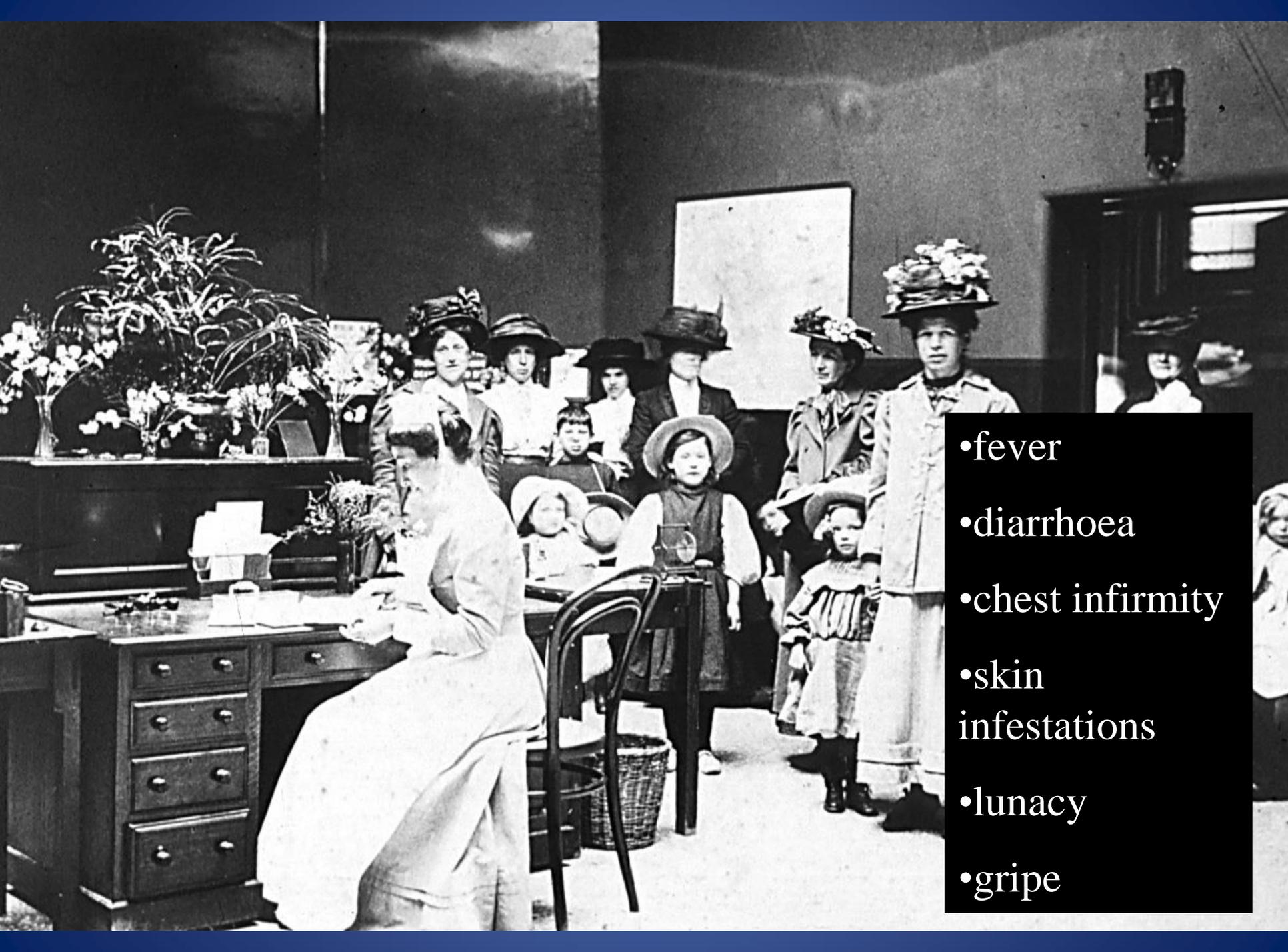


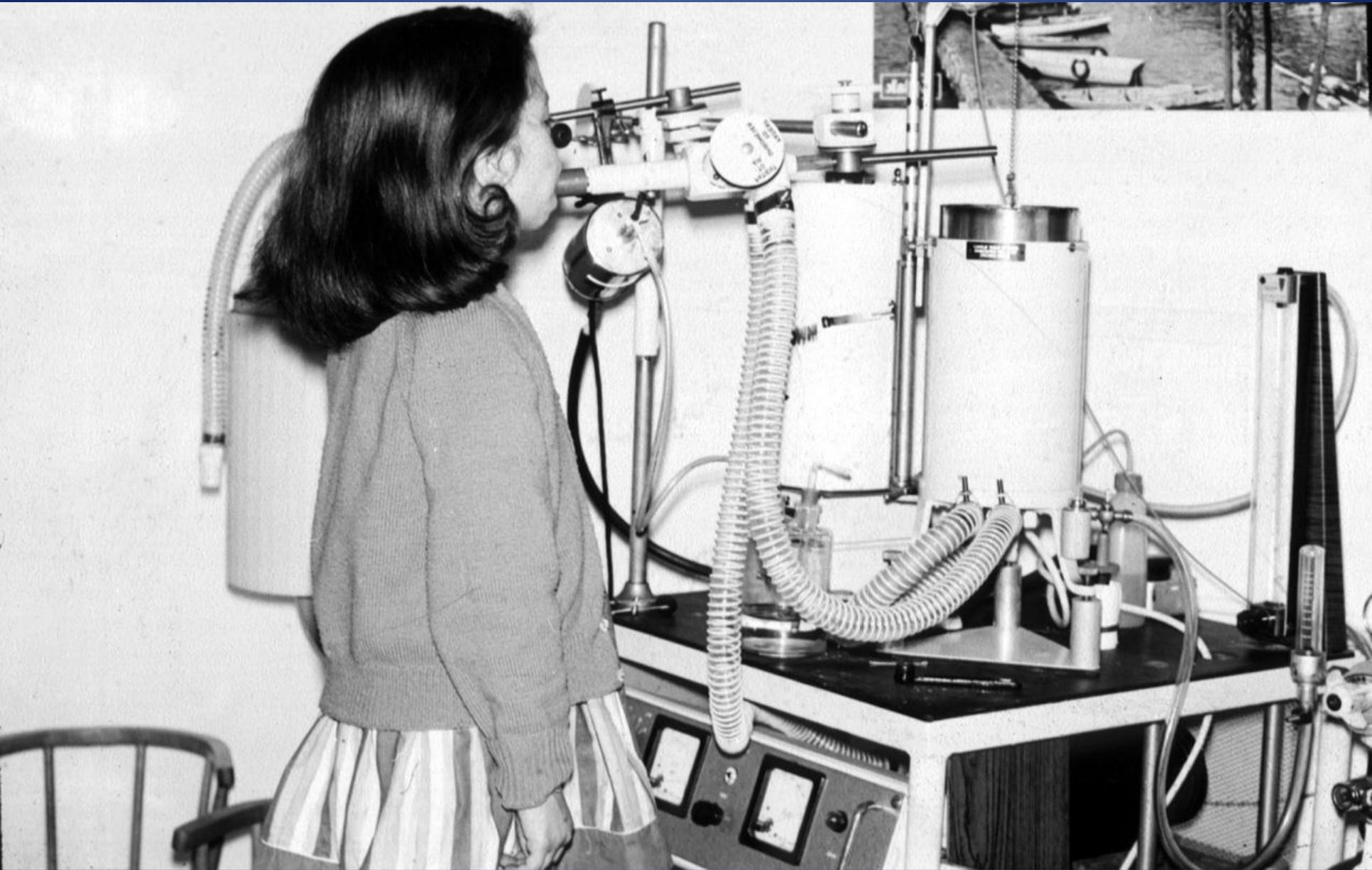
“Difficult” asthma

Evaluation and management

Colin Wallis
Respiratory Paediatrician
Great Ormond Street hospital
London UK



- fever
- diarrhoea
- chest infirmity
- skin infestations
- lunacy
- gripe



“Difficult” asthma

Evaluation and management

- What is asthma?
- What is “difficult” asthma?
- An approach to the difficult asthmatic
- Setting up a difficult asthma service
- Treating beyond the guidelines

