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The Wheezing Child: Evaluation & Management

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Outline

- Wheeze
- Causes of wheeze
- Preschool wheeze
- Asthma
- All that wheezes is not asthma

Wheeze

- High pitched whistling sounds usually in expiration and associated with increased work of breathing, but can sometimes be heard in inspiration

- Wheeze – is the end result of narrowing of intrathoracic airways and expiratory flow limitation – irrespective of the underlying mechanism

- Mis-identified as wheeze

  - Ruttle (rattle) – parents may feel this noise as a vibration over the child back

  - Also used to describe upper airway noises, including snoring, congestion, rattling, gurgling noises, or stridor

Wheeze

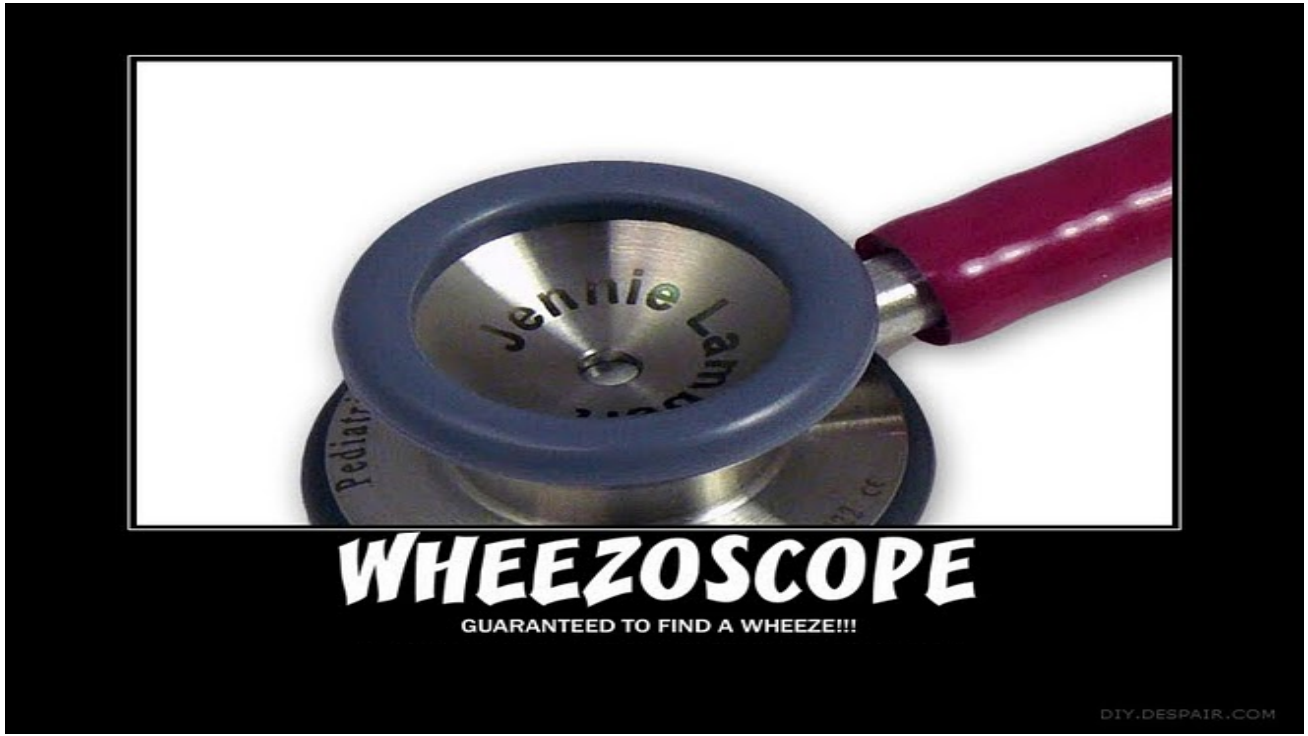
- In general, Parents are not very good in identifying and reporting wheeze as a symptom accurately [1,2]

  Eg: whistling, squeaking, gasping, rate of breathing or same as cough

- Caution in labeling wheeze – based on parental report alone

1. Elphick HE et al. ADC 2001; 84: 35-39; 2. Elphick HE et al. ERJ 2000

How good are doctors ?



How good are doctors ?

Table 3 Reliability of acoustic analysis *v* stethoscope

	Wheeze			Rattles			Crackles		
	Yes	No	Total	Yes	No	Total	Yes	No	Total
A Between-observer agreement for stethoscope									
Yes	13	14	27	10	4	14	3	2	5
No	2	7	9	4	18	22	3	28	31
Total	15	21	36	14	22	36	6	30	36
	$\kappa = 0.18$ (−0.08 to 0.44)			$\kappa = 0.53$ (0.21 to 0.86)			$\kappa = 0.46$ (0.14 to 0.79)		

Inter observer variations among healthcare professionals using a stethoscope

Elphick HE et al. ADC 2004

How can we improve the validity?

- Detailed description of the noise by parents
- Imitate - if you can
- Document presence/absence in notes
- Document response to bronchodilator
- Video / Audio clips

Causes of Wheezing

Common causes

- Preschool Wheeze
- Asthma

Uncommon Causes

Large airway obstruction (Congenital)

- Vascular rings
- Tracheomalacia
- Tracheal stenosis

Large Airway Obstruction (Acquired)

- Foreign body
- Meditational mass
- Endobronchial tumour

Abnormal GI – Airway Anatomy

Persistent Airway Infection states

- Cystic fibrosis
- Immunoglobulin deficiency
- PCD

Aspiration disorder

Vocal Cord dysfunction

Cardiac failure

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Pre-School Wheeze

Prevalence

- 1 in 3 children: at least one episode by 3 years[1,2]
- 1 in 2 children: at least one episode by 6 years[1,2]
- 0.15% of total UK annual healthcare budget[3]

1. *Martinez FD et al. NEJM 1995; 332: 133-138*
2. *Bisgaard H, Szefler S. Pediatr Pulmonol 2007; 42: 723-728*
3. *Stevens CA et al. Eur Respir J 2003; 21: 1000-1006*

Duration of wheeze – Time trend based classification

- Transient wheeze:

  - Symptom onset <3 yrs, and found to have disappeared but age 6 (may be episodic or multi-trigger wheeze)

- Persistent Wheeze:

  - Symptoms that are found to have continue until the age of >6 years (may be episodic or multi-trigger wheeze)

- Late–onset Wheeze:

  - Symptoms that start >3 years (may be episodic or multi-trigger wheeze)

Preschool Wheeze – Symptom based Classification

- Episodic (Viral) Wheeze:

  Wheezing during discrete time periods, often in association with viral cold

- Multiple-trigger Wheeze:

