

Guidelines for difficult to treat asthma in children

Definition: Children with asthma who do not have adequate control of symptoms, despite therapy with more than 800 micrograms/day of inhaled beclometasone or equivalent (e.g. 500 micrograms per day of fluticasone). These children are on therapy above Step 4 of the 2003 BTS/SIGN guidelines¹.

They are designed to be used in the Bristol Children's Hospital, but they will be of use to other centres in the region, particularly for initial investigation & management.

1. Confirm diagnosis

- Ensure careful detailed history has been taken and full examination performed.
- Spirometry. Perform full inspiratory and expiratory loops if possible. The expiratory loop may show small-medium airways obstruction, but it may also be normal in children with difficult asthma who do not yet have fixed airway remodelling. Change in spirometry may occur in some children simply on repeated expiratory forced manoeuvres. Spirometry may also point to other pathology, e.g. large airway pathology.
- Perform reversibility test: calculate difference between FEV₁ pre and post 400micrograms salbutamol via large volume spacer. An increase of 12% is significant.
- A peak flow diary may be useful in some children to show trends.
- Ensure that trials of appropriate therapies have already been tried, e.g. leukotriene receptor antagonist (montelukast), long acting beta agonist (salmeterol or formoterol).
- If not already done, switch separate inhalers to a combination device, e.g. Seretide or Symbicort. Consider use of Symbicort as a reliever device if appropriate^{2,3}.
- Measure exhaled Nitric Oxide (eNO). This can be measured by the BRI Pulmonary function testing (PFT) lab or by us once we have our own equipment. A raised eNO (>20 ppb) is associated with airway inflammation in asthma, and it usually falls if a child is taking inhaled corticosteroids.
- Consider arranging induced sputum examination.
- Sometimes arranging an admission for a few days is useful to observe symptoms, assess compliance in hospital, and record serial spirometry.
- Establish response to oral steroid therapy (or to depot steroid – see 2. below). Consider the use of long term low dose (preferably alternate day) steroid therapy.
- Specific written advice about steroid replacement in the event of a severe intercurrent illness should be part of the management plan for children treated with ≥800micrograms per day of BDP or equivalent. Consider requesting a Synacthen test if high dose inhaled corticosteroids are being used.

2. Reasons for treatment failure

- Inappropriate delivery devices: assess technique and modify device use / choice if necessary.
- Poor adherence: ask for their perception of compliance, quantify number & type of prescriptions, concentrate on education, use adherence chart. Consider a trial of intramuscular triamcinolone (80mg as a single dose, 40mg in <5 yrs)⁴.

- Environmental factors: identify environmental allergens and quantify allergy using skin prick or RAST testing. Suggest allergen avoidance or removal strategies; provide opportunity and help for smoking cessation (patients and family).
- Psychosocial problems: attempt to identify factors, refer to Deb Marriage for CBT trial if appropriate, consider referral to psychology service.

3. Consider alternative diagnoses or possible precipitating factors

- Cystic fibrosis
- Primary ciliary dyskinesia
- Vocal cord dysfunction
- Obliterative bronchiolitis
- Bronchiectasis
- Inhaled foreign body
- Vascular ring / tracheobronchomalacia
- Gastro-oesophageal reflux
- Recurrent aspiration
- Immunodeficiency
- Congenital lung abnormalities
- Congenital heart disease

4. Consider the following investigations

- CXR
- CT thorax (e.g. if interstitial lung disease or obliterative bronchiolitis suspected)
- Total IgE, specific IgE, skin prick testing
- Immune function: IgG, IgA, IgM; (also consider as appropriate: IgG subclasses, complement concentrations, neutrophil function, antibody response (against tetanus, Hib, Pneumococcus))
- Sweat test
- Barium swallow
- pH study
- Nasal brushing for ciliary beat frequency / ultra-structure
- Flexible bronchoscopy
- Micro-laryngoscopy
- Echocardiography

A summary sheet for these investigations is attached as Appendix 1.

Previously, we performed flexible bronchoscopy and endobronchial biopsy to look for features of airway wall inflammation or remodelling (sometimes after high dose steroid therapy). However, on the current published evidence and on a recent audit of our own practice, this does not appear to be very useful in distinguishing phenotypes or in guiding therapy. In some cases, flexible bronchoscopy is still indicated, but not to gain endobronchial tissue alone. This may change if new evidence emerges.