There is no absolute definition of paediatric asthma

- Nothing definitive on history
- Nothing definitive on examination
- No definitive blood test
- No definitive physiological test
- Asthma is a clinical impression

Asthma is a reversible inflammatory condition that results in narrowing of the small airways with breathlessness, wheeze and/or cough and responds to treatments traditionally used in asthma in a setting where asthma is more likely and other conditions have been excluded.

A comparison of asthma and love

They both elude accurate definition and have virtually the same symptoms of breathlessness, chest tightness and nocturnal awakenings.....

but asthma lasts longer!

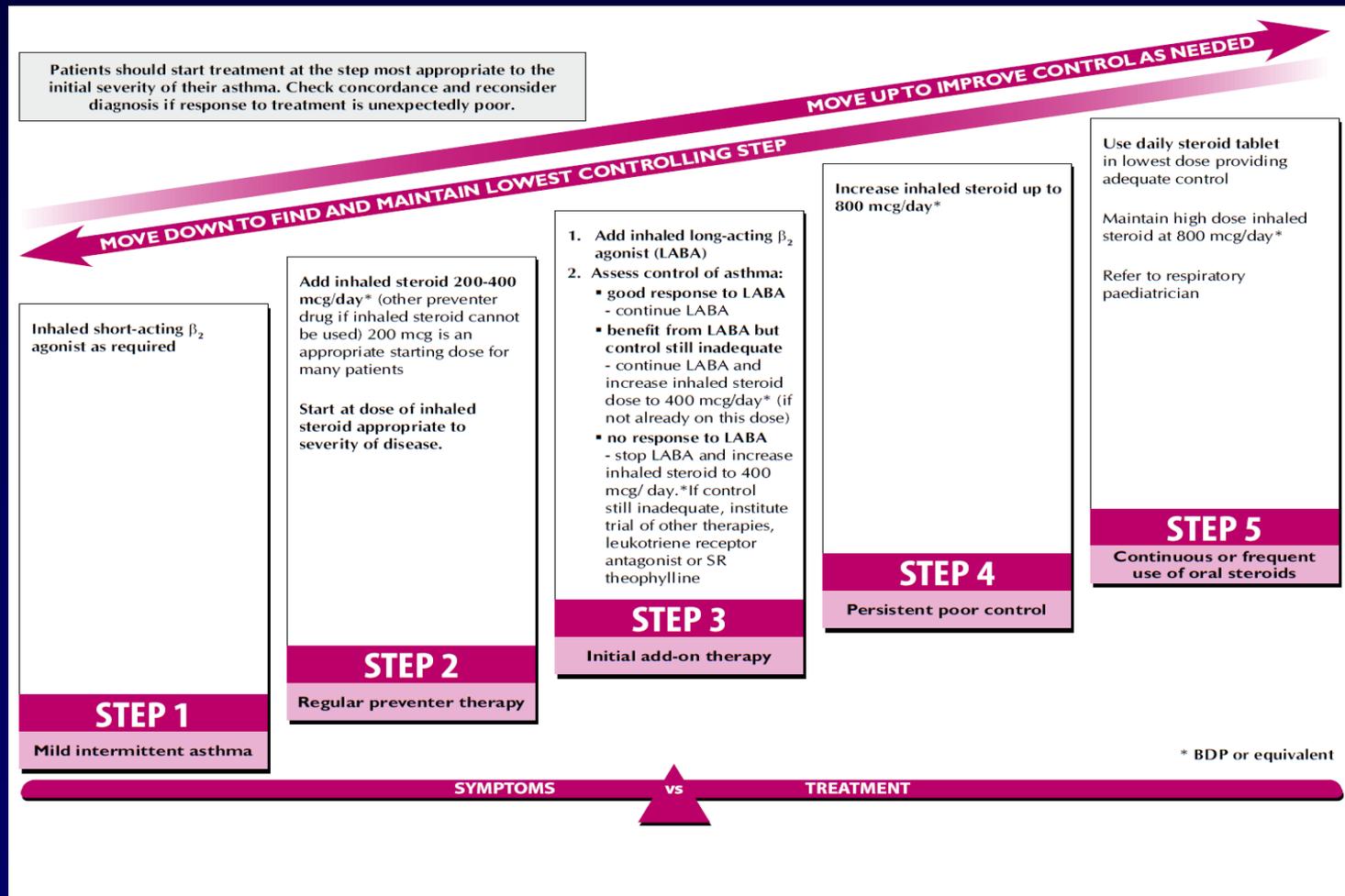
“Difficult” asthma

Evaluation and management

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Definition of difficult asthma or severe problematic asthma

- Continued symptoms despite maximal doses of conventional therapies (BTS steps 4/5)



Definition of severe problematic asthma

- Continued symptoms despite maximal doses of conventional therapies (BTS steps 4/5)
- About 5% of asthmatic patients
- GOSH:
- 5-16 years old
- Asthma with: persistent symptoms (≥ 3 days /week)
 - or
 - frequent exacerbations (≥ 1 /month)
 - or
 - intermittent severe “brittle” attacks
- Despite
 - High dose ICS (800mcg/day bud, 500mcg/day fluticasone)
 - LABA
 - Montelukast
 - Oral steroids

“Difficult” asthma

Evaluation and management

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Severe problematic asthma: difficult or severe?

- Poor adherence
- Behavioural and social issues
- Environmental issues
- A different diagnosis or two diagnoses
- Bad asthma disease
 - Severe allergic response
 - Therapy resistant disease

DIFFICULT ASTHMA:
GETTING THE
BASICS RIGHT
FOR
GOOD OLD FASHIONED
ASTHMA

SEVERE THERAPY
RESISTANT
ASTHMA (STRA)

Difficult asthma protocol

Two stage assessment

- **Stage 1** – detailed multi-disciplinary assessment (why is asthma difficult?)
- **Stage 2** – detailed assessment of pathology & steroid responsiveness (genuine severe therapy resistant asthma)

Difficult asthma protocol

Two stage assessment

- **Stage 1** – detailed multi-disciplinary assessment (why is asthma difficult?)
- **Stage 2** – detailed assessment of pathology & steroid responsiveness (genuine severe therapy resistant asthma)

Stage 1

- Confirm the diagnosis of asthma
- Consider alternative or associated diagnoses
- Assess adherence to treatment
- Look for evidence of environmental factors
- Impact of asthma on daily life

Difficult asthma protocol

Two stage assessment

- **Stage 1** – detailed multi-disciplinary assessment (why is asthma difficult?)
- **Stage 2** – detailed assessment of pathology & steroid responsiveness (genuine severe therapy resistant asthma)