  Wheezing that shows discrete exacerbations and also symptoms in between episodes

ERS Task force- ERJ 2008

Episodic (Viral) wheeze

- Most common phenotype in preschool children
- Most common causative agents

  - Rhinovirus, RSV, Corona virus, Human metapneumovirus, Parainfluenza virus, Adenovirus

- Mostly declines over time, disappearing by the age of 6 years
- But can continue as episodic wheeze into school change, change into multi-trigger wheeze or disappear at an older age *(Marinez etal, NEJM 1995, Doull et al BMJ 1997)*

Multi-trigger Wheeze

- Viral respiratory tract infection is the most common

- Other trigger factors:
  - Tobacco smoke
  - may also wheeze in response to mist,crying, laughter or exercise[1]

1. Martinez et al, Martin Dunitz 2003

Features suggesting a diagnosis of asthma in children < 5 years

Cough	- Recurrent / Persistent non productive cough that may be worse at night or accompanied by some wheezing and breathing difficulties - Cough occurring with exercise, laughing or exposure to tobacco smile in the absence of an apparent respiratory infection
Wheezing	- Recurrent wheezing, including during sleep or with triggers such as activity, laughing, crying or exposure to tobacco smoke or air pollution
Difficult or heavy breathing or shortness of breath	- Occurring with exercise, laughing or crying
Reduced activity	- Not running, playing or laughing at the same intensity as other children, tires earlier during walks (want to be carried)
Past or family history	- Other allergic disease (atopic dermatitis or allergic rhinitis) - Asthma in first degree relative

Tests to assist diagnosis of asthma

While no tests diagnose asthma with certainty in < 5 years
Following are useful adjuncts

1. Therapeutic trial: 2-3 months SABA and regular low dose ICS

- Evaluate symptoms control (day and night time symptoms)

- Marked clinical improvement during Rx and deterioration when Rx stopped, support a diagnoses of asthma

Tests to assist diagnosis of asthma

2. Atopy testing

SPT – for sensitisation , Allergen specific - Ig E

SPT Less reilable in infants

More reliable in older children

Many children with asthma have atopy

Absence of atopy doesn’t rule out asthma

Tests to assist diagnosis of asthma

- CXR – useful to rule out other causes
- Lung function test: 4 - 5 years if coached properly – they can perform reproducable spirometry
- Exhaled Nitric oide – FeNO – can be measured with tidal breathing *(Ven Der Heijden et al, Pediatr Pulmonol 2014: 49:291-5)*

FeNO – Reference Values – Preschool Children

TABLE 1— Anthropometric Characteristics and Reference Values of FeNO

	Male (n = 23)	Female (n = 28)	Total (n = 51)
Mean age (SD), months	33.2 (10.6)	31.8 (12.3)	32.5 (11.8)
Mean weight (SD), kg	14.7 (3.0)	13.6 (2.9)	14.1 (3.0)
Mean height (SD), cm	95.3 (9.6)	93.2 (10.2)	94.1 (9.9)
Geometric mean FeNO (95% CI), ppb	7.4 (2.4–12.4)	6.9 (3.1–10.7)	7.1 (2.8–11.5)
Median FeNO (1–3 quartile), ppb	8.6 (6.3–14.2)	7.4 (5.0–10.0)	7.9 (5.7–11)
95th percentile, ppb	29.3	19.5	22.6
Range FeNO, ppb	1–30.4	0.8–21.0	0.8–30.4

Ven Der Heijden et al, Pediatr Pulmonol 2014: 49:291-5

Assessment

- History & Examination
- Identify possible trigger factors
- Other diagnoses/associated conditions

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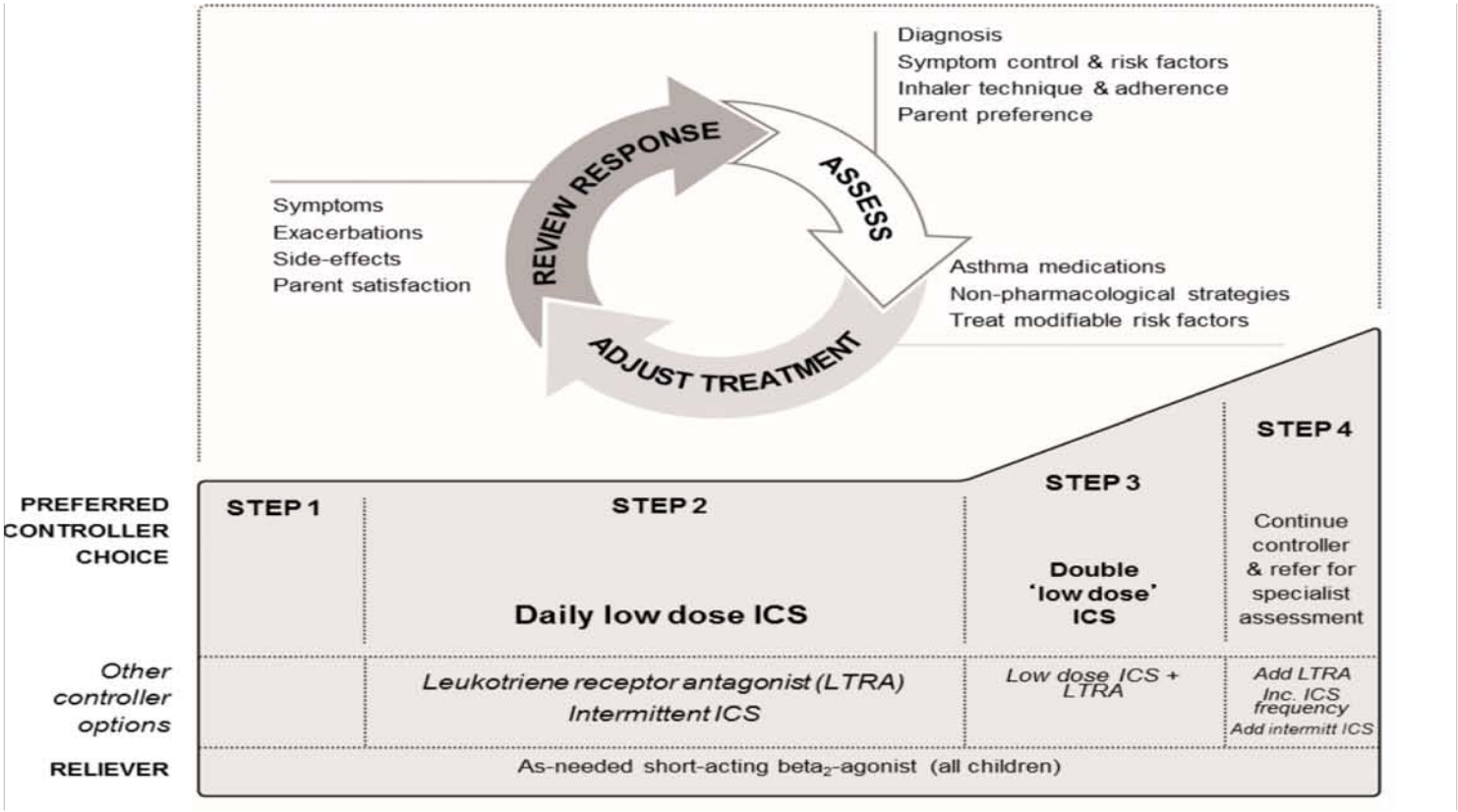
Global Initiative for Asthma (GINA) Guideline

