Drug therapy in the management of acute asthma

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If our management of children with asthma was optimal, there would be no need for this article as we would be able to prevent the development and progression of any asthma exacerbation. In reality, we are quite a long way from optimal care of childhood asthma in the UK and although hospital admissions for acute asthma are at last beginning to decline, having reached their peak in the late 1980s, acute asthma remains the most common reason for emergency admission to hospital. The vast majority of children respond well to treatment with oral steroids and inhaled bronchodilators, with deaths from childhood asthma remaining low: approximately 25 UK children die each year. However, identifiable causes of death include suboptimal routine and emergency care in a third to half of all children. The initial management of children with acute asthma has changed little over the last 20 years. However, data continue to emerge on how best to manage the small number of children who respond poorly to first-line treatment. This article aims to review the recent evidence (or highlight the lack of it) and gives suggestions for treatment strategies when faced with a child who is failing to respond.

As background to this article, we interrogated the MEDLINE database for articles concerning “acute asthma” AND “treatment” OR “therapeutics”. By limiting the search to articles about children and excluding reviews, we initially retrieved 494 abstracts. For the sake of clarity we have attempted to exclude opinions and keep the evidence separate whenever possible. At the end of each section of the review we offer a brief description of our own views and experience in managing children with acute severe asthma with particular reference to the clinical cases described.

CASE 1
A 4 year old child was admitted to the paediatric wards at 10 am with a 24 h history of cough and wheeze. He had been seen previously as an outpatient by a colleague and diagnosed as having asthma. He usually inhaled 200 mg of budesonide twice a day using a large volume spacer and had excellent inhaler technique. Until the day before admission his symptoms had been well controlled. Despite bronchodilator treatment for most of the day, he continued to deteriorate and needed oxygen via a face mask at 5 l/min to maintain oxygen saturations above 92%. You are asked to review him to decide whether he needs further treatment.

Drug delivery: large-volume spacer versus nebuliser
There is good evidence to support the view that pressurised metered dose inhalers (pMDI) in combination with large volume spacers are at least as effective as nebulisers for bronchodilator inhalation to treat moderate or more severe asthma. In mild attacks two to four puffs of salbutamol (200–400 µg) may be sufficient, but in moderate or severe attacks 10 puffs of salbutamol may be required. Allowing up to 30 s for salbutamol to be inhaled by tidal breathing means that it takes 5–6 min to deliver 10 puffs of salbutamol. During this time it is difficult to administer supplemental oxygen and significant hypoxia may practically preclude the use of spacers in the first instance. For children who do not initially require supplemental oxygen, β2 agonists given via a pMDI+spacer are less likely to provoke hypoxia or tachycardia than when the same drug is given by a nebuliser. The case for and against a pMDI+spacer in severe asthma is less clear and this is reflected in the current National Asthma Guidelines. Recent experience from Australia in the use of large volume spacers found that only 3% of children admitted to hospital with an exacerbation of asthma were unable to use a pMDI+spacer, although 7.5% of 200 admissions eventually received nebulisation.

In our experience, however, there are a small number of children who seem to derive more benefit from nebulisers. In severe asthma this may be because there is insufficient inspiratory flow to move the valve of the large volume spacer. However, failure to move the valve is rare in our experience and
failure of pMDI±spacer treatment occurs more commonly because patients are unfamiliar with spacer devices or are too agitated to use them.

**Intermittent versus continuous nebulisation**

Salbutamol is a partial agonist. It therefore reaches its maximal bronchodilating effects at relatively low doses. Increasing the dosage does not increase the absolute bronchodilatation but does prolong the bronchodilator effect. It is therefore not surprising that bronchodilators nebulised every 20 min are more effective than bronchodilators nebulised hourly. Continuous nebulisation in low dosages (0.15 mg/kg in 5 ml) is the most effective as it provides sustained stimulation of the pulmonary β2 receptors and prevents the rebound bronchoconstriction that may occur with intermittent therapy.

Our own observations in the emergency room have shown that a standard nebuliser driven with 8 l/min of oxygen takes approximately 10 min to complete. In children we usually nebulise 0.15 mg/kg of salbutamol up to a maximum of 5 mg made up to 5 ml with normal saline. The team looking after the patient is instructed to start a new nebuliser as soon as the previous nebuliser is completed which leads to approximately six nebulisations per hour being given.

**Combined inhaled anticholinergics and β2 agonists**

The evidence also supports the use of nebulised ipratropium bromide (125–250 μg per dose) in addition to β2 agonists for the first 2 h of a severe attack in children. A systematic review and meta-analysis conducted in 2005 demonstrated a reduction in hospital admissions (relative risk of admission 0.73, 95% CI 0.63 to 0.85, \( p = 0.001 \)) and a significant increase in spirometric parameters (standardised mean difference (SMD) = –0.54, 95% CI –0.28 to –0.81, \( p = 0.001 \)). In the seven published studies reporting change in FEV\(_1\), children treated with one or two doses of anticholinergic agents had a mean difference of change in FEV\(_1\) of 12.4% (95% CI 5.4 to 19.4) compared with those who did not receive anticholinergics. Children who received more than two doses did even better, demonstrating a mean difference of 16.3% (95% CI 8.2 to 24.5). This reinforces the recommendations of the British Thoracic Society/SIGN Guidelines for the management of asthma. If symptoms are refractory to initial β2 agonist treatment, then ipratropium bromide mixed with the nebulised β2 agonist solution should be given. It is recommended that this is repeated every 20 min for the first hour and every 4 h thereafter.

