:1487-1495

- 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

- Bisgaard et al. N Eng J Med 2007;357:1487-1495

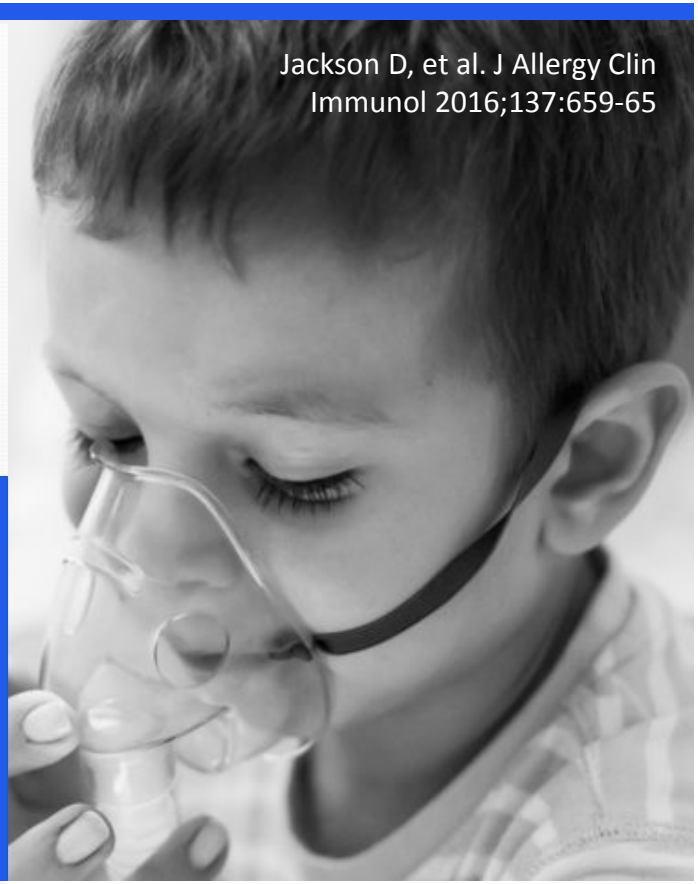
- 21% Newborns colonised with:
  - *H influenzae*
  - *S pneumoniae*
  - *M catarrhalis*
- Colonisation @ 1 month associated with 2-4x increased risk:
  - Acute severe exacerbation of wheeze (HR 2.99; 95% CI, 1.66-5.39)
  - Persistent wheeze (HR 2.4; 95% CI, 1.45-3.99)
  - Hospitalisation for wheeze (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

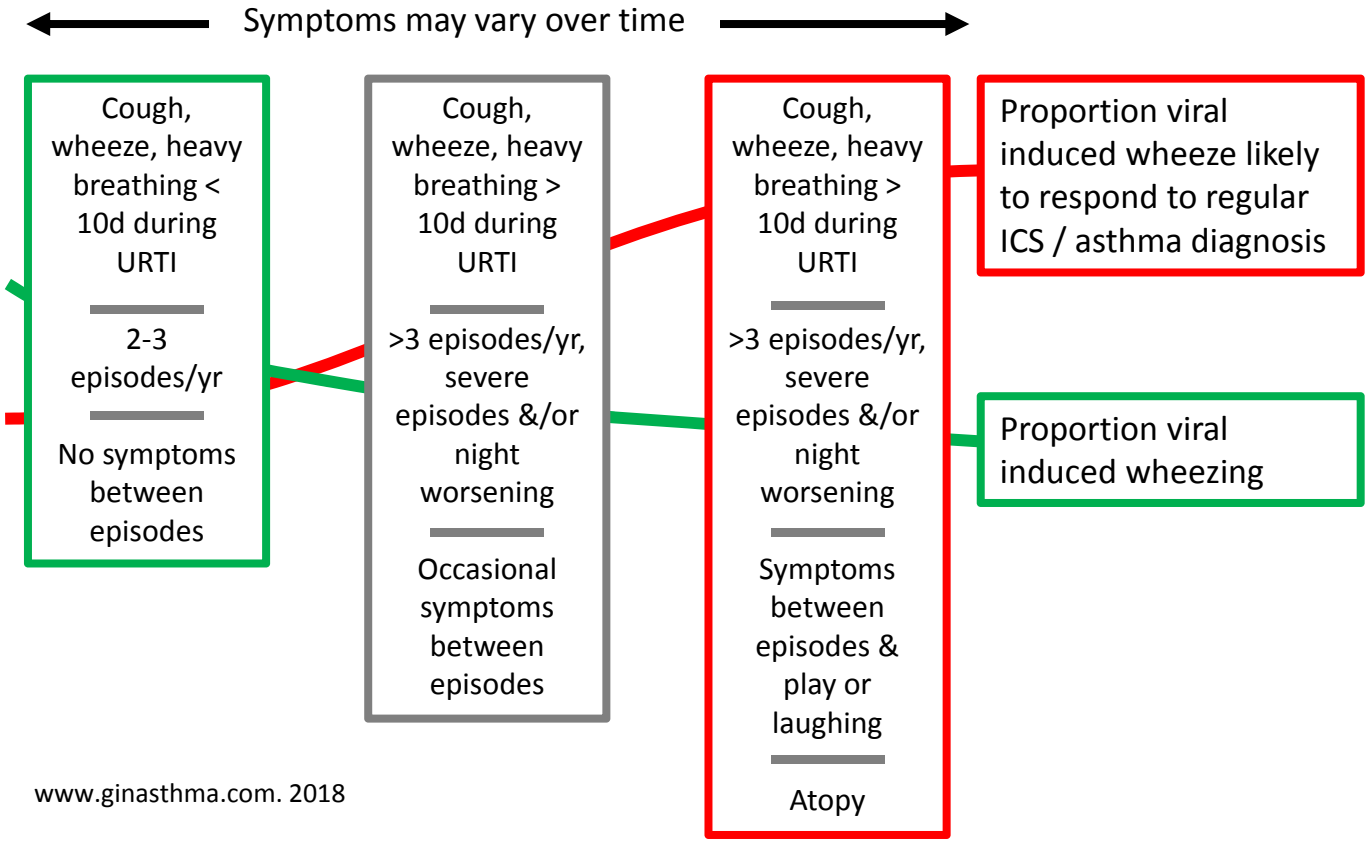
1. Early development of allergic sensitisation – especially multiple aeroallergens
2. Recurrent wheezing respiratory tract infections - viruses & bacteria



Jackson D, et al. J Allergy Clin Immunol 2016;137:659-65

History: the story of the 'chest events'!

