“Difficult” asthma
Evaluation and management

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• 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
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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
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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 multidisciplinary 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

- Psychosocial Factors
- Ongoing allergen presence
- Passive / active smoking
- Adherence
- Other medication issues
- VCD

Number

0
10
20
30

Psychosocial Factors
Ongoing allergen presence
Passive / active smoking
Adherence
Other medication issues
VCD
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
Investigations for alternative diagnoses

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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”
Investigations for alternative diagnoses

- Chest x-ray
- Peak flow / Spirometry
- Assess basic immunity
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Investigations for alternative diagnoses

- Chest x-ray
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TRACHEAL CYSTS

Subglottic stenosis

HAEMANGIOMA

TRACHEAL MALACIA
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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

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
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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.

**STEP 1**
Mild intermittent asthma

**STEP 2**
Initial add-on therapy

**STEP 3**
Persistent poor control

**STEP 4**
Continuous or frequent use of oral steroids

**STEP 5**
Increase inhaled steroid up to 800 mcg/day*

1. Add inhaled long-acting β₂ agonist (LABA)
2. 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

Use daily steroid tablet in lowest dose providing adequate control
Maintain high dose inhaled steroid at 800 mcg/day*
Refer to respiratory paediatrician

* BDP or equivalent

Inhaled short-acting β₂ agonist as required

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.
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
  - Resilizumab (anti IL-5)
  - Dupilumab (anti IL-4alpha)
Current approach to therapy

Severe asthma in children: therapeutic considerations.

Pathogenesis and prevention strategies of severe asthma exacerbations in children

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

No inflammation
Reduce steroids
Review diagnosis

Yes

Maximise long acting β2 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

Subcutaneous terbutaline started

Peak flow (l/min)

Days

Pediatr Pulmonol 2002
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
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

Lipworth BJ, Basu K, Donald H, Tavendale R, Macgregor DF, Ogston SA, Palmer CNA, Mukhopadhyay S. Clinical Science 2013
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Clinical Science 2013
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Clinical Science 2013
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

THE END