<5 years

GINA 2018


Diagnosis
Symptom control & risk factors
Inhaler technique & adherence
Parent preference
REVIEW RESPONSE
ASSESS
ADJUST TREATMENT
Symptoms
Exacerbations
Side-effects
Parent satisfaction
Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors
PREFERRED CONTROLLER CHOICE
STEP 1
STEP 2
Daily low dose ICS
STEP 3
Double 'low dose' ICS
STEP 4
Continue controller & refer for specialist assessment
Other controller options
Leukotriene receptor antagonist (LTRA)
Intermittent ICS
Low dose ICS + LTRA
Add LTRA
Inc. ICS frequency
Add intermitt ICS
RELIEVER
As-needed short-acting beta2-agonist (all children)

GINA 2018

CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms (Box 6-2)	Symptom pattern consistent with asthma (Box 6-2) and asthma symptoms not well-controlled (Box 6-4), or ≥3 exacerbations per year Symptom pattern not consistent with asthma (Box 6-2) but wheezing episodes occur frequently, e.g. every 6–8 weeks. Give diagnostic trial for 3 months.	Asthma diagnosis, and not well-controlled on low dose ICS	Not well-controlled on double ICS
			First check diagnosis, inhaler skills, adherence, exposures	

KEY ISSUES

ALL CHILDREN

- **Assess** symptom control, future risk (Box 6-4), comorbidities
- **Self-management:** education, inhaler skills, written asthma action plan, adherence
- **Regular review:** assess response, adverse events, establish minimal effective treatment
- (Where relevant): environmental control for smoke, allergens, indoor/outdoor air pollution

Oral Corticosteroids for Exacerbations

- Oral prednisolone 1-2 mg/kg/day – maximum dose 20 mg/day for children <2 years and 30mg/day for children 2-5 years [1]

- 3 - 5 days duration

- Reduced risk of hospitalization when administered in the children's emergency

Castro-Rodriguez et al; Pediatr Pulmonol 2016;51:868-76

Lancet Respir Med. 2014 Oct;2(10):796-803. doi: 10.1016/S2213-2600(14)70186-9. Epub 2014 Sep 8.

Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial.

Nwokoro C[1], Pandya H[2], Turner S[3], Eldridge S[1], Griffiths CJ[1], Vulliamy T[1], Price D[1], Sanak M[4], Holloway JW[5], Brugha R[1], Koh L[1], Dickson I[1], Rutterford C[6], Grigg J[7].

Author information

Abstract

BACKGROUND: The effectiveness of intermittent montelukast for wheeze in young children is unclear. We aimed to assess whether intermittent montelukast is better than placebo for treatment of wheeze in this age group. Because copy numbers of the Sp1-binding motif in the arachidonate 5-lipoxygenase (ALOX5) gene promoter (either 5/5, 5/x, or x/x, where x does not equal 5) modifies response to montelukast in adults, we stratified by this genotype.

METHODS: We did this multicentre, parallel-group, randomised, placebo-controlled trial between Oct 1, 2010, and Dec 20, 2013, at 21 primary care sites and 41 secondary care sites in England and Scotland. Children aged 10 months to 5 years with two or more wheeze episodes were allocated to either a 5/5 or 5/x+x/x ALOX5 promoter genotype stratum, then randomly assigned (1:1) via a permuted block schedule (size ten), to receive intermittent montelukast or placebo given by parents at each wheeze episode over a 12 month period. Clinical investigators and parents were masked to treatment group and genotype strata. The primary outcome was number of unscheduled medical attendances for wheezing episodes. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01142505.

FINDINGS: We randomly assigned 1358 children to receive montelukast (n=669) or placebo (n=677). Consent was withdrawn for 12 (1%) children. Primary outcome data were available for 1308 (96%) children. There was no difference in unscheduled medical attendances for wheezing episodes between children in the montelukast and placebo groups (mean 2·0 [SD 2·6] vs 2·3 [2·7]; incidence rate ratio [IRR] 0·88, 95% CI: 0·77-1·01; p=0·06). Compared with placebo, unscheduled medical attendances for wheezing episodes were reduced in children given montelukast in the 5/5 stratum (2·0 [2·7] vs 2·4 [3·0]; IRR 0·80, 95% CI 0·68-0·95; p=0·01), but not in those in the 5/x+x/x stratum (2·0 [2·5] vs 2·0 [2·3]; 1·03, 0·83-1·29; p=0·79, pinteraction=0·08). We recorded one serious adverse event, which was a skin reaction in a child allocated to placebo.

INTERPRETATION: Our findings show no clear benefit of intermittent montelukast in young children with wheeze. However, the 5/5 ALOX5 promoter genotype might identify a montelukast-responsive subgroup.

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Global Initiative for Asthma (GINA) Guideline

>6 years

Asthma

- Heterogenous disease
- Chronic airway inflammmation
- Symptoms of wheeze, shortness of breath, chest tightness and cough
- Vary over time, intensity
- Expiratory airflow limitation

Asthma Phenotype

- Allergic Asthma – Childhood onset, family history of allergic disease, eosinophilic airway inflammaiton