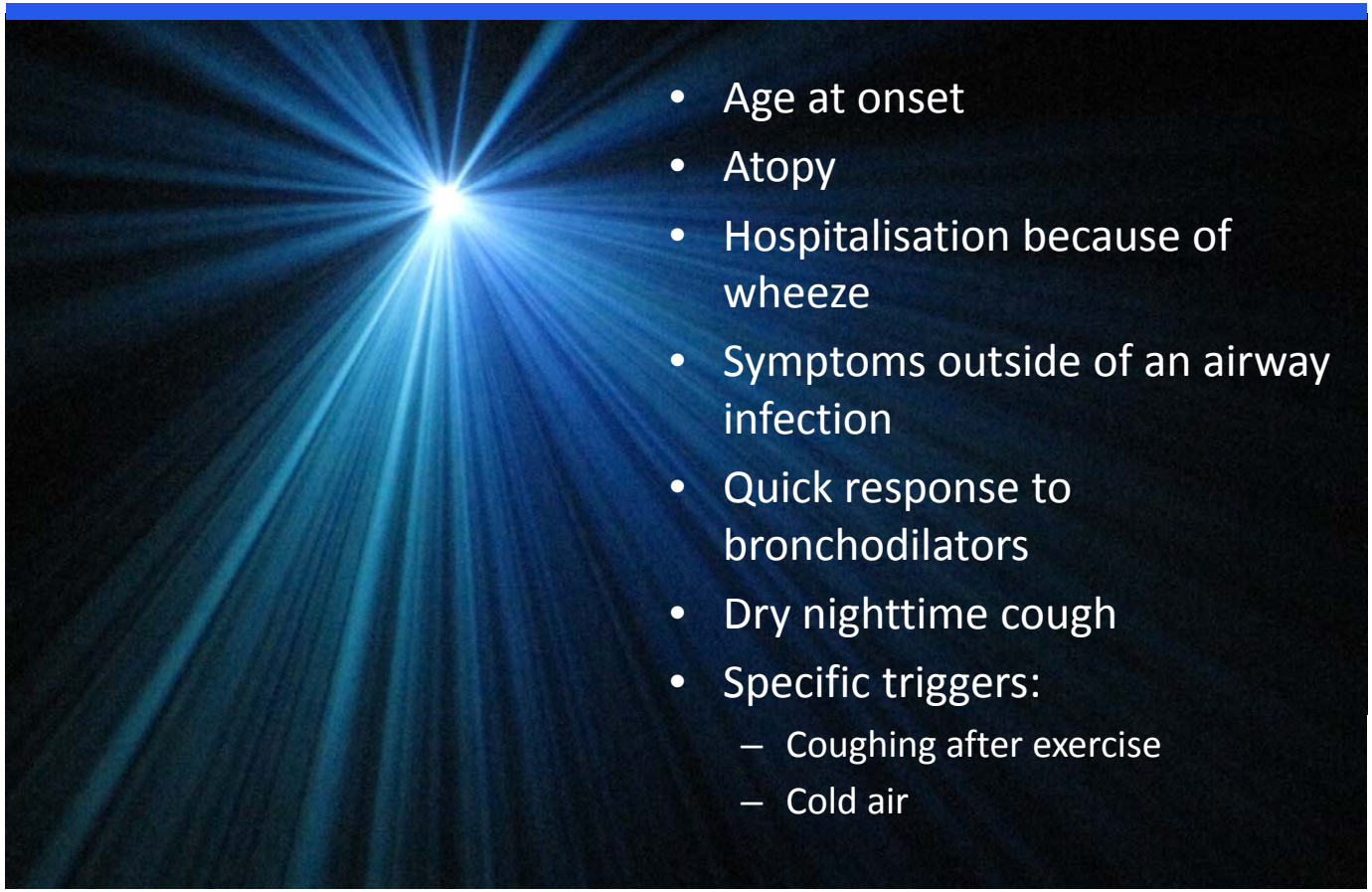
Severity, duration, frequency, between & atopy



www.ginasthma.com. 2018

History: the story of the 'chest events'!