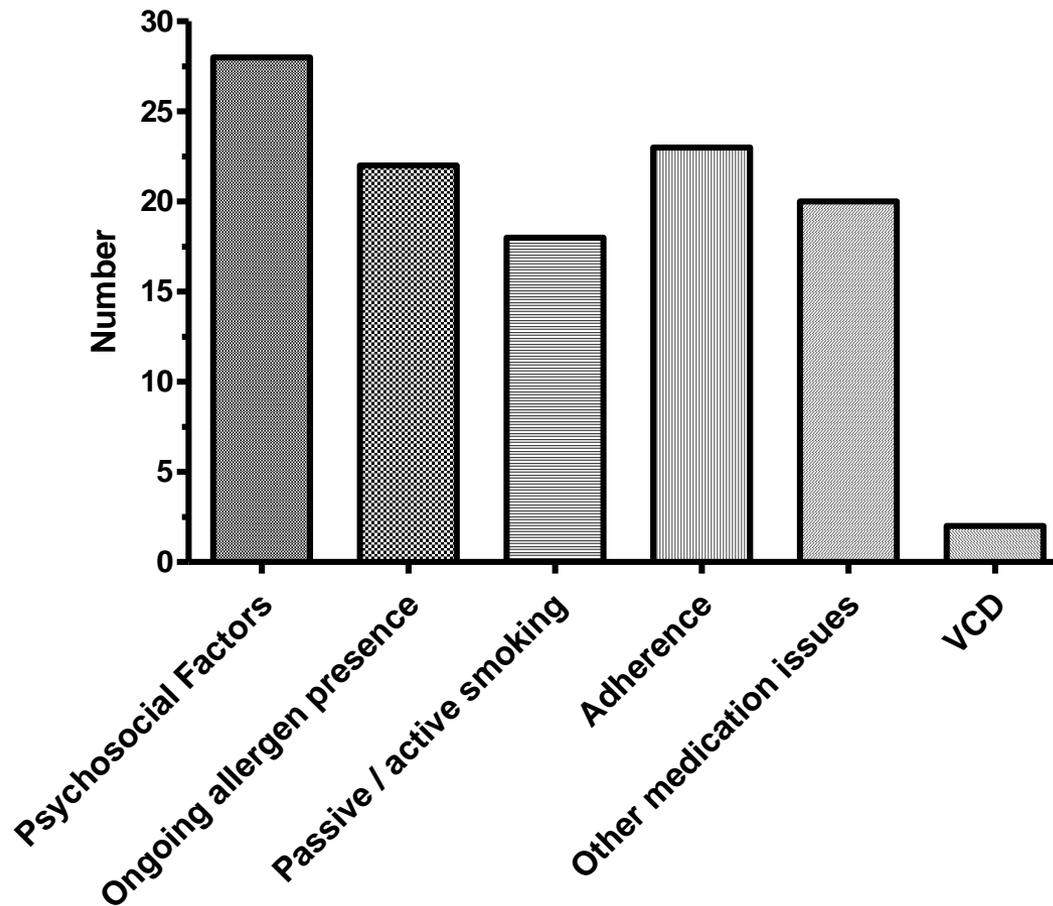
THE HOME VISIT

- Smoke exposure
- Allergen advice (where necessary)
 - Pets
 - Dust
- Check location of medication, expiry dates, appropriate inhaler devices etc
- Observation of child in home environment
- Anxiety levels within the family

Stage 1 results

- Feb 2005 – June 2008 – 71 subjects underwent stage 1 assessments
- 56/71 (79%) – potentially remediable factors identified after stage 1

Reasons for difficult asthma



Alternative or associated diagnoses

- Tracheo / bronchomalacia
- Airway compression (eg vascular ring)
- Inhaled foreign body
- Vocal cord dysfunction
- Bronchiectasis
- Obliterative bronchiolitis
- Gastroesophageal reflux

A careful history:

- Is it really wheeze?
- Upper airway symptoms prominent?
- Symptoms from first day of life
- Sudden onset symptoms
- Chronic moist cough/sputum
- Worse after meals, irritable feeder,
- Other systemic illness
- Continuous, unremitting symptoms
- What happens during sleep?

Alternative & additional diagnoses (9 out of 71)

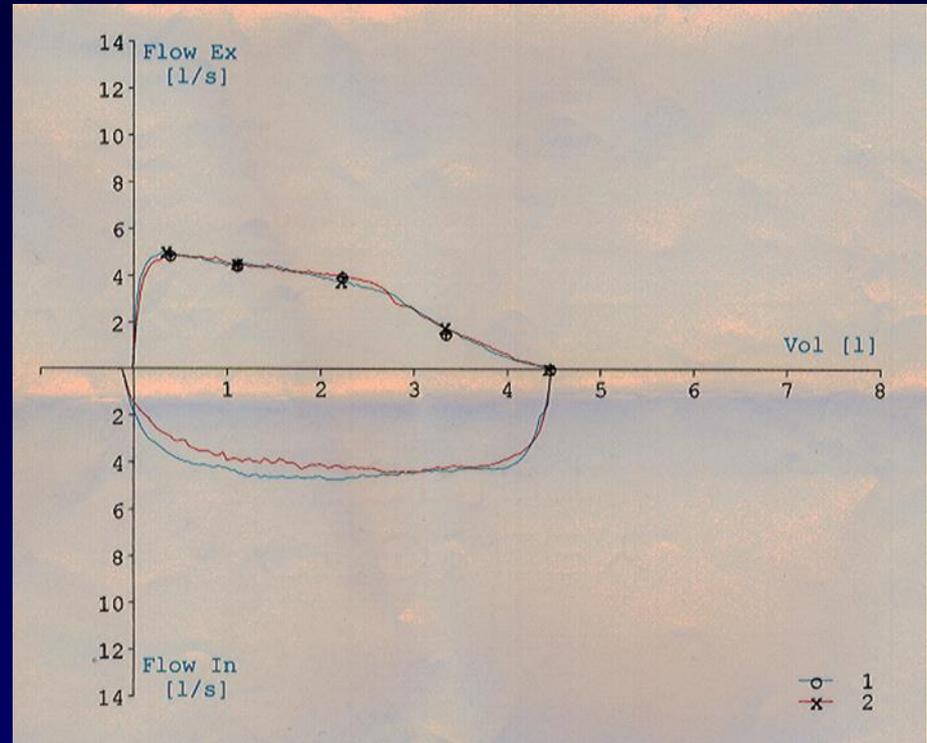
- Additional diagnosis (n=4)
 - Severe gastro-oesophageal reflux and immune abnormality
 - Vocal cord dysfunction
 - Severe gastro-oesophageal reflux alone (n=2)
- Alternative diagnosis (n=5)
 - Vascular ring
 - Primary ciliary dyskinesia
 - Bronchiectasis
 - Sinus disease
 - Job's syndrome

Investigations for alternative diagnoses

- Chest x-ray
- Peak flow / Spirometry
- Assess basic immunity
- pH study
- SALT review
- CT scan
- Bronchoscopy

