NEW DEVELOPMENTS IN CHILDHOOD ASTHMA TREATMENT

In the last *BJFM* we looked at diagnosing asthma. Now, with an increasing number of children being diagnosed with the condition, the authors focus on effective treatments

Dr Rebecca Devaney
Speciality trainee year 3, Paediatrics, Nottingham University Hospital

Mr Peter Foxon
MRPharmS Dip Clin Pharm

Dr Jayesh Bhatt
Consultant Respiratory Paediatrician, FRCPCH, Nottingham Children's Hospital

Asthma is a clinical condition characterised by recurrent symptoms of wheeze, cough, chest tightness and breathlessness. It is common, affecting up to 1 in 11 children in the UK, according to NHS figures, and is an important cause of morbidity and mortality.[1] According to the National Review of Asthma Deaths, 28 children died of asthma between February 2012 and January 2013 in the UK. Of the children that died, 80% of those under 10 years of age and 72% of those aged 10-19 years died before reaching hospital.[2]

The aim of good asthma management should be to allow children to be symptom free and able to participate in the same activities as their peers.[3] As a long-term condition, often requiring daily medication, work is continuing into developing new treatment options for patients. These include treatments that may be more effective for patients that have difficult-to-control asthma, and treatments that minimise side effects eg, from high dose oral steroids.[4] New treatments may also help to aid compliance by using simpler dosing regimens eg, once daily inhalers.

Adherence

It is important to acknowledge the difficulties some families experience in administering asthma treatments and the British Thoracic Society (BTS) guidance[5] reminds us of the need to check patient's understanding of their medication, their inhaler technique, compliance and exposure to triggers before new treatments are considered.

Health care professionals should work with children and their families to improve their adherence to treatment by considering the practicalities of treatment and individual preferences eg, choice of inhaler device. It is recognised that adherence to inhaled corticosteroid treatment in children with asthma can be poor.[6,7] It is important to ensure families understand the differences between treatments eg, the lack of an immediate effect from inhaled corticosteroids (ICS), as these agents are not relievers like salbutamol or terbutaline. They should understand the importance of regular use of ICS as 'controller therapy' as this has been shown to provide benefit in improving lung function and quality of life and reducing exacerbations.[5,6] 'Barriers' to compliance, such as concerns over side effects, should be discussed.

Triggers

While the BTS guidance recognises that evidence for the non-pharmacological treatment of asthma is limited,[5] it is important to ensure families are aware of and avoid known triggers to help their child's asthma management.[6] A study in a tertiary centre of children with problematic asthma showed that many of these children had modifiable trigger factors eg, known allergen or smoke exposure, which could be addressed.[8,9]

> *It is recognised that adherence to inhaled corticosteroid treatment in children with asthma can be poor*

The Airsonett temperature-controlled laminar airflow device for persistent allergic asthma is a new treatment which is thought to reduce aeroallergen exposure in patients at night. It may be considered as an add-on therapy by specialist respiratory paediatricians managing patients with poorly controlled persistent allergic asthma. It works by producing a downward current of cool, filtered air which is thought to displace aeroallergen particles, such as cat dander, from the zone of air which the patient will inhale from. It has the benefits of being non-invasive and non-pharmacological and has been shown in research studies to reduce particle exposure, which may help to improve quality of life.[10] It is less expensive than alternative treatment options for allergic asthma eg, omalizumab, but has not been shown to reduce medication use or exacerbations according to NICE.[11,12]

Current pharmacological treatments for asthma

There is clear stepwise guidance on the initial management of asthma in children produced by the BTS. Treatment is started at the level which is most likely to gain rapid control of symptoms and then adjusted as necessary to balance symptom control with minimising the treatment needed.[5]

A short acting inhaled beta 2 agonist (eg, salbutamol) is the first line treatment recommended for all symptomatic children. Salbutamol is recognised as effective and works quickly to offer symptomatic relief. Advice on management of exacerbations is available in the BTS guidance.[5]