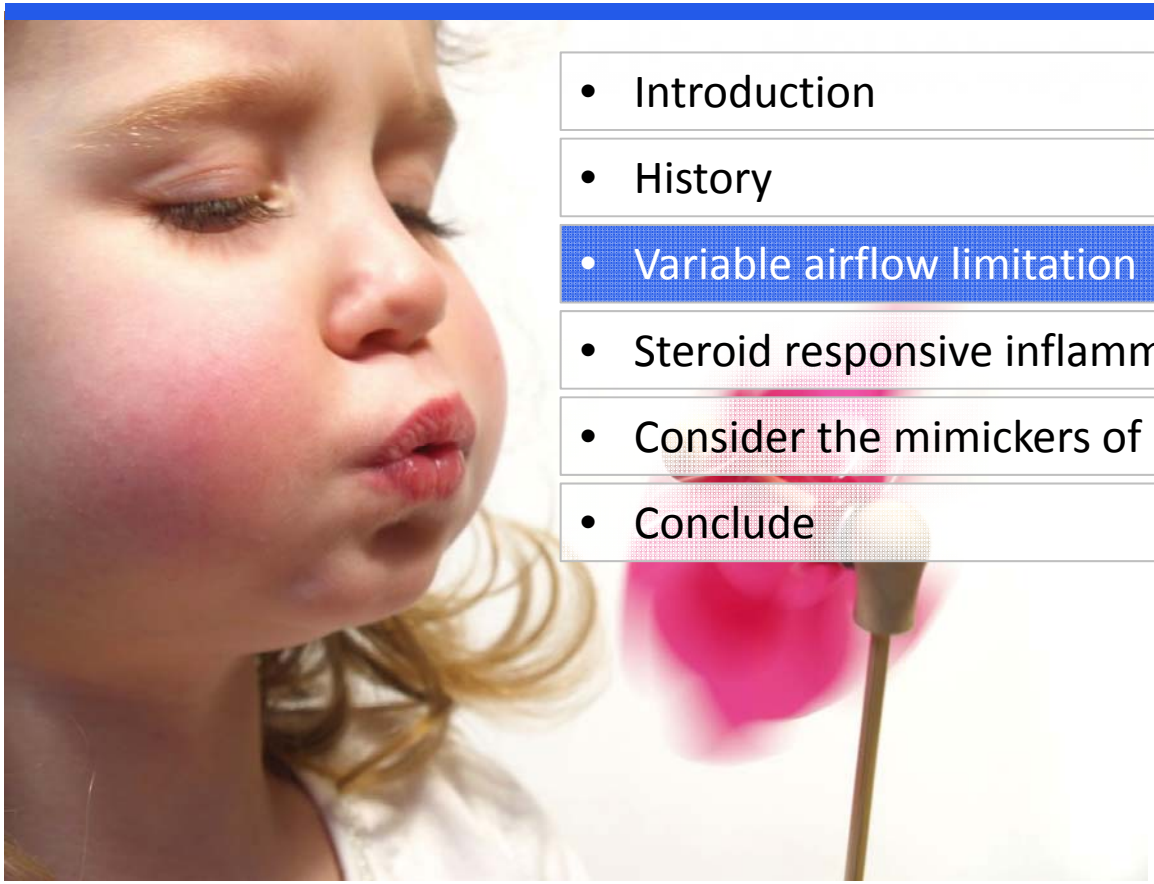
Defining points in the history



- 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

Summary



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- Conclude

Variable airflow limitation

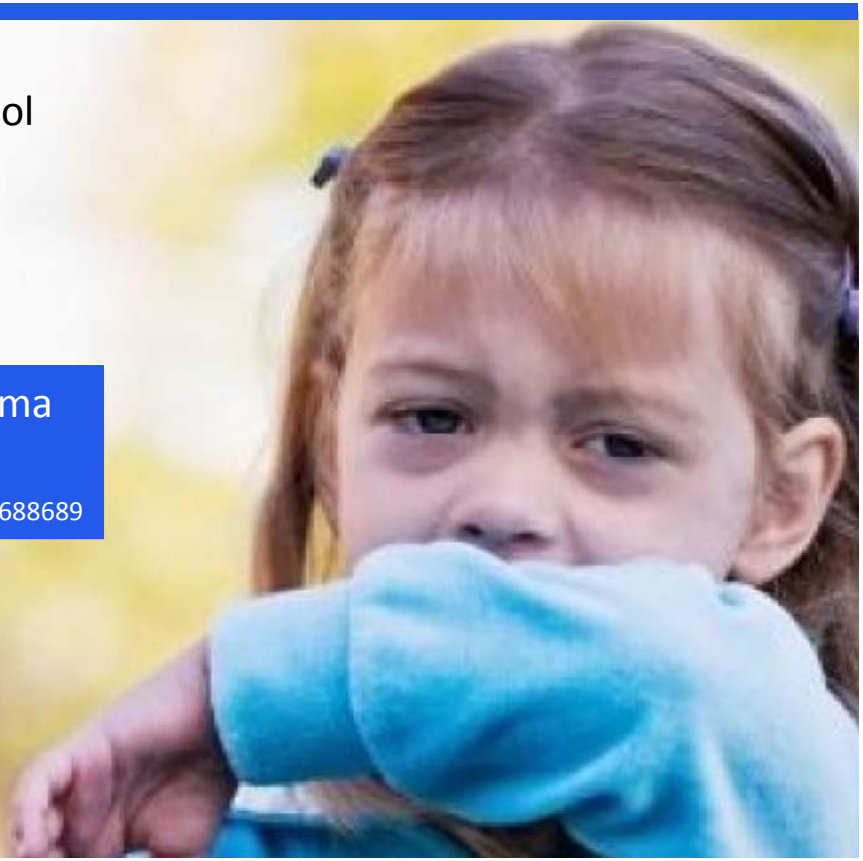
Seek objective evidence of variable airflow limitation

Can be difficult in preschool children . . .

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

‘Objective testing for asthma must become a reality’

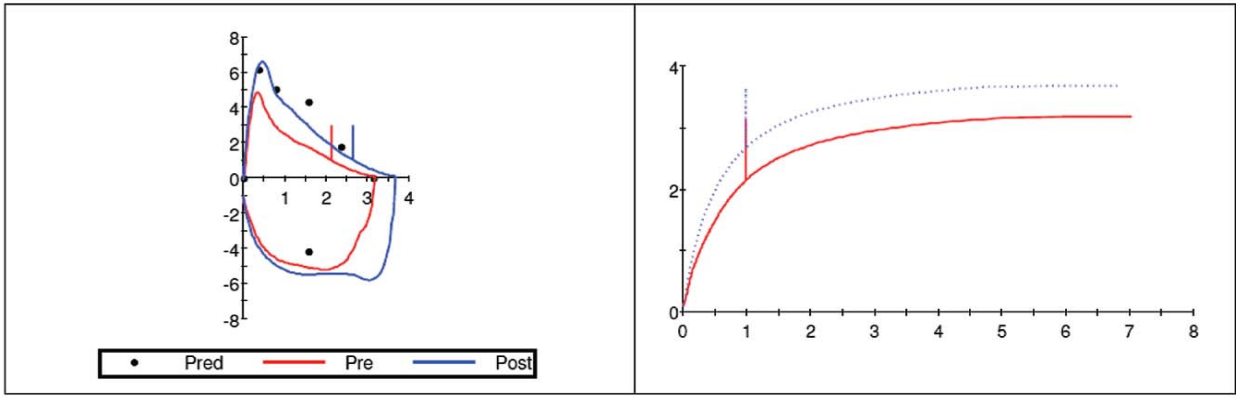
- Bush et al Arch Dis Child. 2016;101(8):688689