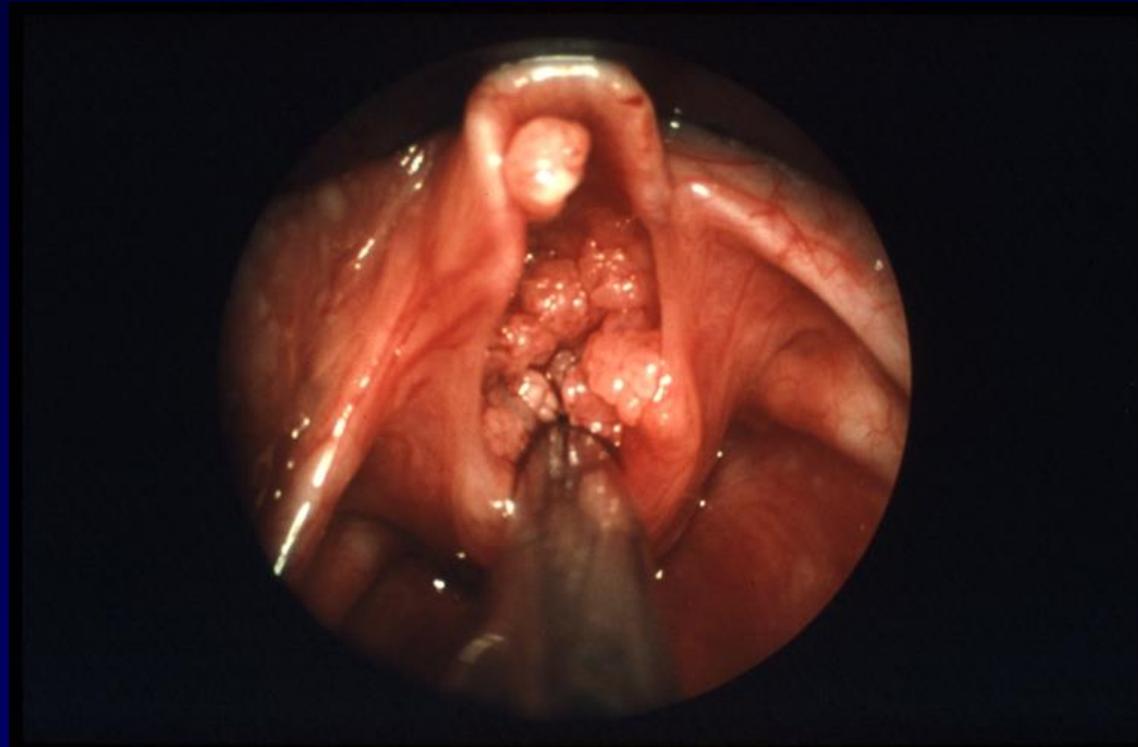
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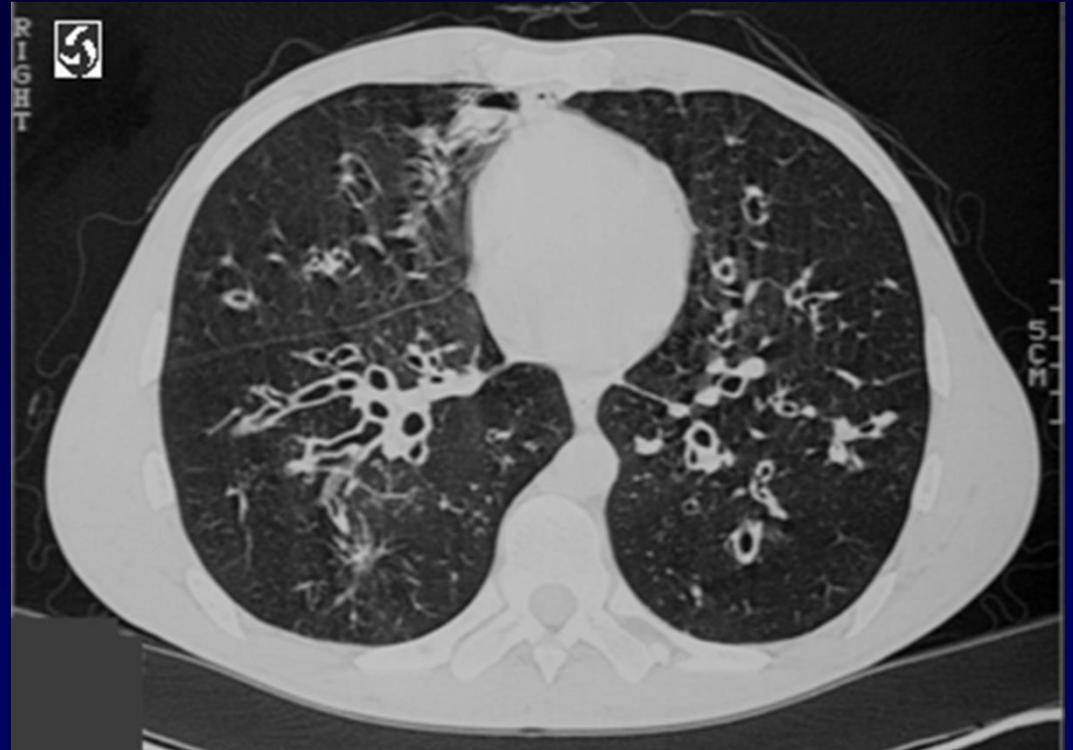


Gastro-oesophageal reflux and pH / impedance study

- Gastro-oesophageal reflux is common in difficult asthma
- Beware the chicken and the egg
- Treatment often has little effect on asthma symptoms
- Hard to identify potential responders
- Consider aspiration “over the top”

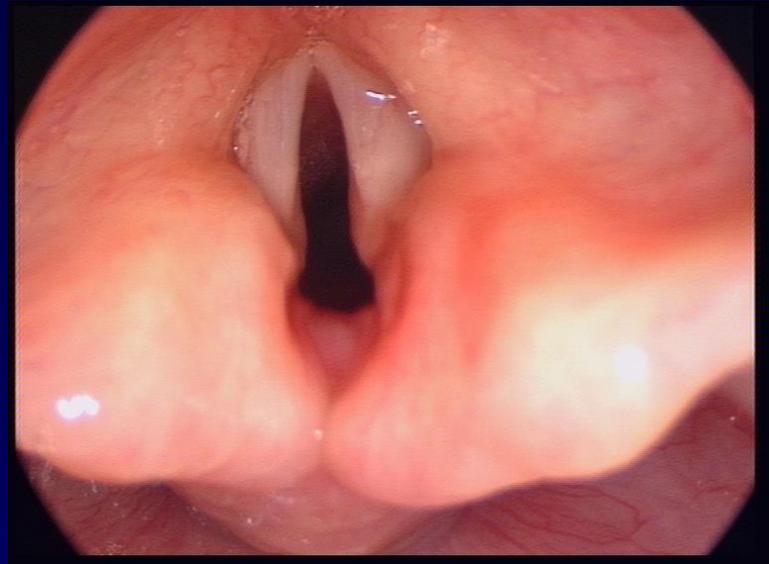
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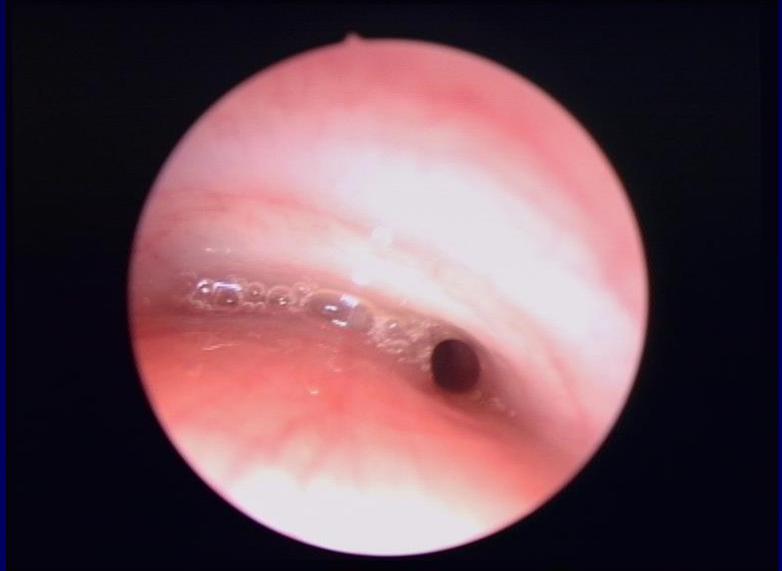
Subglottic stenosis