  Respond well to inhaled corticosteroid Rx

- Non-allergic asthma – Not associated with allergic disease

  neutrophilic, eosniophilic or few inflammatory cells

  often – don't respond well to ICS

- Late onset asthma – adults

- Asthma with fixed airflow limitation – long standing asthma

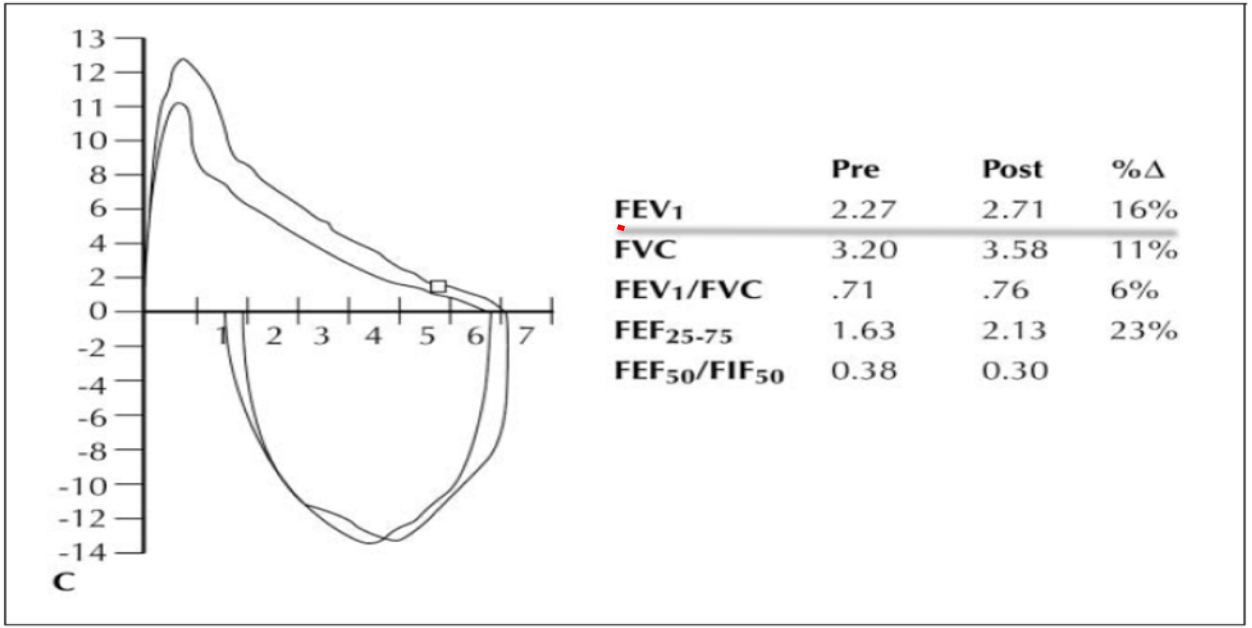
Asthma - Diagnosis

- Respiratory symptoms – wheezing, shortness of breath, chest tightness and cough
- Expiratory airflow limitation
- Nocturnal /early morning symtpoms
- Triggered by – viral infections, exercise, allergen eposure, changes in weather, laughter or irritant such as car exhaust fumes, smoke or strong smell
- Expiratory airflow limitation

Asthma - Diagnosis

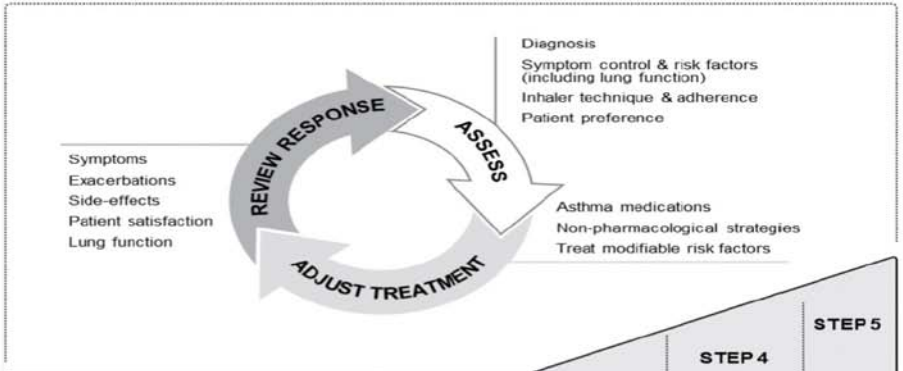
- Variable expiratory airflow limitation
- Positive bronchodilator reversibility: FEV_1 >12 % predicted
- Positive exercise challenge test: fall in FEV_1 of >12% predicted
- Postive bronchial challenge test:
  - fall in FEV_1 >20% - methacholine or
  - fall in FEV_1 >15% - hypertonic saline

Spirometry



	Pre	Post	%Δ
FEV_1	2.27	2.71	16%
FVC	3.20	3.58	11%
FEV_1/FVC	.71	.76	6%
FEF_{25-75}	1.63	2.13	23%
FEF_{50}/FIF_{50}	0.38	0.30	

GINA 2018



	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,*† anti-IgE, anti-IL5*
Other controller options	*Consider low dose ICS*	*Leukotriene receptor antagonist (LTRA) Low dose theophylline**	*Med/high dose ICS Low dose ICS + LTRA (or + theoph*)*	*Add tiotropium*† Med/high dose ICS + LTRA (or + theoph*)*	*Add low dose OCS*
RELIEVER	As-needed short-acting beta$_2$-agonist (SABA)		As-needed SABA or low dose ICS/formoterol#		

REMEMBER TO...

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if ... uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS, provided FEV1 is >70% predicted
- Consider stepping down if ... symptoms controlled for 3 months + low risk for exacerbations. Stopping ICS is not advised.

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids; SLIT: sublingual immunotherapy. See Box 3-6 (p.45) for low, medium and high doses of ICS for adults, adolescents and children 6–11 years. See Chapter 3 Part D (p.67) for management of exercise-induced bronchoconstriction.

* Not for children <12 years.
** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.

All that wheezes is not Asthma

Causes of Wheezing

Common causes

- Preschool Wheeze
- Asthma

Uncommon Causes

Large airway obstruction (Congenital)

- Vascular rings
- Tracheomalacia
- Tracheal stenosis

Large Airway Obstruction (Acquired)