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

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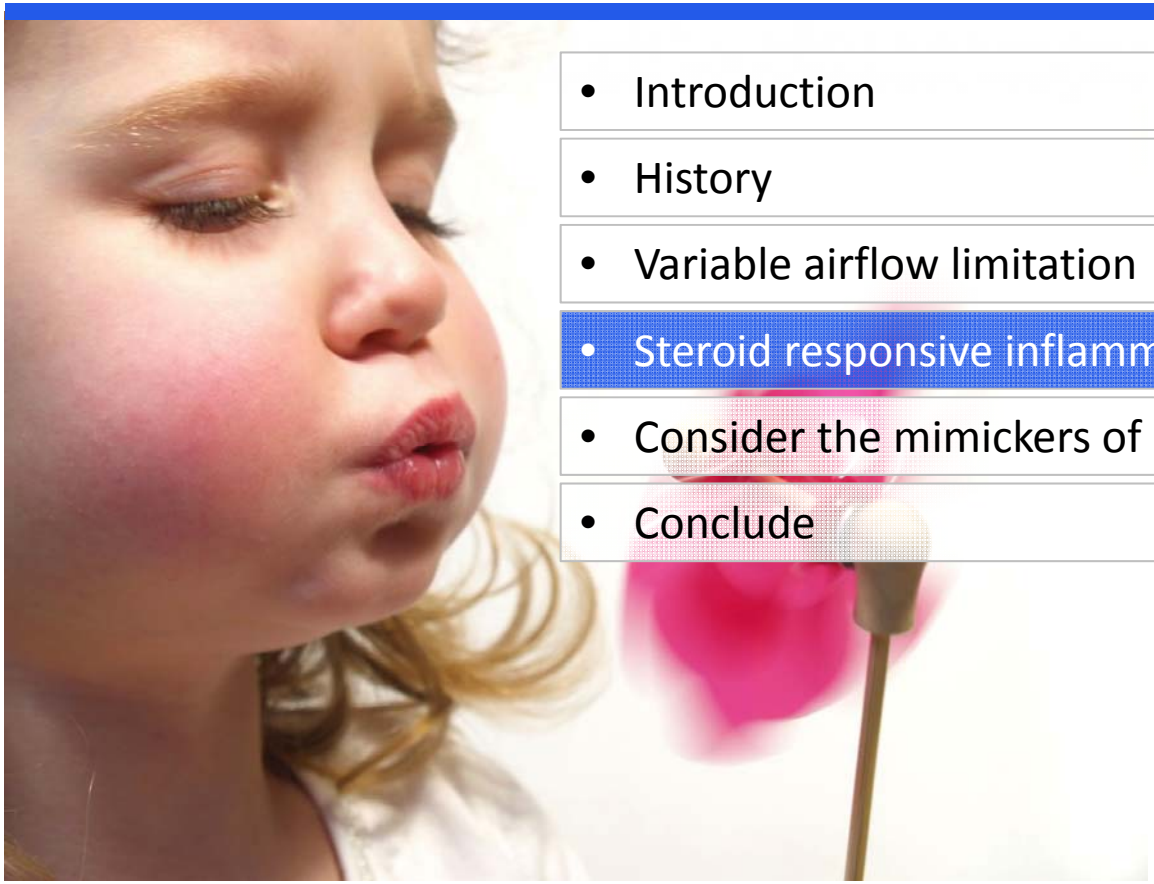

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Corticosteroid responsive inflammation