TRACHEAL CYSTS



HAEMANGIOMA



TRACHEAL MALACIA

“Difficult” asthma

Evaluation and management

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A difficult asthma service

- 2 staged approach
- A team approach
- Facilities for specialist investigations



A difficult asthma service

- 2 staged approach
- **A team approach**
- Facilities for specialist investigations
- Asthma specialists with allergy
- Asthma nurse (with allergy experience)
- Physiotherapist (with knowledge of dysfunctional breathing techniques)
- Speech and language therapy (with interest in swallow and VCD)
- Psychologist
- Social worker
- Pharmacist

Bracken M, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. Arch Dis Child. 2009;94:780–784

A difficult asthma service

- 2 staged approach
 - A team approach
 - Facilities for specialist investigations 
- Assessment of asthma control
 - Assessment of QoL; psychology
 - Adherence checks & technique
 - Lung function
 - Skin prick testing
 - Blood tests (IgE, SpIgE, vit D)
 - Bronchoscopy
 - Reflux studies
 - Imaging
 - Exercise testing

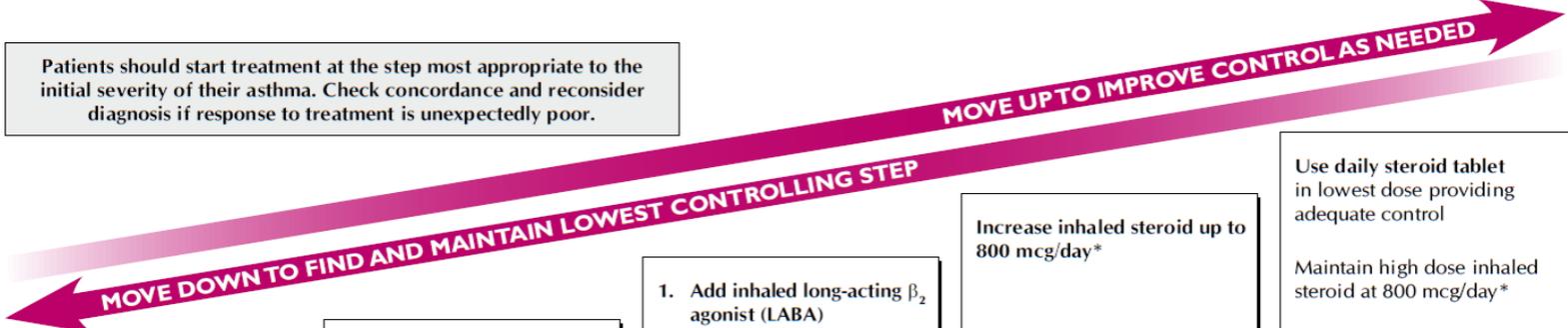
“Difficult” asthma

Evaluation and management

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Severe therapy resistant asthma

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.



Inhaled short-acting β_2 agonist as required

STEP 1

Mild intermittent asthma

Add inhaled steroid 200-400 mcg/day* (other preventer drug if inhaled steroid cannot be used) 200 mcg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

STEP 2

Regular preventer therapy

- Add inhaled long-acting β_2 agonist (LABA)
- Assess control of asthma:
 - good response to LABA - continue LABA
 - benefit from LABA but control still inadequate - continue LABA and increase inhaled steroid dose to 400 mcg/day* (if not already on this dose)
 - no response to LABA - stop LABA and increase inhaled steroid to 400 mcg/day.*If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 3

Initial add-on therapy

Increase inhaled steroid up to 800 mcg/day*

STEP 4

Persistent poor control

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 800 mcg/day*

Refer to respiratory paediatrician

STEP 5

Continuous or frequent use of oral steroids



* BDP or equivalent

A pharmacological approach to severe therapy resistant asthma

- No one size fits all
 - No magic bullet
 - Emergence of novel therapies
 - Different pathological subgroups:
 - Eosinophilic
 - Neutrophilic
 - Individual genetic mutations
 - To beta agonist receptors
 - To steroid non-responders
- Monoclonal anti IgE AB
 - Omalizumab
 - Mepolizumab
 - Oral steroids - I/M steroids
 - Steroid sparing treatments
 - Methotrexate
 - Azathioprine
 - Cyclosporin
 - Novel biologicals
 - Reslizumab (anti IL-5)
 - Dupilumab (anti IL-4alpha)

Current approach to therapy

Severe asthma in children: therapeutic considerations.

Selby, L. Curr Opin Allerg Immunol 2019 Apr;19(2):132-140. 4.

Pathogenesis and prevention strategies of severe asthma exacerbations in children

Cook J. Curr Opin Pulm Med. 2016 Jan;22(1):25-31

Severe therapy resistant asthma in children: translational approaches to uncover sub-phenotypes.

Martin Alonso A, Expert Rev Respir Med. 2017 (11):867-874

Management based on pathophysiological findings

Inflammatory phenotype:

Eosinophilic

Neutrophilic

Non inflammatory phenotype

Treatment determined by:

1. Pattern of inflammation in induced sputum, BAL and biopsy (pre-steroids); FeNO; bloods
2. Response of inflammation to steroid trial
3. Presence of BDR

Eosinophilic inflammation – steroid sensitive

Eosinophilic sputum, BAL or biopsy
Good response to steroid trial



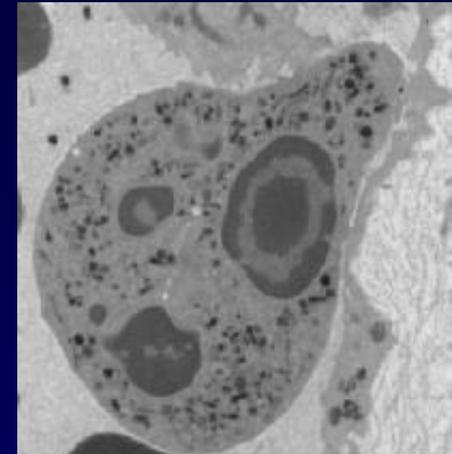
- Give 3-6 month trial of triamcinolone
- Maximise inhaled steroid therapy
(?prn combination therapy)
- Try steroid sparing agents (azathioprine)
- Consider anti-IgE

Monoclonal Anti IgE Ab omalizumab / mepolizumab

- IgE mediated asthma:
 - Better symptom control
 - Reduction in ICS dose
- Current recommendations:
 - ≥ 12 years old
 - Atopic
 - Inadequate control / systemic steroids
 - Associated allergic diseases (eczema, hayfever)
 - Add-on therapy
- Dose determined by baseline IgE & weight
 - Recommended baseline level 30 - 700 IU/ml
 - Approx 25% of DA patients have IgE>700

Neutrophilic inflammation

Neutrophilic sputum, BAL, biopsy



Azithromycin –add on therapy
As a steroid sparing agent

Phenotype switching in children

- 44 children produced >1 sputum
- 27 demonstrated only 1 phenotype or changed between a single inflammatory phenotype and a non-inflammatory phenotype
- 17 children demonstrated more than one inflammatory phenotype:

| | |
|-------------------------------------|---|
| Eosinophilic + neutrophilic | 4 |
| Eosinophilic + mixed | 9 |
| Eosinophilic + neutrophilic + mixed | 4 |

A total of 29 inflammatory phenotype changes were seen

'Non-inflammatory' asthma

Evidence of ongoing response to bronchodilator?

