Treatment Options for Problematic Severe Asthma: Beyond the Guidelines

Dr Louise Fleming
Clinical Senior Lecturer and Paediatric respiratory Consultant
Problematic Severe Asthma

• Account for 5 – 10% of the asthmatic population

• Consume a disproportionate amount of resources

• Highest morbidity

• What is problematic severe asthma?
Features of Problematic Asthma

Level of treatment
- High dose ICS
- Add on therapies

Control
- Daily symptoms
- Nocturnal symptoms
- SABA use

Lung Function
- Low FEV$_1$
- Bronchodilator response

Exacerbations
- Courses of OCS
- Hospital admissions
- PICU admissions

Quality of life
- Ability to participate in desired activities
- Side effects
- Time off school (work)
Problematic Severe Asthma
High dose treatment (Step 4/5 BTS guidelines or higher
AND
poorly controlled asthma
AND / OR
frequent exacerbations

ADDRESS THE BASICS OF ASTHMA MANAGEMENT

Poor control due to modifiable factors

Ongoing poorly controlled symptoms despite attention to modifiable factors

“Difficult Asthma”

“Severe Therapy Resistant Asthma”

RBH Paediatric DA Protocol

ERS Taskforce on Difficult Asthma: an integrated approach is needed for this complex group (ERJ, 1999)

**Stage 1**
- Confirm diagnosis
- Investigation of additional diagnoses
  - Spirometry and BDR
  - Measurement of inflammation
  - Allergy testing (SPTs)
  - Assessment of adherence
  - Psychosocial questionnaire
  - Home visit

**Identify contributing factors**

**Interventions recommended**

- Ongoing poor control
- Control improved

**Stages 2 and 3**
Basics of Asthma Management

- Adherence
- Allergens
- Smoking
- Psychosocial

Bracken, Arch Dis Child. 2009;90:780-784
Adherence

• Major obstacle to effective management
• Biggest single reason treatment fails
• Reasons for non-adherence / barriers to adherence
  – Lack of understanding of correct usage
  – Regime complexity
  – Forgetfulness, chaotic lifestyle
  – Supervision
  – Patient beliefs, perceived immediate gratification
  – Concerns regarding side effects
  – Visibility

WHO 2003; Bosworth 2006
Assessment of Adherence

• Ask the patient / parent
• Doctor assessment
• Prescription checking
• Drug levels
• Presence of medications in the home
• Electronic monitoring devices

2/3 collect <80% of intended prescriptions
Which Device?

- MDI plus spacer with mask
- MDI plus spacer with mouthpiece
- Breath actuated device
  - Dry powder
  - Aerosol

If a LABA is prescribed always use a combination inhaler
Asthma Plan

- Asthma plan reviewed at each clinic appointment
- NICE Quality Standard

How to use your inhaler

**Spacer device with mouth piece**
1. Remove Inhaler cap, shake and attach it to the end of the spacer
2. Place lips around mouthpiece
3. Press down on the inhaler once
4. Breathe slowly, 5 – 10 times
5. Repeat above steps for every puff you need to take further doses
6. Wash your spacer regularly in warm soapy water and allow to air dry (do not put in the dishwasher)

**Turbohaler**
1. Unscrew and lift off cover
2. Hold Turbohaler upright and twist backwards and forwards until you hear a click
3. Breathe out gently
4. Place mouthpiece gently between teeth and breathe in deeply
5. Hold breath for 10 seconds before slowly breathing out
6. Repeat steps 2 – 5 for further doses

**Accuhaler**
1. Slide the outer case open until it clicks
2. Hold the mouthpiece towards you
3. Slide lever away from you until it clicks
4. Breathe out gently
5. Breathe in deeply through Accuhaler
6. Hold breath for 10 seconds before slowly breathing out
7. Close Accuhaler by sliding the outer case back towards you before taking further doses

Where can I find out more?
You can call one of the respiratory nurses at the Royal Brompton Hospital for advice. We are not always in the office but you can leave a message on our answer phone. If you need urgent medical advice please call NHS Direct (111) or in an emergency call an ambulance (999).

Respiratory Nursing Team at the Royal Brompton Hospital
020 7355 8714
Email: paednursespc@rbht.nhs.uk

Asthma UK
Asthma UK is dedicated to improving the health and well-being of the 5.4 million people in the UK with asthma including 1.1 million children.
Asthma UK Advice line: 0800 121 62 44
www.asthma.org.uk or www.littleasthma.org.uk

Information about inhalers:
- **Reliever inhalers:** These are blue (Ventolin and Bricanyl) and work by relaxing the muscles in the airways which opens them up relieving symptoms. They start to work within a few minutes of taking them.
- **Preventer inhalers:** These are usually brown (eg Clenil) or orange (eg Flectotide). They contain small amounts of steroid which prevents asthma symptoms. They must be taken every day.
- **Combination inhalers:** These are usually red (Symbicort) or purple (Seretide) and contain an inhaled steroid and a long acting reliever medication. They must be taken every day.

Unless your child has been given a dry powder device (Turbohaler, Accuhaler or Easybreathe) they should always use a spacer device.