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

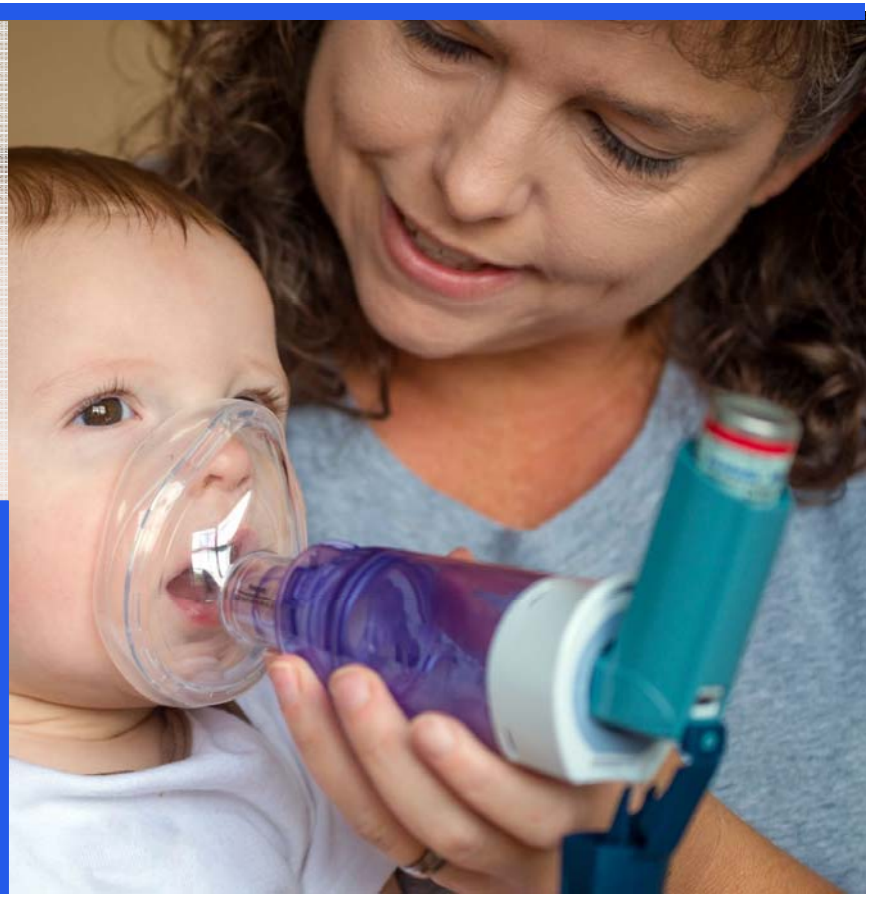
Corticosteroid responsive inflammation

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



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Consider the mimickers of asthma

Differential diagnosis of preschool wheeze

Infective	Structural	Functional
Bronchiolitis	Trachea / bronchomalacia	Wheezy phenotypes
Atypical infection	Tracheal stenosis / webs	PCD
Bacterial airway infection	Tumor / lymphadenopathy	CF
Laryngotracheobronchitis	Vascular rings	GORD
PBB	Cystic lesions / masses	Pulmonary oedema
		Retained foreign body
		Interstitial lung disease
		Bronchiolitis obliterans
		Perceived tight chest
		Bronchiectasis
		Immunodeficiency
		BPD

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)

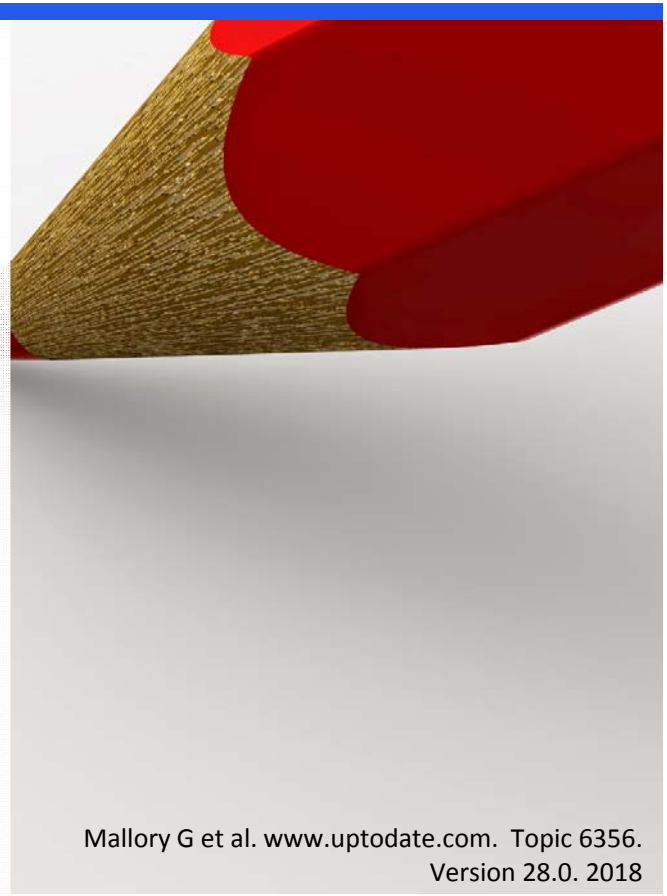
- Usually young children <5 yr
- Persistent cough (>4 weeks):
  - 'Wet' cough on reclining & early morning.
  - May last the whole night
  - 'Out of breath' during cough
  - Worse during exercise
  - Coloured sputum
- Response to antibiotic therapy
- Associated:
  - 'Noisy chest' with chest ruttles
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

Craven V et al. Arch Dis Child. 2013;98(1):72-76.