- Foreign body
- Meditational mass
- Endobronchial tumour

Abnormal GI – Airway Anatomy

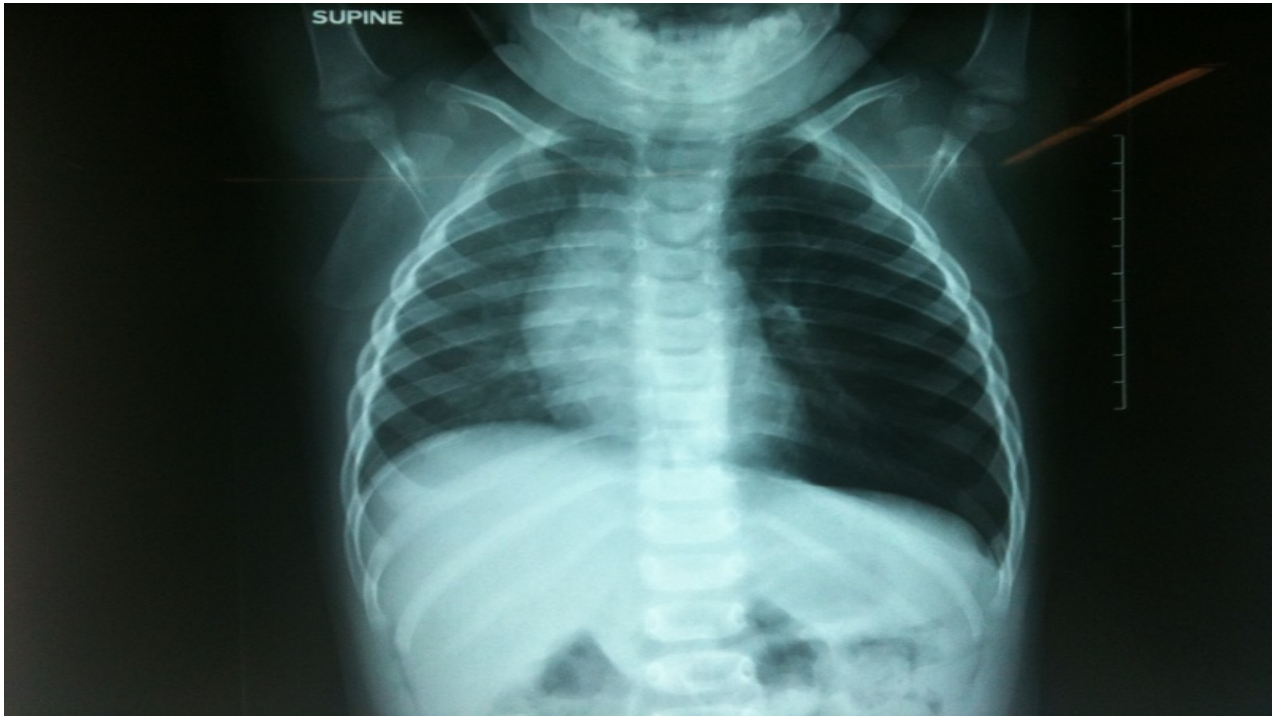
Persistent Airway Infection states

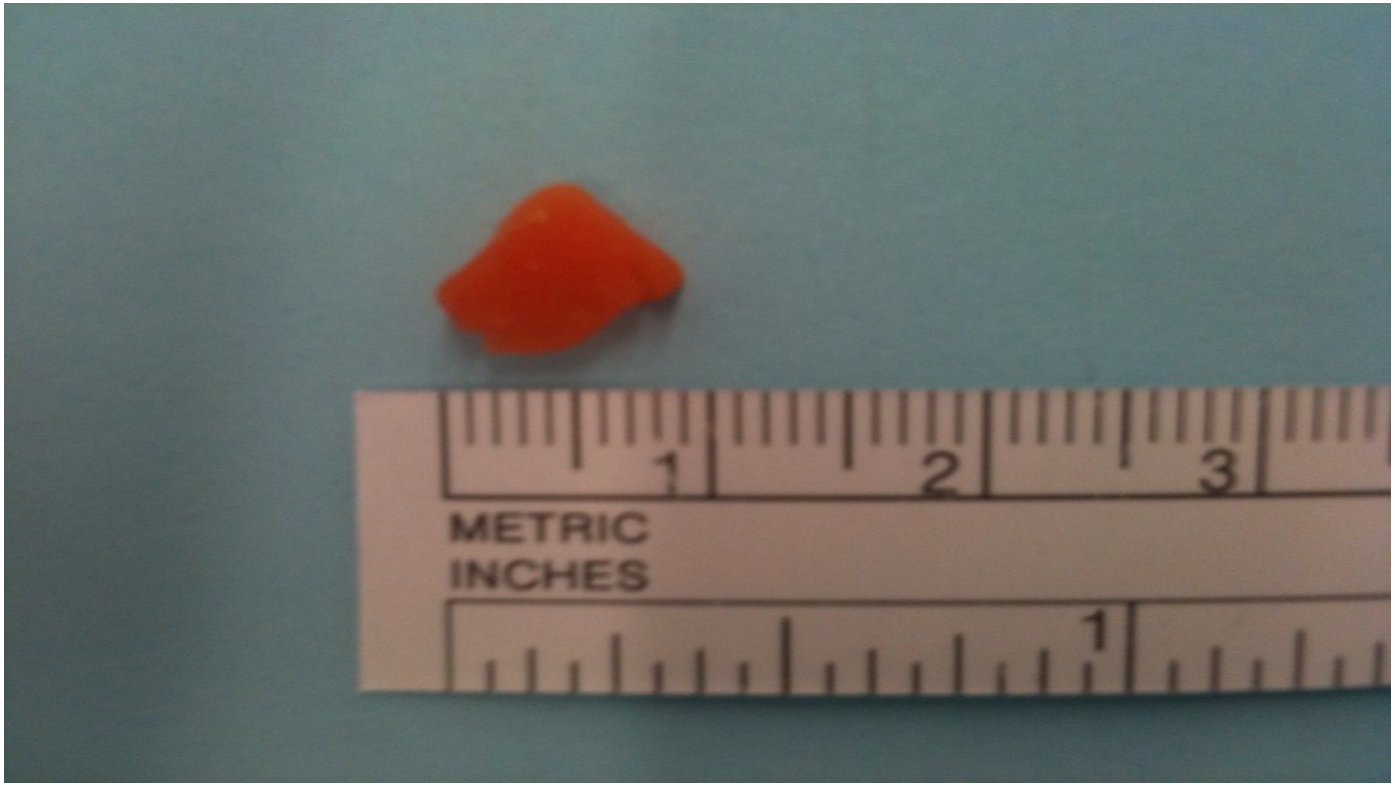
- Cystic fibrosis
- Immunoglobulin deficiency
- PCD