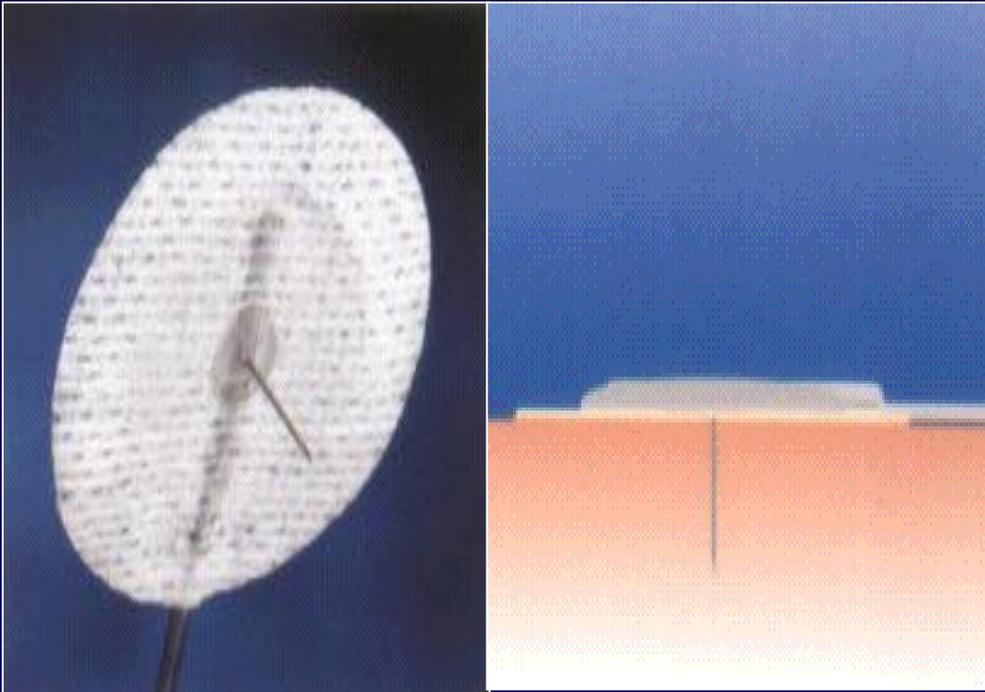
No

Yes

No inflammation
Reduce steroids
Review diagnosis

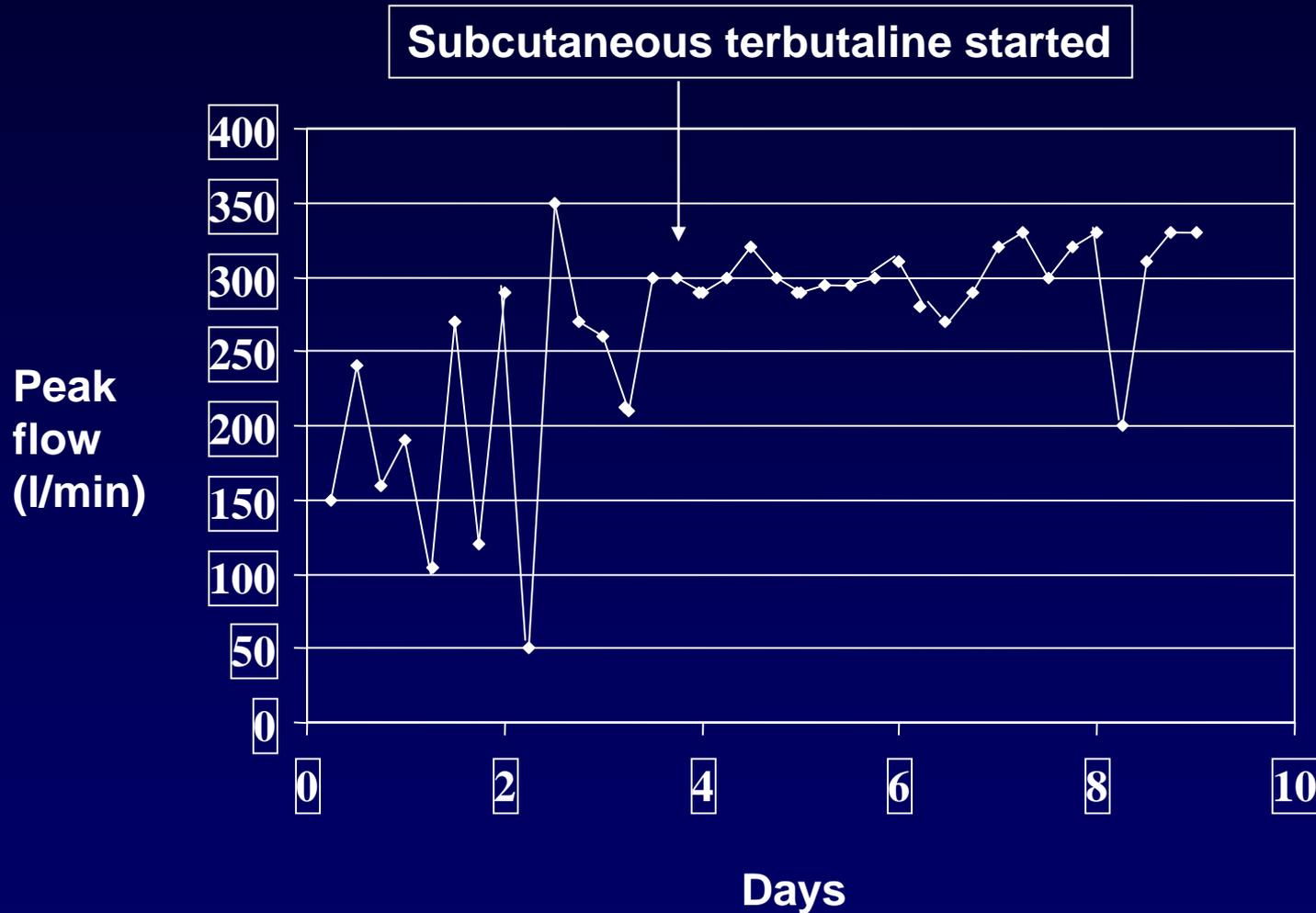
Maximise long acting β 2 agonists
S/c terbutaline

Subcutaneous terbutaline



- Double-blind placebo controlled trial
- 2 doses (2.5 – 7.5mg / 24 hrs)
- Over 2 weeks
- Regular lung function

Effect of subcutaneous terbutaline on peak flow



Genetic variation may result in varied responses to pharmacological and environmental factors