Consider the mimickers of asthma

Diagnostic criteria for PBB

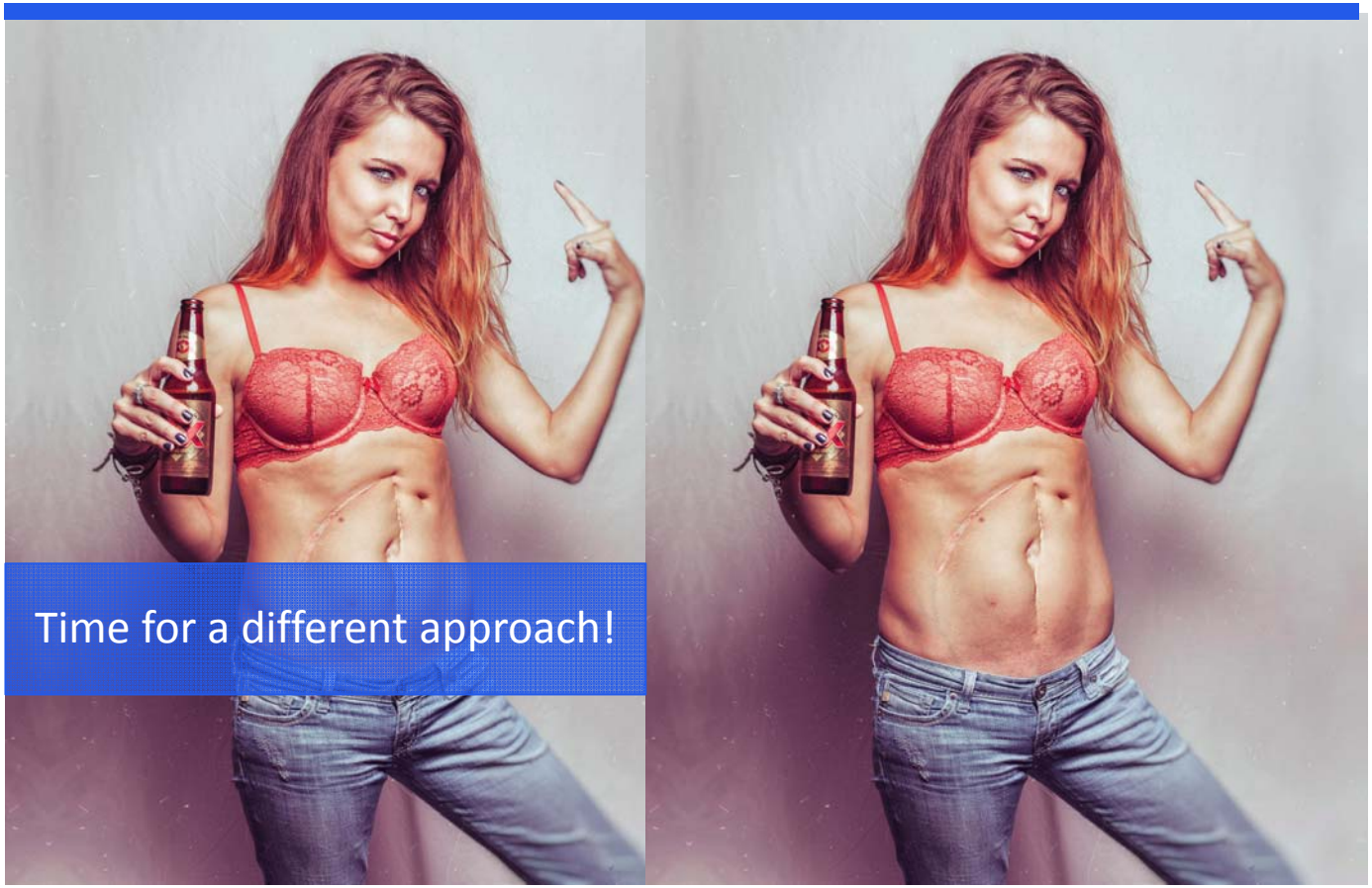
- Chronic, daily wet cough > 4 weeks
- No evidence of an alternative diagnosis:
  - Normal spirometry
  - Normal CXR other than bilateral peribronchial accentuation
- No symptoms or signs of other causes
- Must confirm resolution after appropriate treatment



Mallory G et al. www.uptodate.com. Topic 6356. Version 28.0. 2018

Consider the mimickers of asthma

Cystic fibrosis (CF)



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

http://www.uptodate.com.uplib.idm.oclc.org/contents/cystic-fibrosis-genetics-and-pathogenesis?

Consider the mimickers of asthma

CF class mutations & phenotype modifiers

Class of mutation	Basic defect	Example of mutation
Class I	Absence of gene synthesis, nonsense mutations and large deletions	621+1G→T, 3659delC, 1717-1G→A
Class II	Premature stop degradation or incomplete maturation	p.Phe508del, G85E, R506T, N1303K
Class III	Disordered regulation such as diminished ATP binding ad hydrolysis	**G551D,** S1251N, S1255P, G551S, G970R, G178R
Class IV	Defective chloride conductance or channel gating	R117H, R334W, R347P
Class V	Reduced number of CFTR transcripts due to promoter or splicing abnormality	2789+5G→A, 3849+10KcC→T, A455E
Class VI	Accelerated cell turnover from cell surface	

Many CF patients present with mild and 'atypical' symptoms

Adapted from Solomon GM, Marshall SG, Ramsey BW, Rowe SM. Breakthrough therapies: cystic fibrosis (CF) potentiators and correctors. Pediatr Pulmonol 2015;50(40)S3-S13

Consider the mimickers of asthma

Sweat the sweat test

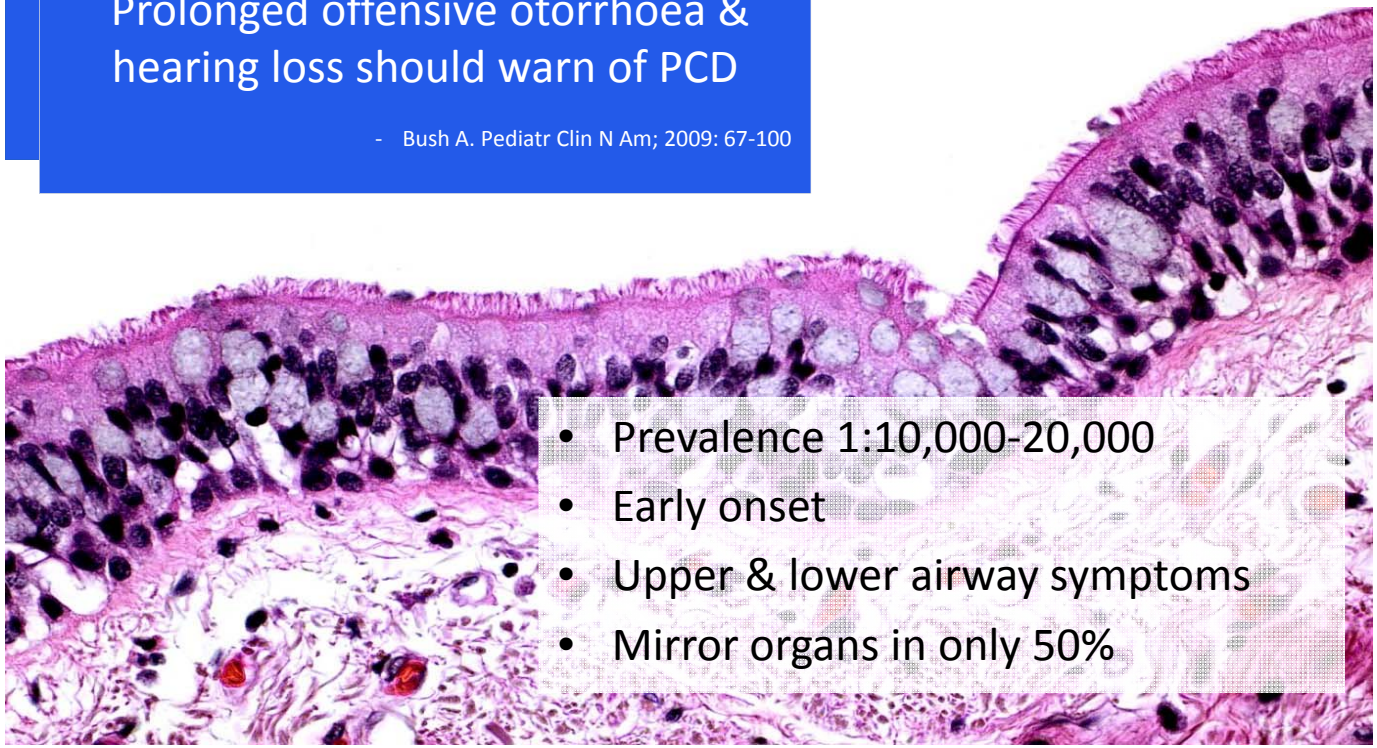
- 3d – 6months:
  - CF unlikely ≤29mmol/l
  - Intermediate 30-59mmol/l
  - CF ≥60mmol/l
- > 6months:
  - CF unlikely ≤39mmol/l
  - Intermediate 40-59mmol/l
  - CF ≥60mmol/l