Aspiration disorder

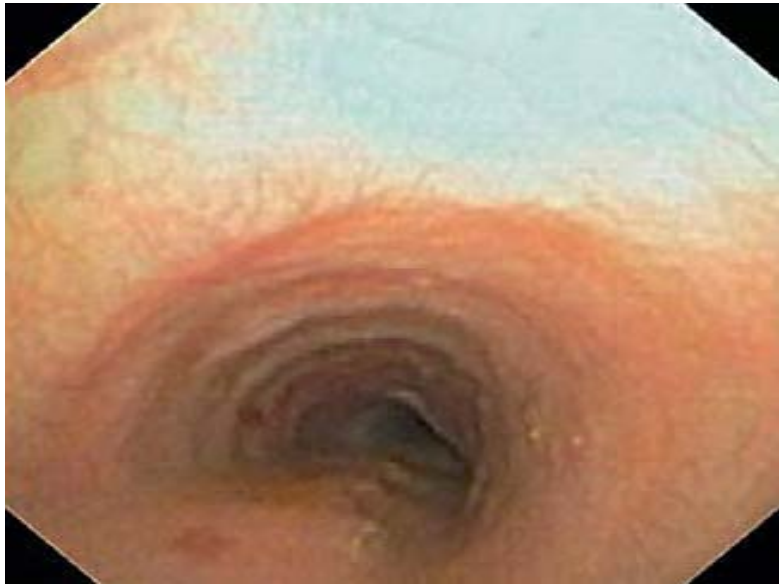
Vocal Cord dysfunction

Cardiac failure

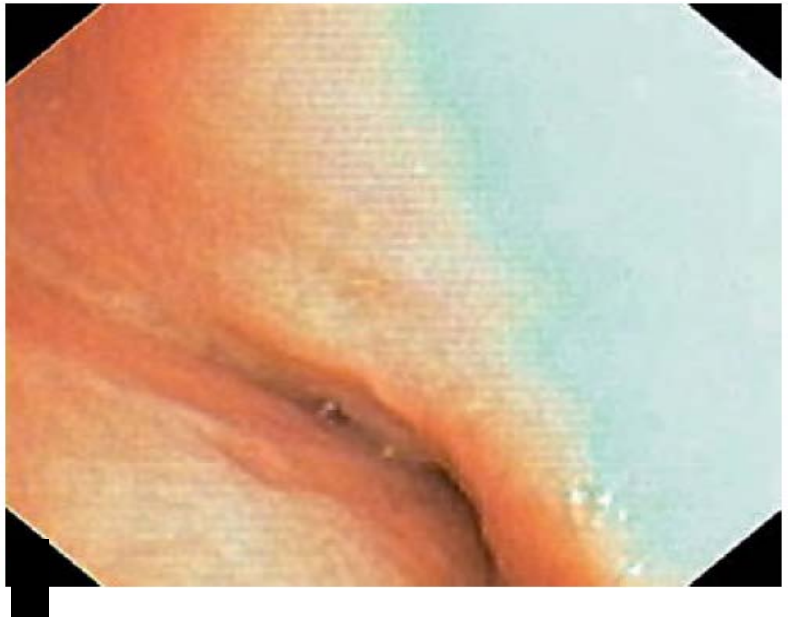




Tracheomalacia

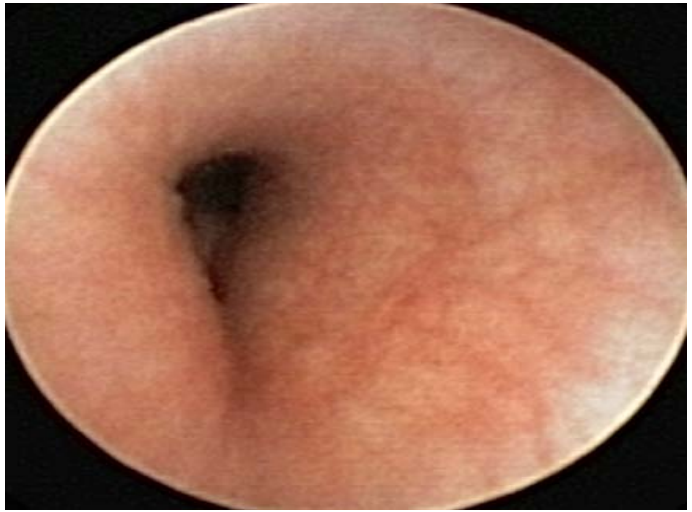


Inspiration

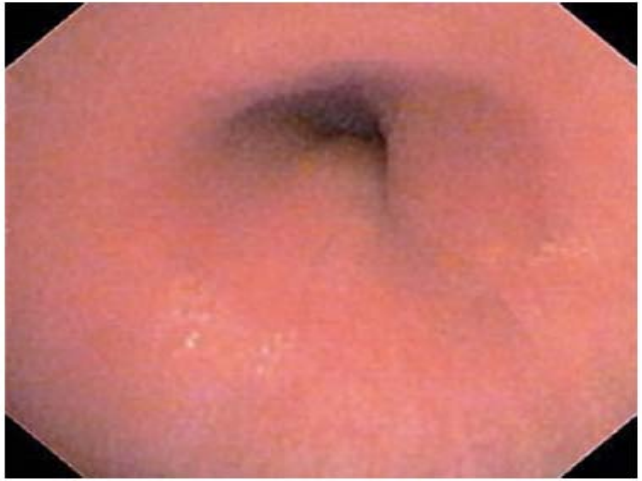


Expiration

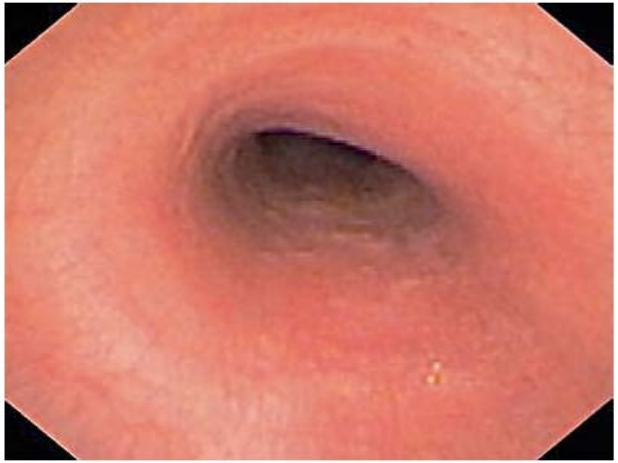
Bronchomalacia

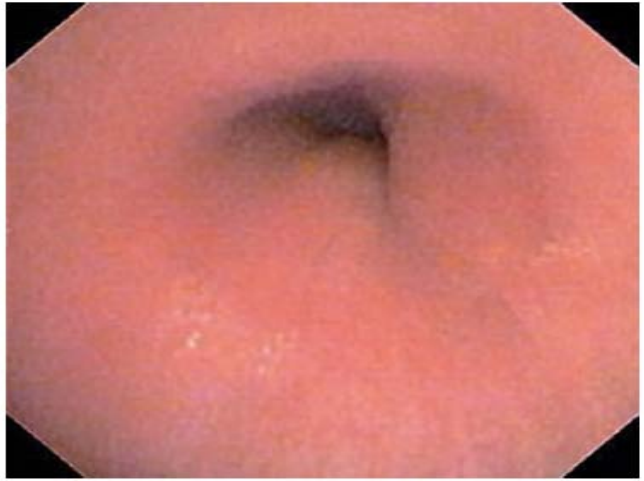


Double aortic arch

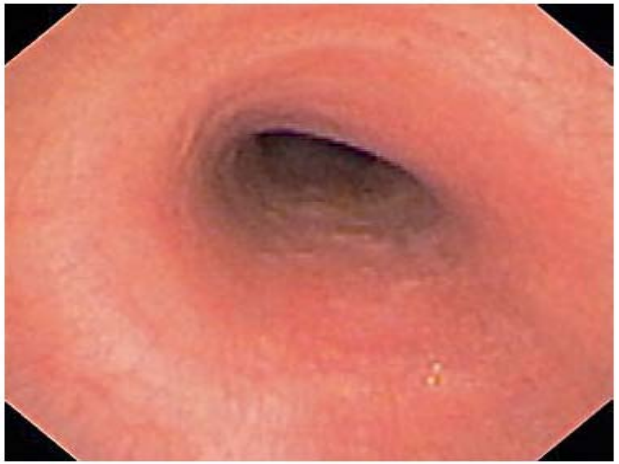


Aberrant innominate artery

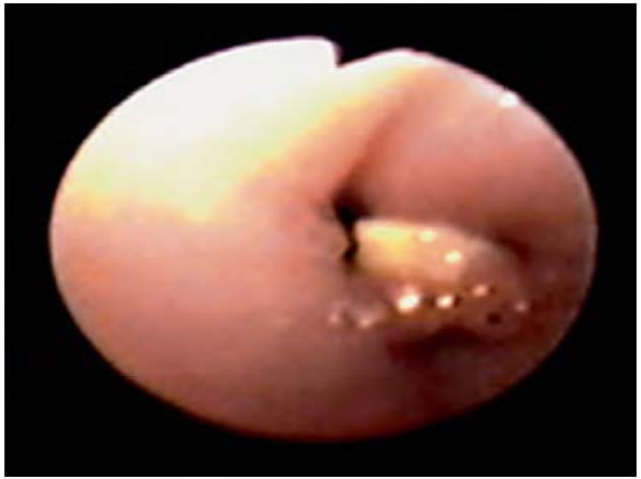




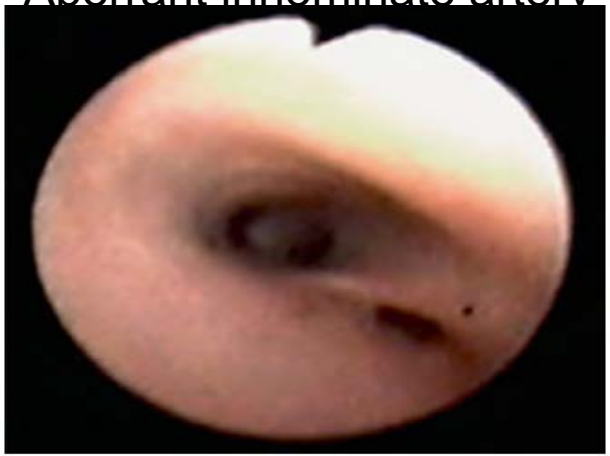
Double aortic arch



Aberrant innominate artery



Foreign body



H-type tracheo-oesophageal fistula

Differential Diagnosis of Wheezing in pre-school children and suggested investigations

Diagnosis	Key clinical features	Investigations
Episodic viral wheeze	Clear history of viral trigger	None required as a routine
Multiple-trigger wheeze	Strong family h/o atopy	Consider Skin prick testing
Bronchiolitis	Coryza, crepts, wheeze	NPA for respiratory viruses
Gastro esophageal reflux	Vomiting ± poor weight gain	pH/Impedance
Foreign body inhalation	History +/-, chronic cough	CXR, Bronchoscopy
Immune deficiency	Severe/Persistent/Unusual/ Recurrent (SPUR) infections	IgG, A, M, E, functional Abs, T&B cells, C3, C4, NBT etc…
Bronchomalacia	Harsh, monophonic wheeze	Flexible bronchoscopy