- Skin barrier variation may lead to differential allergen entry – filaggrin gene mutation
- Beta2- receptor variation results in differential response to inhaled beta2-agonists
- Variation in proteins along steroid and leukotriene response pathways and steroid receptors may lead to differential response to inhaled steroids and leukotrienes

Hypothesis

In this genetically selected sub-group of children with asthma carrying the 'faulty' beta2 receptor gene, medicine that **does not act** through beta2 receptor molecule **will work better** than medicine that **acts** through beta2 receptor molecule,

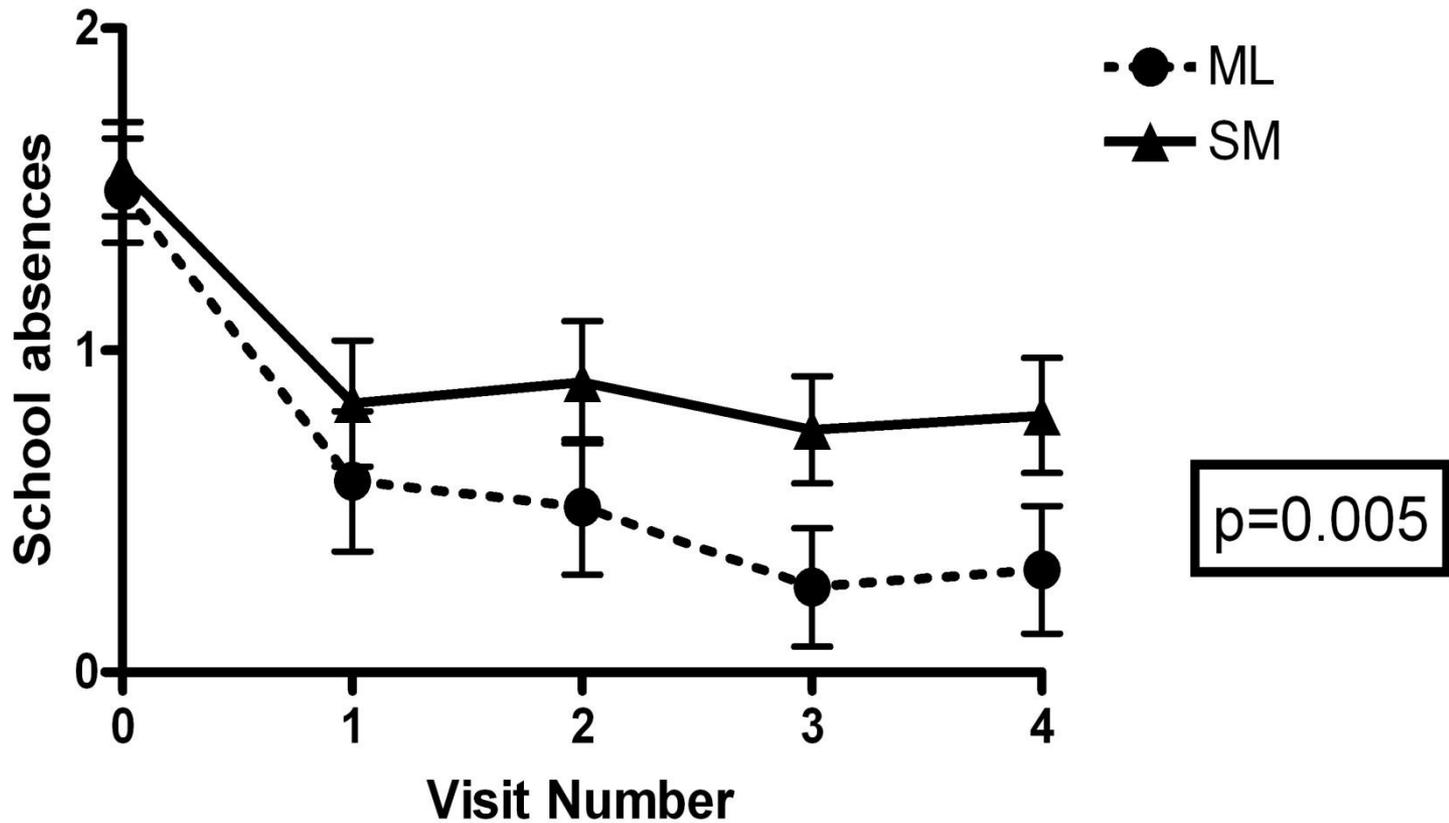
Children with asthma carrying 2 copies of the 'faulty' beta2 receptor gene

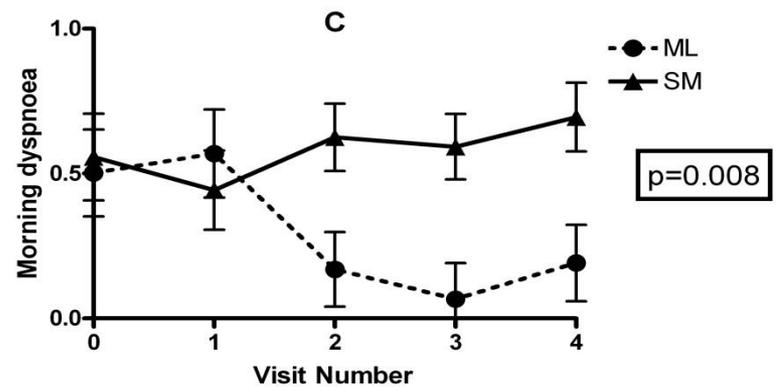
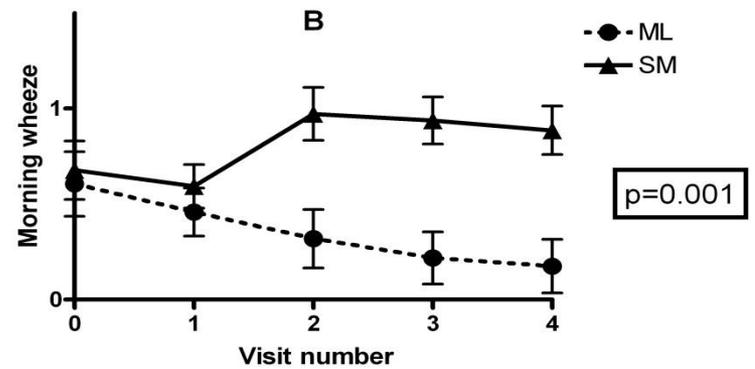
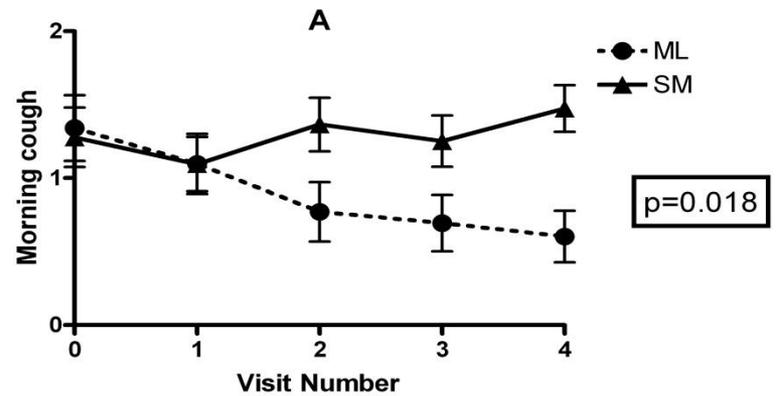
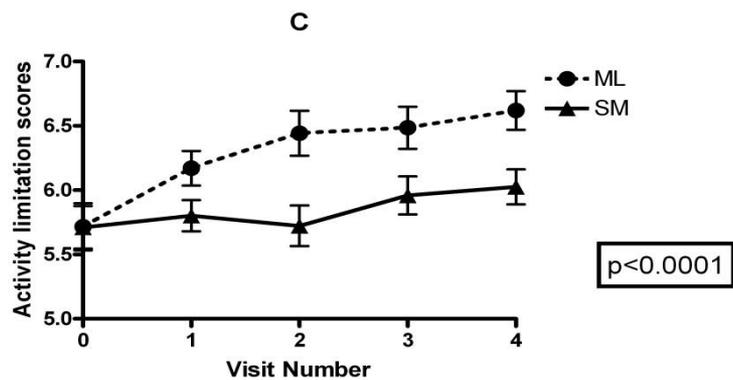
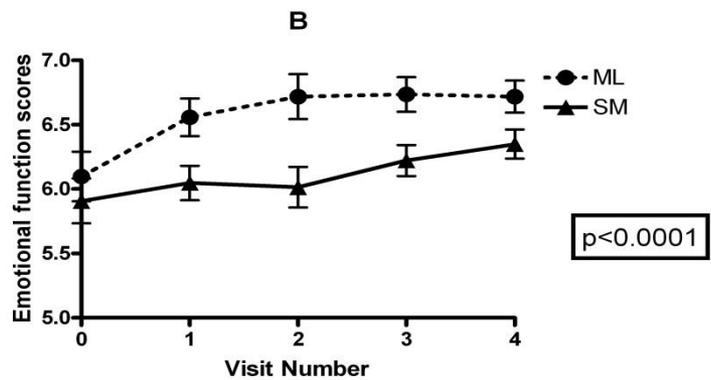
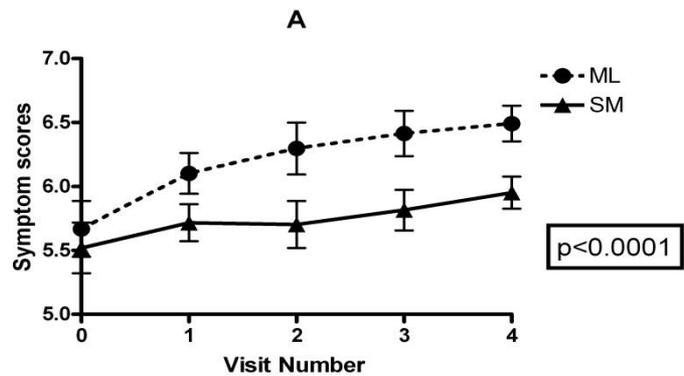
Randomisation