Common mimickers of asthma

Ciliary function disorders (PCD)

Prolonged offensive otorrhoea & hearing loss should warn of PCD

- Bush A. Pediatr Clin N Am; 2009: 67-100



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

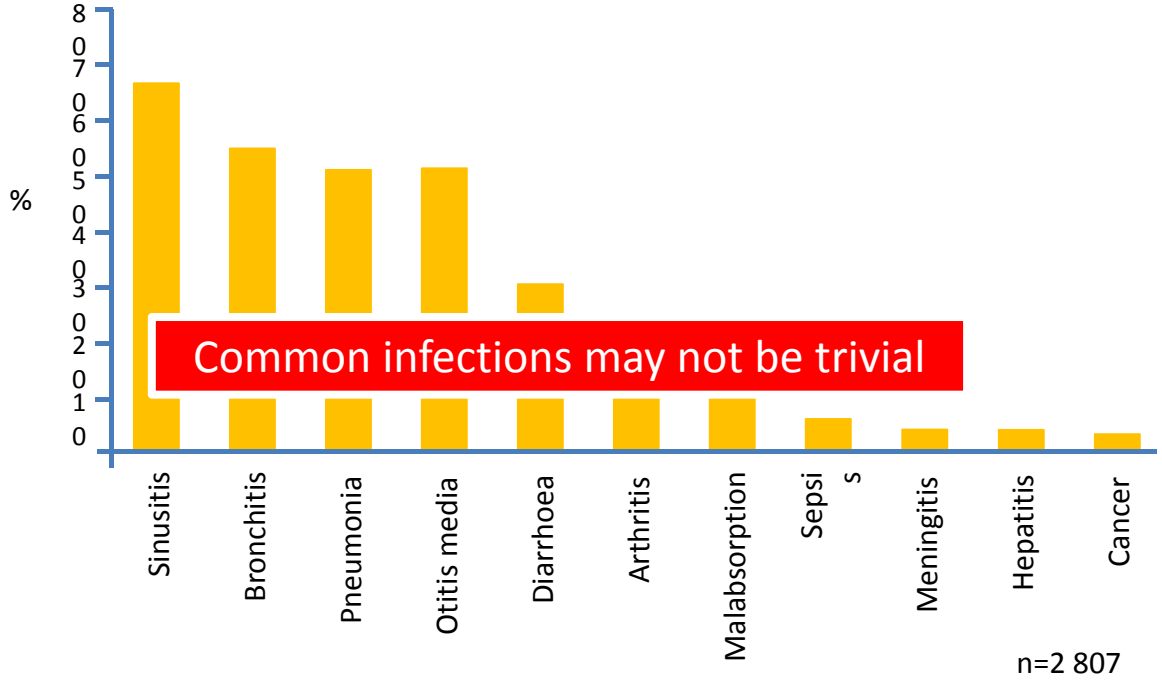
Consider the mimickers of asthma

Think PID

Severe, **p**ersistent, **u**nusual & **r**ecurrent infections

Consider the mimickers of asthma

PID-asthma overlap



IDF: Primary immune deficiency diseases in America: the first national survey of patients and specialist. 1995, Available at: http://209.251.35.238/publications/surveys/ First_National_Survey_of_Patients_and_Specialists_(1995).