Spacer devices:
- Make the inhaler easier and more efficient to use
- Increases the amount of medication that gets into the lungs
- Reduce the side effects as more medication goes directly to the lungs
Allergens

Assessment
• History
• SPTs +/- specific IgEs
• Home visit

RBH Cohort
• 80% sensitised to at least one aeroallergen
• 41% pet owners
• Half +ve SPT to own pet
• 33% no HDM avoidance measures
• 43% some avoidance measures
Smoking

- Environmental tobacco smoke (ETS) is linked with impaired lung function and worsening of asthma
- Increased bronchial hyper-reactivity
- Heightened sensitisation to allergens
- Irritant effect
- Increased steroid resistance
- 9,500 hospital admissions per year due to exposure to ETS

Chan-Yeung, Respirology 2003;8:131-9
Interventions

- Smoking cessation advice given
- Public health interventions
- Evidence that the ban on smoking in public places has led to improved respiratory health
Common Psychological Issues

• Anxiety
  – Fear of needles, anxiety about death, anxiety about school issues e.g. bullying, missing school, fear of exercise induced symptoms

• Low mood
  – Feeling different, unable to do the activities their peers are doing

• Adherence
  – Cost/benefit of medication, anxiety about side effects,

• Family support
Psychosocial Issues

Worsening of asthma symptoms

Asthma → Stress / anxiety / depression

Social factors

Psychological manifestations

Panic attacks / disordered breathing

1 Sandberg Lancet 2000;368:982-987
2 Chen JACI 2006;117:1014-1020
3 Roy-Byrne Lancet 2006;368:1023-1032
4 Richardson Pediatrics 2006;118:1042-1051
Safeguarding

• Neglect
  – Poor adherence
  – Inappropriate environment

• Exaggerated or fabricated symptoms
  – Secondary gain
  – Fabricated and induced illness
  – Deliberately withholding treatment

• Place of safety
Basics of Asthma Management

- 79% potentially modifiable factors
- 48% medication issues
- 55% no further investigations or escalation of treatment

Bracken, Arch Dis Child 2009 October;94(10):780-4
Stage 1 Outcomes

A. DA - FEV₁ % predicted

B. STRA - FEV₁ % predicted

C. DA - Daily ICS dose

D. STRA - Daily ICS dose

Sharples, ERJ 2012:40:264-278
Stage 1 Outcomes - Exacerbations

Sharples, ERJ 2012:40:264-278
RBH Paediatric DA Protocol

**Stage 1**
- Confirm diagnosis
- Investigation of additional diagnoses
  - Spirometry and BDR
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  - Home visit

- Identify contributing factors
- Interventions recommended
  - Ongoing poor control
  - Control improved

**Stages 2 and 3**
- Bronchoscopy
- Immunology screen
- Autoimmune screen
- Assessment of adherence
- Allergy testing (SpIgEs)
- Measurement of inflammation
- Assessment of steroid responsiveness

**DEFINE PHENOTYPE**

**Targeted treatment plan**
Assessment of Steroid Responsiveness

Stage 2
Asthma control (ACT)
Spirometry
Induced sputum
$FE_{NO}$
Bronchoscopy
i/m triamcinolone given

Stage 3
Asthma control (ACT)
Spirometry
Induced sputum
$FE_{NO}$
Exacerbations
Symptom diary

1 month

Stage 3
Repeated (up to 3 doses of triamcinolone)
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Severe Therapy Resistant Asthma

Meets clinical criteria for omalizumab?

Yes

Trial of omalizumab

No

Trial of other agents (patient involvement) including:
- macrolides
- steroid sparing agents
- novel monoclonals (clinical trial)

No response
Atopic (IgE) Mediated Asthma

- IgE binds to allergens triggering the release of mediators which causes inflammation

**Omalizumab**

- Recombinant IgG\(_1\) monoclonal anti-IgE antibody
- IgE level 30 – 1500IU/ml
- Licensed for children ≥6 years
- Reduction in exacerbations in children with moderate - severe asthma
- Injections every 2 to 4 weeks

Lanier, JACI, 2009;124(6)
Omalizumab at RBH

- ACT, AQLQ, courses of OCS, unscheduled health visits, spirometry, induced sputum, FE$_{NO}$ measured every 4 weeks
- 33 commenced on omalizumab since June 2008
- 13 stopped at 16 week assessment (or before), 10 currently receiving omalizumab
- Range of IgE 105 – 2350IU/ml
- Reassess every 16 weeks
- “Xolair holidays”
NICE Guidance

• Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years or older:
  • who need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)
• Optimised standard therapy is defined as a full trial of and documented compliance with inhaled high-dose corticosteroids, long acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate

www.nice.org.uk/TA278
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Treatment targeted at sputum eosinophilia - adults

Severe exacerbations (cumulative number)

Time (months)

BTS guidelines

p=0.01

Green, Lancet 2002; 360 (9347):1715-1721
Treatment targeted at sputum eosinophilia - children