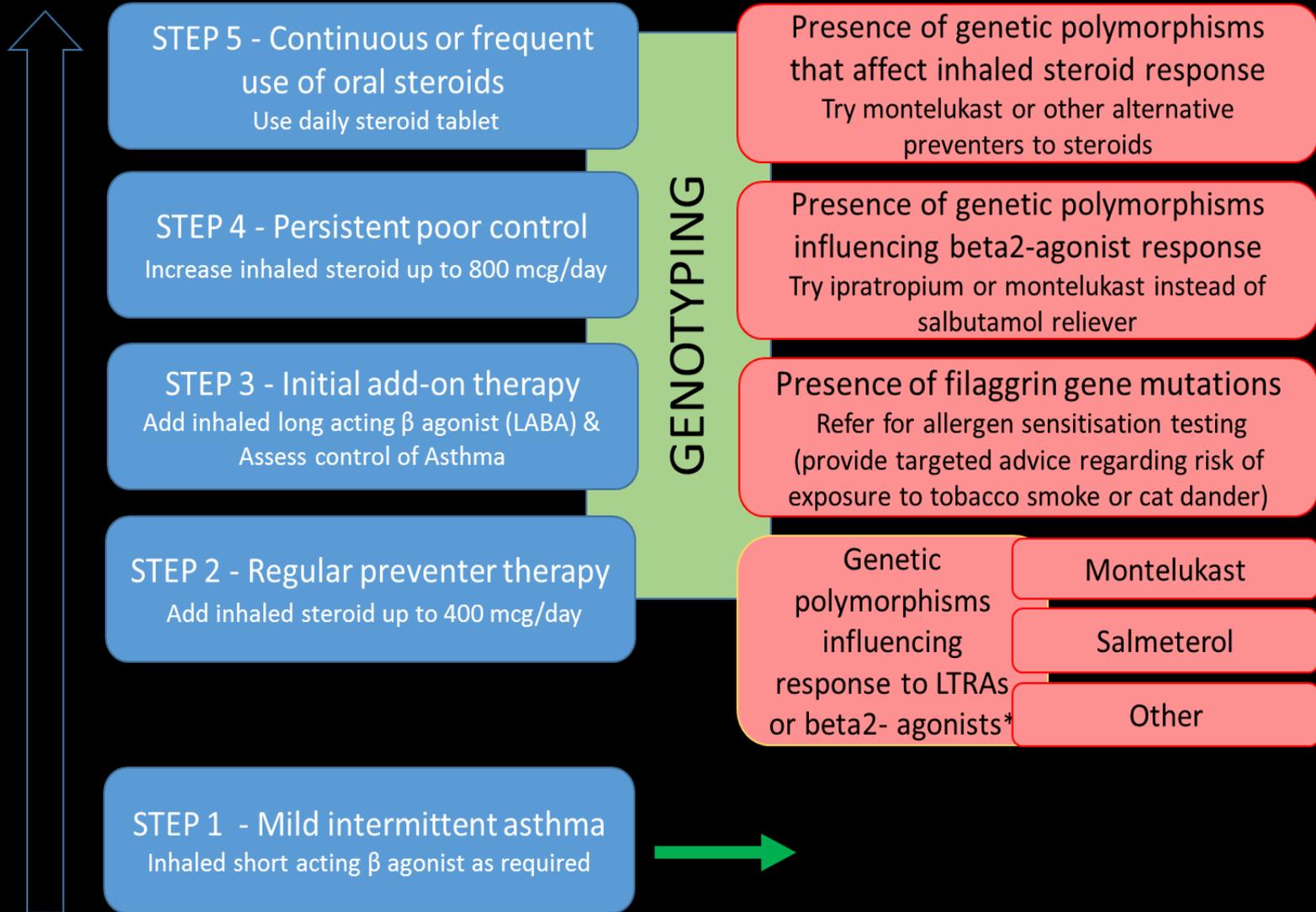
Salmeterol (*medicine that **works** via beta 2 receptor molecule*)

Montelukast (*medicine that **does not** work via beta 2 receptor molecule*)

3 monthly follow-up for total 1 year







Current algorithm versus current algorithm modified by genomics: EU application – outcome awaited

Summary

Severe problematic asthma

- Is this asthma – exclude other diagnoses – asthma plus?
- Why is the asthma difficult – DA or STRA?
- Address adherence and psychological issues early
- Implement targeted non-pharmacological treatments
- Genuine severe therapy resistant asthma is very rare:
 - Use pattern of inflammation and response to steroid trial to aid treatment choice
 - Implement targeted and patient specific pharmacological treatments and monitor for efficacy and side effects
 - The role of gene mutations may play an important future role

Severe asthma in children.
Respirology. 2017 Jul;22(5):886-897.

THE END