Cardiac abnormalities	Evidence of heart disease	CXR, ECG, ECHO
Primary Ciliary Dyskinesia	Chronic ENT/chest infections	Ciliary studies
Cystic Fibrosis	Respiratory / GI features	Sweat test, Genetics
Obliterative Bronchiolitis	H/o severe viral LRTI	HRCT – mosaic perfusion

Vocal Cord Dysfunction (VCD)

- First described clinically in1842 - as dysfunction of the laryngeal muscles sometimes seen in hysterical women
- Munchausen's stridor, hysteric croup, emotional laryngeal wheezing
- VCD - refers to inappropriate adduction of the vocal cords during inhalation and sometimes exhalation
- Functional disorder
- Can be difficult to treat as the condition is often underappreciated and misdiagnosed in clinical practice

Vocal Cord Dysfunction

VCD is most likely due to laryngeal hyperresponsiveness, with increased sensitivity of the laryngeal sensory receptors and heightened response of the glottic closure and cough reflexes to a number of triggers [1]

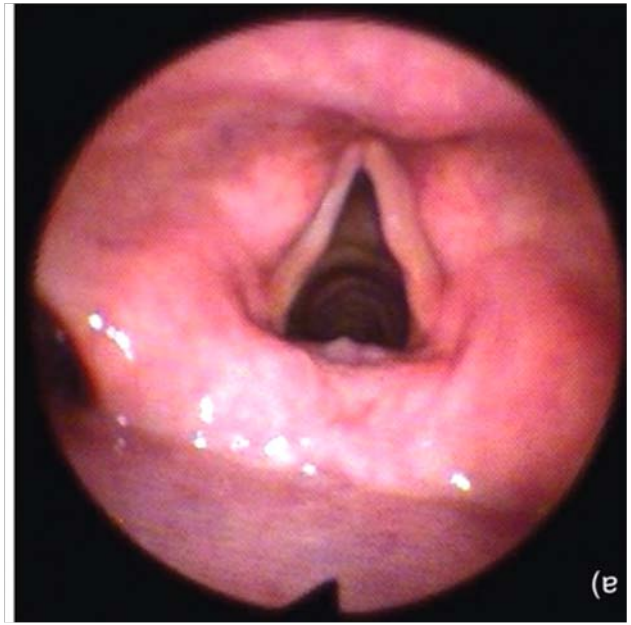
- Exertional triggers (Maximal exercise, athletic competition, routine exercise)
- Psychological triggers – Anxiety, depression etc.
- Irritant triggers – reflux, rhinitis, chemical irritants, olfactory or even visual stimuli

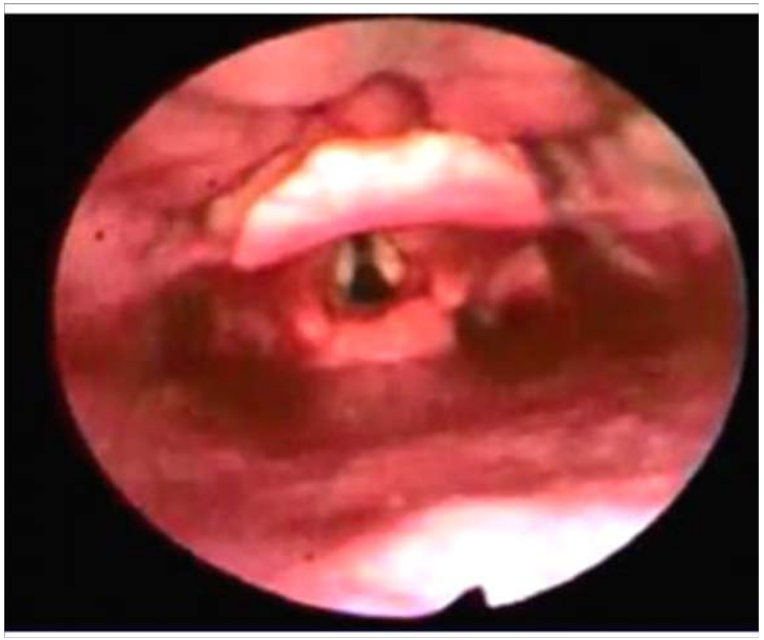
1. Hoyte et al, Immunol Allergy Clin N Am, 2013