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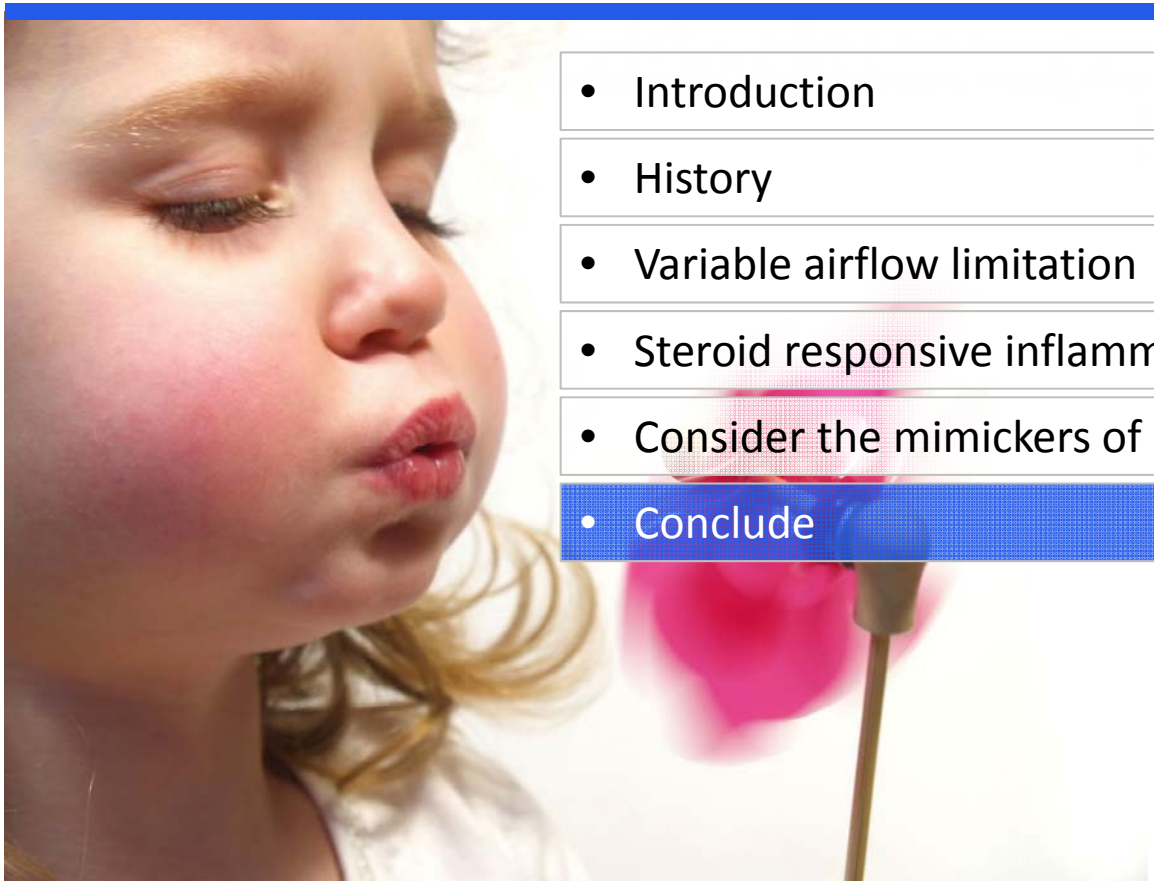

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Conclude

Do not trivialise childhood asthma

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

Conclude

Get the diagnosis right

Conclude

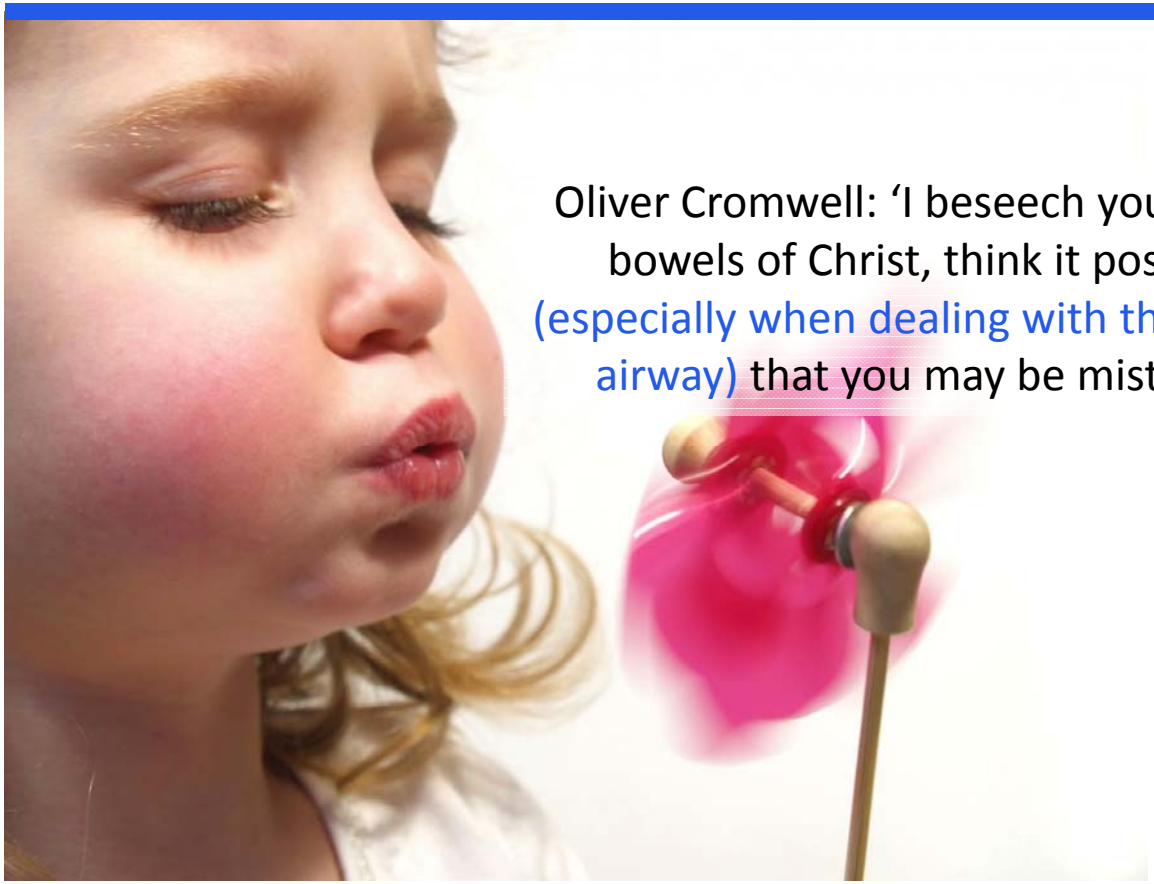
The 4 steps to finding the asthmatic

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?

Conclude

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

DRS·VAN NIEKERK
DEMOPOULOS·CHIBA
Paediatricians & Sub Specialists

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