If a child needs more than one inhaler a month, the BTS recommend that they should urgently be assessed to look at their asthma control and need for regular preventative medication. Other reasons to consider inhaled corticosteroid treatment include children who have had an asthma attack in the last two years, those who report symptoms or use their reliever inhaler at least three times a week, and those who are woken at night by symptoms once a week.[5]

Inhaled corticosteroids

Inhaled corticosteroids are the first line preventative medication of choice for children with asthma.[5]

The use of good inhaler technique is crucial in ensuring a therapeutic drug dosage reaches the lungs

Beclometasone and budesonide are considered to be of equivalent effectiveness but fluticasone is felt to be equally clinically effective at half the dosage.[13] It is very important to consider this when switching between drugs. Adrenal suppression can occur at higher doses of inhaled corticosteroid.[14] A suggested starting dose for children is 100-200 microgram per day of beclometasone. The only licensed inhaled corticosteroid for children under 5 years is Clenil but it is important to consider whether these children will benefit from inhaled corticosteroid or not (as non-atopic children may not).[5] Preschool wheeze is outside the scope of this article, but guidance is available on the management of this.[15]

Most inhaled corticosteroids are given twice daily but ciclesonide is once daily, which may help compliance. ICS are recognised to be highly effective and the dose should be titrated. The guidelines recommend that children who do not respond to the equivalent dose of 400 micrograms per day of beclometasone inhaled corticosteroid are referred to a specialist (systemic side effects may be seen at doses higher than this). Children should have their dose of ICS reduced as their asthma is controlled and have their growth monitored at least annually while on this ICS.[5]

The BTS guidelines discuss add-on therapies to inhaled corticosteroids[16] (long acting beta 2 agonists in children over 5 years and leukotriene receptor antagonist eg, Montelukast in children 5 years or younger). Long acting beta agonists (LABA) should not be used without ICS as this is associated with increased mortality and the use of combination inhalers is recommended in the National Review of Asthma Deaths to help ensure this does not occur.[2] Combination inhalers eg, Seretide (a combination of inhaled salmeterol and fluticasone), may also help treatment compliance. If children less than 5 years are unable to take ICS, due to difficulty administering these, leukotriene receptor antagonists are recognised as an alternative preventative treatment by the BTS.[5,17]

Devices

Inhaler devices are based around two main concepts; pressured metered dose inhaler (pMDI) and dry powder inhalers (DPIs). New devices that come to market are mostly variations on these concepts, but the delivery method and particle size has an impact on the therapeutic effect of the device. For example, a QVAR has twice the therapeutic effect compared to Clenil at the same dose of beclometasone. This is due to reduced particle size (although this does not reduce adverse drug reactions).[18] It is therefore recommended that beclometasone inhalers are prescribed by brand name.[18] Individual inhaler monographs should be reviewed in the British National Formulary for Children (BNFC) when prescribing to confirm dose equivalence.

The use of good inhaler technique is crucial in ensuring a therapeutic drug dosage reaches the lungs. It is important to check patients and families are confident using their inhaler devices and to change this only with careful consideration and after consultation.[19]

Spacers should be changed every 6-12 months. They should be washed monthly in water with mild detergent and left to air dry.[5] Choice of spacer is governed by factors such as the inhaler, the age of child and what they have previously used. Advice on this is available in the BNFC.

There are insufficient studies comparing pMDI + spacer and DPIs in children under 5. A pMDI + spacer is as good as a nebuliser for mild to moderate asthma attacks and therefore pMDI + spacer is usually recommended for stable asthma in children under 5.[5]