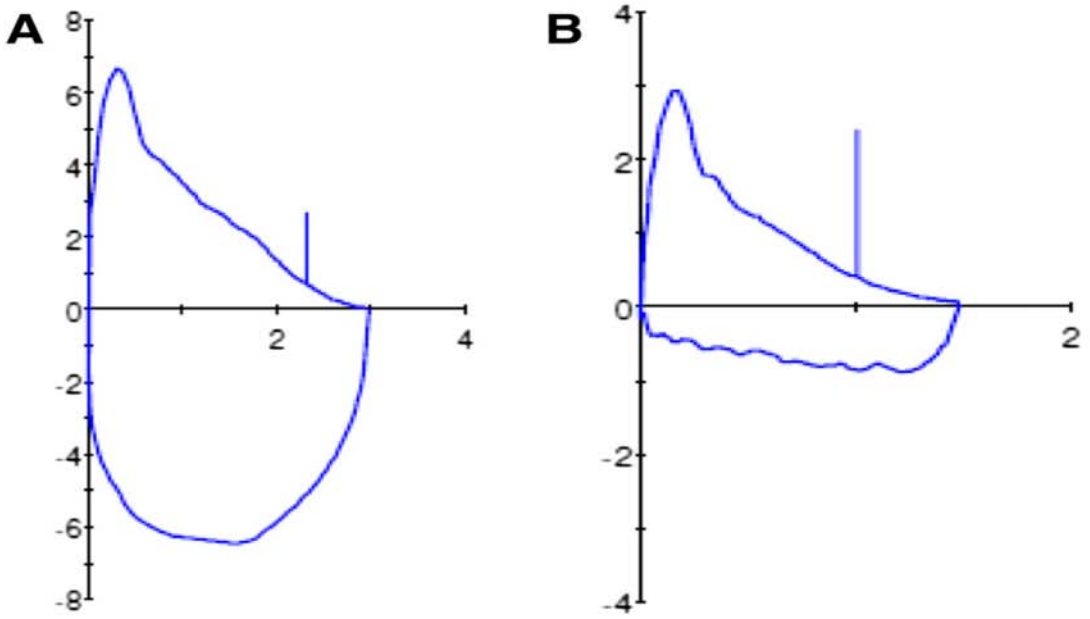
VCD - Diagnoses and Testing

- History
- Examination
- PFT
- Laryngoscopy
  - Sniff, sequential phonation, normal breathing, panting and repetitive breaths
- Bronchial provocation challenge – perform laryngoscopy immediately after a bronchial challenge – Asthma vs VCD or both

VCD - Laryngoscopy



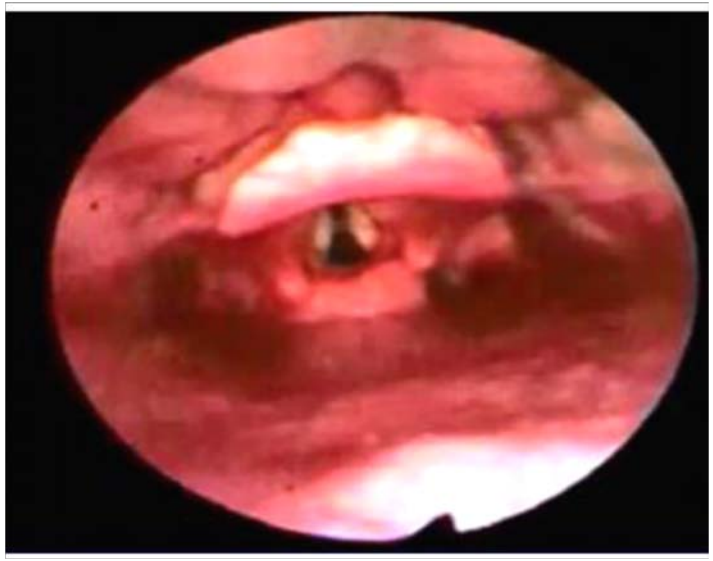




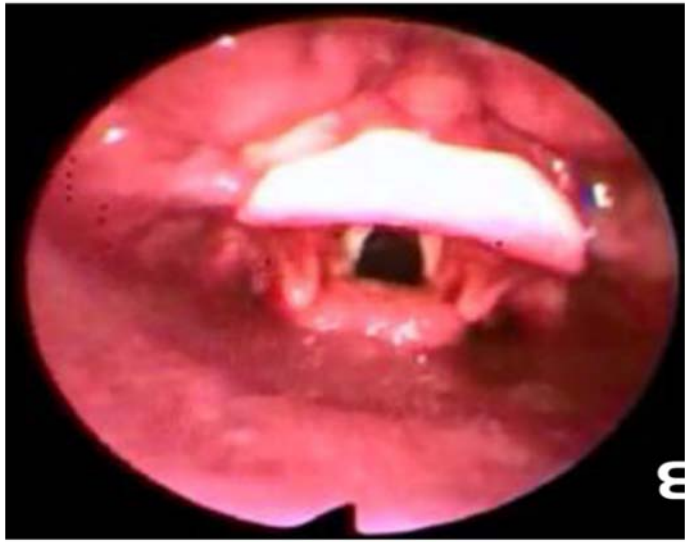
VCD - Management

- MDT management
- Patient education
- Speech therapy & Psychotherapy
    - Most common – long term treatment
    - Breathing techniques (quick-release techniques)

Laryngoscopy



Before Treatment



Following Speech Therapy

Summary

- Careful clinical assessment to rule out alternate diagnosis is important
- Assess and treat co-existing morbidities
- Avoid passive tobacco smoke exposure
- Preschool wheeze - ICS (upto 400 mcg BDP)/ Montelukast trial may be considered

Summary

- Review diagnosis and consider for further investigation if response to Rx is poor
- Once symptoms are resolved, consider step-down +/- trial off ICS
- Monitor growth (linear growth) when on regular ICS
- In the absence of wheeze or dyspnea, very few children with non specific isolated cough have asthma