Fleming, Thorax, 2012;67:193
Sputum inflammatory phenotypes are not stable in children with asthma

Louise Fleming,1,2 Lemonya Tsartsali,2 Nicola Wilson,2 Nicolas Regamey,3 Andrew Bush1,2
**T\textsubscript{H}2 High**

- \(T\textsubscript{H}2\) inflammation is mediated by IL-4, IL-5 and IL-13
- Gene expression analyses have identified \(T\textsubscript{H}2\) high and \(T\textsubscript{H}2\) low phenotypes
- Lung function improvements with ICS only seen with \(T\textsubscript{H}2\) high
T_{H2} High vs T_{H2} Low
**Anti IL-5**

- IL-5 is a key cytokine in eosinophil function
- Mepolizumab: recombinant monoclonal antibody to IL-5

Flood-Page, Am J Respir Crit Care Med; 2007:176:1062
Mepolizumab: enrolment based on sputum inflammatory phenotype

Haldar, NEJM 2009;360(10):973-984
Nair, NEJM 2009;360(10):985-993
DREAM Study

Pavord Lancet 2012;9842:651
Anti IL-13

- Lebrikizumab is a monoclonal antibody to IL-13
- Treatment with lebrikizumab led to improvements in FEV₁, which was greater in the high periostin subgroup
Pediatric severe asthma is characterized by eosinophilia and remodeling without TH2 cytokines

Cara J. Bossley, MBChB, Louise Fleming, MD, Atul Gupta, MBBS, Nicolas Regamey, MD, Jennifer Frith, MBBS, Timothy Oates, BSc, Lemonya Tsartsali, MD, Clare M. Lloyd, PhD, Andrew Bush, MD, and Sejal Saglani, MD

London, United Kingdom, and Bern, Switzerland
Neutrophilic Inflammation

- **Macrolides**
  - Affect on neutrophil chemotactic activity
  - Reduced levels of IL-8
  - Impairment of oxidative burst
  - Direct effect on chlamydia pneumonia?

- **Theophylline**
  - Accelerates human granulocyte apoptosis
  - Reduced sputum neutrophils, IL8 levels and neutrophil chemotaxis
  - Enhances histone deacetylases (HDAC) activity, inhibits acetylation of core histones necessary for inflammatory gene transcription

Jaffe Pediatr Pulmonol 2001;31:464-473
Yasui J Clin Invest 1997;100:1677-1684
Culpitt, AJRCCM;2002: 165:1371
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Steroid sparing agents

Summary of Cochrane reviews (randomised placebo controlled trials):

**Azathioprine (2008)**
- 2 studies (23 participants)
- No data on OCS use
- Significant difference in SGaw
- Myelosuppression

**Methotrexate (2004)**
- 10 studies (185 participants)
- Reduction in OCS dose
- Hepatotoxicity

**Cyclosporin (2010)**
- 3 studies (106 patients)
- Reduction in OCS dose (small effect)
- Improvements in spirometry
- Case series from RBH 5 paediatric patients, 3 improved
- Nephrotoxicity
- RPLE syndrome

Very little outcome data for our patients

Coren ADC 1997;77:522-523
Methotrexate

• Mode of action
  – Inhibition of replication of T and B lymphocytes
  – Interferes with neutrophil chemotaxis

• Limited evidence
  – Cochrane review (updated 2004)
    • 10 studies (n=185)
    • Reduction in OCS dose
    • Hepatotoxic
  – 3 small studies in children (n=20)

• Dose
  – Target dose: 10mg/m²/week
  – Initially 2.5mg weekly, increased in 2.5mg/week increments according to response and tolerance
  – Folic acid 5mg 48hrs after MTx
Ciclosporin

- **Inhibits T-cell activation**
  - T-cell driven, eosinophilic inflammation persists, despite ICS/OCS.
- **Limited evidence**
  - Cochrane review (updated 2010)
    - 3 studies (n=106)
    - Reduction in OCS dose (small effect)
    - Improvements in spirometry
  - Case series from RBH 5 paediatric patients, 3 improved
  - Nephrotoxicity
  - Hypertension
- **Dose**
  - 2.5mg/kg PO BD. Target range 80-150mg/l

Coren et al. Arch Dis Child 1997;77:522-23
SC Terbutaline

- ‘Placebo effect’
  - Double blind placebo controlled assessment
  - Terbutaline 5mg/day vs saline
  - Now at home

- Successful assessment:
  - > 15% improvement in PEF or FEV1
  - Reduction in symptom scores
  - Reduced short acting beta 2 use
  - Improved coefficient of variation of PEF
The Future

1. New combinations / devices
   - Combinations of existing (generic) drugs
   - Once daily formulations
   - Triple combinations (ICS+LABA+LAMA)
   - Single molecule combinations

2. New monoclonals
   - Anti IL-5 (mepolizumab); Anti IL-13 (lebrikizumab)

3. Personalised medicine
The Future?

Sittka, Paediatric Research, in press
Summary

• Most children can be treated effectively with low dose ICS
• Remember the basics of asthma management
• Treatment beyond the guidelines should be targeted
• Treatment trials