TABLE 1 INHALER DEVICE TYPES, ADVANTAGES AND DISADVANTAGES

Device	Examples (not a comprehensive list)	Advantages	Disadvantages
Pressurised metered dose inhaler (pMDI)	Seretide Evohaler Clenil Modulite	■ Does not require forceful inhalation to deliver dose ■ Portable	■ Requires coordination between activation and inhalation ■ Oropharyngeal deposition is high especially if high inspiration rate
PMDI + spacer	Seretide Evohaler Clenil Modulite	■ Does not require coordination with activation ■ Reduced oropharyngeal deposition compared to pMDI	■ Portion of dose lost due to static adherence to spacer ■ Bulky
Breath Actuated MDI	Salamol Easi-Breathe	■ Does not require coordination between inhalation and activation ■ Portable	■ Requires sufficient inhalation velocity to activate device ■ High inspiration velocity will increase oropharyngeal deposition ■ Not compatible with spacers
Dry Powder inhaler (DPI)	Turbohaler Accuhaler Relvar Ellipta	■ Does not require coordination with activation ■ Portable ■ No propellant required	■ High oropharyngeal deposition ■ Requires Forceful inspiration to deliver dose ■ Not compatible with spacers
Respimat®	Spiriva Respimat	■ Fine mist increases lung deposition ■ Low velocity dose delivery decreases oropharyngeal depostion ■ Portable	■ In UK currently only available with tiotropium

Adapted from ERS/ISAM Taskforce report What the pulmonary specialist should know about the new inhalation therapies, Laube *et al* European Respiratory Journal, 2011.[19]

In children over 5 years, a DPI and pMDI + spacer are not believed to differ in efficacy as long as good technique is achieved. Breath actuated pMDIs are not compatible with spacers and therefore unlikely to be of use in children under 5 years of age. Oropharyngeal deposition is also more likely with breath actuated pMDI.[18] There are no clinically significant differences between a pMDI and Clickhaler (a DPI).[5] A Budesonide turbohaler (DPI) is 1:1 equivalent with a beclometasone pMDI.[5]

When choosing an inhaler device with a child and carer consider their age and what treatment is most likely to be adhered to. Where possible, for patients on multiple inhalers, the same device type should be used. Multiple devices and techniques are more likely to result in poor overall technique due to confusion.[5]

Theophylline

An option for children who have failed a trial of combination LABA and ICS is the bronchodilator theophylline.[5] BTS recommends only initiating outside specialist centres in children over 5, but the BNFC includes a dosage from 6 months for Slo-Phyllin.[20]

A narrow therapeutic range makes theophylline dosing a challenge. This is compounded by the limited available dosage forms. An important practice point is that different brands of theophylline are not dose equivalent and therefore patients should be maintained on the same brand. Theophylline levels should be monitored.

Nuelin SA and Uniphyllin Continus are only available in a non-crushable tablet form likely to be unacceptable to many children. However, Slo-phyllin is available in capsule form and the contents can be sprinkled onto a spoonful of soft food for administration.[20] The enteric coated granules must not be chewed, which may provide an additional compliance barrier.

Theophylline derivatives with antibacterial properties are being considered as potential future treatments for asthma.[21,22] While this is an interesting area of research, work on this concept is in its early stages and therapies may never reach market.

Biologics

There has been research into new biological treatments for patients with eosinophilic asthma in adults and older children eg, benralizumab (a humanised monoclonal antibody which helps with apoptosis of eosinophils)[23] and mepolizumab (a humanised monoclonal antibody against IL-5).[24]

Omalizumab

Omalizumab is a humanised monoclonal antibody to IgE administered by subcutaneous injection once every two-four weeks. It is an expensive, specialised treatment recommended by NICE for the treatment of severe persistent IgE mediated allergic asthma in children over 6 years of age who are requiring regular oral steroid treatment (at least four courses in 12 months) and where it is available with the discount agreed in the patient access scheme.[25] It can help to reduce oral steroid exposure[26] and reduce exacerbations.[27] To qualify for omalizumab treatment, children must have had their asthma treatment optimised, have good compliance and inhaler technique, and efforts should be made to minimise exposure to environmental triggers eg, smoking. They should have this treatment started by, or in conjunction with, a specialist respiratory paediatrician and have their response to treatment assessed at 16 weeks. The dose is determined by weight and level of IgE.[25] NICE have produced guidance on the use of omalizumab in children.[25]

Tiotropium

Tiotropium is a long acting (once daily) anticholinergic bronchodilator used in adults which has been trialled for the management of asthma in symptomatic children (6-11 years old), despite medium doses of inhaled corticosteroids. It has been shown to have a similar safety profile to placebo and offer a statistically significant increase in FEV^1 three hours post dosing.[28] It is not currently licensed in children.