5. Consider alternative anti-inflammatory therapy

If the suggestions as highlighted above have not improved asthma control, then we would consider using an alternative anti-inflammatory agent. We currently use (ciclosporin), with careful monitoring of its efficacy, drug levels, and toxicity. It has however, not been subject to a randomized trial in children with asthma. We had previously requested a GFR before ciclosporin initiation but we stopped doing this in 2006. We aim for trough (approximately 12 hour) levels of 70-120 micrograms/l. Alternative therapies are azothioprine, azithromycin, and omalizumab (see separate guideline).

- Discuss with family potential benefits of an alternative agent, and possible adverse effects of ciclosporin (nausea, headache, renal toxicity, increased hair growth, gum inflammation, hypertension, tremor – however these should be unusual at the lower serum levels that we aim for).
- Consider stopping azithromycin (it may increase serum level of ciclosporin).
- Start ciclosporin at 2.5mg / kg twice per day.
- Warn that it should not be taken with grapefruit or grapefruit juice.
- Arrange 1st trough level after 1 week and thereafter as on chart below.
- Book patient onto CIU for their blood tests on Wednesdays at 9am so that they can then come to the respiratory clinic for spirometry and review. Ensure OPA is also made. **Make sure that they have taken ciclosporin the previous evening (ideally at 9pm), but not that morning.**
- Give forms to CIU for ciclosporin level (record dose and timing), U&E, LFTs.
- Record the ciclosporin level in the clinic letter and on the table below.
- Adjust the ciclosporin dose if necessary; this may involve readjusting the monitoring schedule.
- We suggest that the initial ciclosporin monitoring is performed at BCH – once stable this can be done in conjunction with the family's local hospital if appropriate.
- If possible, slowly reduce long term steroids once ciclosporin therapy is established. You may need to request a Synacthen test once oral steroids are reduced and patients may need hydrocortisone therapy once steroids are withdrawn (in conjunction with advice from endocrinology).

6. Subcutaneous continuous bronchodilator therapy

If alternative anti-inflammatory agent treatment is unsuccessful, consider continuous subcutaneous infusion of terbutaline⁵. This often improves symptom control but has less effect upon lung function.

- Discuss with family potential benefits and possible adverse effects of therapy (tremor, headache, bruising or infection of infusion site, inconvenience of carrying device around, need to change needle site every 2-3 days). Ensure that family are aware of the need to start therapy with a Graseby syringe driver before changing to a pressure infusor device if funding is obtained from the PCT. This may take up to 3 months.
- Ask Respiratory Nurses to arrange a 4 day admission to commence therapy.
- Usual starting dose is between 2 and 3mg via a Green 24hr Graseby syringe driver and Thalaset needle, increased daily according to Terbutaline infusion table until symptom improvement is achieved.
- Parent must be assessed as competent to draw up, insert and remove infusion before discharge home.
- Follow up support is provided by the respiratory specialist nursing team.

References

1. Anon. British guideline on the management of asthma. *Thorax* 2003;58 Suppl 1:i1-94.
2. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekstrom T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-136.
3. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744-753.
4. Panickar JR, Kenia P, Silverman M, Grigg J. Intramuscular triamcinolone for difficult asthma. *Pediatr Pulmonol* 2005;39:421-425.
5. Payne DN, Balfour-Lynn IM, Biggart EA, Bush A, Rosenthal M. Subcutaneous terbutaline in children with chronic severe asthma. *Pediatr Pulmonol* 2002;33:356-361.

Ciclosporin monitoring chart

Patient Name

Patient Number

	Week 1 Date:	Week 2 Date:	Week 4 Date:	Week 6 Date:	Week 10 Date:	Week 14 Date:	Week 18 Date:	Week 26 Date:	Week 34 Date	
Ciclosporin Dose (mg) (Record change)										
Weight (kg)										
Blood Pressure										
Spirometry FEV ₁ /FVC										
Ciclosporin trough level (Aim 70-120 micrograms/l)										
K ⁺										
Urea										
Creatinine										
LFTs (?normal)										

Ciclosporin Dose (mg) (Record change)										
Weight (kg)										
Blood Pressure										
Spirometry FEV ₁ /FVC										
ciclosporin trough level (Aim 70-120 micrograms/l)										
K ⁺										
Urea										
Creatinine										
LFTs (?normal)										

Appendix 1 Summary of investigations

Patient Name

Patient Number

Investigation	Date	Result
Latest CXR		
CT thorax		
IgE		
Specific IgE		
Skin prick testing		
Ig G, A, M		
IgG subclasses		
Complement levels		
Neutrophil function		
Antibody responses		
Sweat test		
Barium swallow		
pH study		
Nasal ciliary brushing		
Flexible bronchoscopy		
Micro laryngoscopy		
Echocardiography		
Induced sputum		
(Endobronchial biopsy)		