Conclusions

Asthma is an important contributor to childhood illness. It is important to ensure it is diagnosed and managed appropriately. New treatments are being developed that offer exciting new options for clinicians treating children with asthma, including those with the most severe disease.[29] In difficult-to-manage asthma, it is important to remember the importance of good compliance and to help this there needs to be a good understanding of asthma treatment within families. The importance of personalised asthma management plans as recommended by the BTS should be recognised. If children are requiring escalation of treatment it is useful to seek the help of secondary care colleagues. The BTS offer guidance on when it is most appropriate to consider this.[5]

KEY POINTS

- Always consider compliance with current treatment, inhaler technique, appropriateness of the device and trigger exposure in children with difficult asthma
- Follow the BTS guidance for the initial management of asthma and step up or down as needed
- New trigger avoidance methods eg, laminar airflow devices are being researched
- Omalizumab is a biologic approved by NICE for use in cases of severe allergic asthma; it is given via s/c injection every 2-4 weeks
- Other treatment options, eg the use of theophylline derivatives with antibacterial properties, alternative biologics and tiotropium use are being researched

References

1. http://www.nhs.uk/conditions/asthma/Pages/Introduction.aspx
2. *Why Asthma Still Kills? National Review of Asthma Deaths*, May 2014, Royal College of Physicians
3. http://www.asthma.org.uk/advice-children-and-asthma
4. Sharek Pj, Bergman DA. *Pediatrics* 2000;106(1):E8.
5. British Thoracic Society/SIGN British Guideline on the Management of Asthma revised 2014
6. Morton *et al.* Archives of Disease in Childhood, 2014
7. Klok *et al. Breathe*, 2013
8. Bracken *et al. Archives of Disease in Childhood*, 2009
9. Ehrlich R, jordaan E, Du Toit D, Potter P, volmink j *et al. J Asthma* 2001;38(3):239-51
10. Gore *et al. Indoor Air*, 2015
11. Boyle *et al. Thorax*, 2011
12. The Airsonett temperature controlled laminar airflow device for persistent allergic asthma, NICE Medtech Briefing, 2014
13. Adams *et al. Cochrane Review*, 2007
14. Patel *et al. Archives of Disease in Childhood*, 2001.
15. Bhatt, JS. *BJFM*, 2013
16. Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.11b: add-on drugs for inhaled steroids: long acting or oral B2 agonists. [cited 11 jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/ published/support/guideline63/table4.11b.html.
17. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, *et al. Pediatrics* 2001;108(3):E48
18. 3.2. Corticosteroids. Paediatric Formulary Committee. BNF for Children (online) London: BMJ Group, Pharmaceutical Press, and RCPCH Publications <http://www.medicinescomplete.com> [Accessed on [01.05.15]
19. Laube *et al. European Respiratory Journal*, 2011
20. 3.1.3. Theophylline. Paediatric Formulary Committee. BNF for Children (online) London: BMJ Group, Pharmaceutical Press, and RCPCH Publications <http://www.medicinescomplete.com> [Accessed on [01.05.15]
21. https://www.nice.org.uk/guidance/ta38/chapter/3-The-technologies
22. Alaa M. Hayallah *et al. Arch Pharm Res* Vol 35, No 8, 1355-1368, 2012
23. Laviolette M, *Journal of Clinical Immunology*, 2013
24. Ortega *et al. New England Journal of Medicine*, Sept 2014
25. Omalizumab, NICE guidance Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201) Issued: April 2013
26. Brodlie *et al. Archives of Disease in Childhood*, 2012
27. Brodlie *et al. European Respiratory Disease*, 2011
28. Vogelberg *et al, Respiratory Research*, 2015
29. Olin, Weschler, *BMJ* 2014