**Steroids in acute asthma: route and dose**

Children with an acute exacerbation of asthma should receive steroid treatment as early as possible. This has been shown to reduce the risk of admission to hospital and prevent a relapse in symptoms after initial presentation. The limited available data suggest that inhaled steroids are no more effective than oral steroids in moderate to severe asthma and both begin to work within 3–4 h. Intravenous hydrocortisone (4 mg/kg) should therefore be reserved for children who are unable to tolerate oral fluids. Despite their widespread use, very few studies have addressed the optimal dose of oral steroid required for the treatment of acute childhood asthma. There is limited evidence from a single small study to suggest that doses of 0.5 mg/kg of prednisolone might be as effective as higher doses. Unfortunately, this study was not powered to determine therapeutic equivalence and given the wide therapeutic index and the obvious clinical benefits, doses of 1–2 mg/kg are currently recommended for children with acute severe asthma. Although inhaled corticosteroids form the cornerstone of chronic asthma treatment, they have been poorly studied in the management of the acute phase. The widely held practice of doubling the inhaled corticosteroid dosage in an acute exacerbation has been tested in children and has been found to be wanting. Garrett and colleagues from Dunedin saw no benefit whatsoever from doubling the dose of inhaled corticosteroids and recommended that this statement should not be part of any written management plan. Similar data have been seen in adult studies with two separate reports in adults demonstrating no benefit from doubling inhaled corticosteroids at the onset of symptoms. For children who have arrived in hospital, 2 mg inhaled fluticasone propionate is less effective than oral corticosteroids (2 mg/kg) in the treatment of an acute exacerbation.

Clinical observations regarding the rapid onset of action of inhaled corticosteroids and a recent meta-analysis have reinvigorated the debate about the utility of inhaled steroids in the acute setting. This analysis of the data from adults and children suggests that inhaled corticosteroids have additional early benefits (between 1 and 2 h) that precede those which might be expected from oral steroids. However, as only two small studies examined the benefits of inhaled corticosteroids in addition to oral corticosteroids, further randomised controlled trials are needed to clarify their exact role in the acute setting.

**CASE 2**

A 10 year old child is admitted at 8 pm following an acute asthma attack triggered by a cold. He had been well controlled until 2 weeks previously, but his parents had noticed a gradual increase in symptoms over the last fortnight and suspect that he had stopped taking his inhalers. He has not had any salbutamol prior to admission as he is unable to generate a high enough inspiratory flow to activate his dry powder inhaler. His oxygen saturations are 90% in high flow oxygen and he is halfway through his second 5 mg salbutamol nebuliser. He is pale with marked respiratory distress and a respiratory rate of 40/min.

**Intravenous salbutamol: bolus versus infusion**

The exact role of intravenous treatment for the management of acute severe asthma in childhood remains controversial. There are a few randomised controlled trials and case reports in the literature on the use of intravenous salbutamol in children with severe acute asthma. In selected children it appears to be effective and offers benefits above and beyond those seen with inhaled treatment alone. Most authors state the need for an initial loading dose of salbutamol (15 μg/kg over 5 min) as without this it takes 10–20 h for a plateau concentration to be reached. However, controversy exists over what doses should be used and whether these should be then followed by a continuous infusion (1–5 μg/kg/min). The plasma half-life of salbutamol in adults is 2–3 h. There are no data in children.

Our clinical experience with intravenous salbutamol is reflected in the published literature. A single bolus of...
salbutamol is less likely to be effective than repeated boluses or a bolus followed by an infusion. If a child is ill enough for treatment with intravenous salbutamol, or intravenous aminophylline as below, to be considered, this should be in a high-dependency unit or in a paediatric intensive care setting wherever possible. Hypokalaemia is a common consequence of salbutamol and aminophylline administration regardless of route and should be carefully monitored in children with severe asthma.

**Intravenous aminophylline versus salbutamol versus nothing**

Despite an established role in the management of acute severe asthma, the most recent Cochrane review of this topic demonstrated the paucity of data on which treatment guidelines have been established. Whilst there are limited data to suggest an improvement in lung function indices at 6 h following intravenous aminophylline, there is no apparent reduction in symptoms, in the number of nebuliser treatments required or in the length of hospital stay. There is insufficient evidence to assess the impact on oxygenation, a paediatric intensive care unit admission or the need for mechanical ventilation. It is clear though that aminophylline infusions are associated with unpleasant side-effects with a three-fold increase in the risk of vomiting. However, the jury is still out on whether this is more or less effective than the better-tolerated intravenous salbutamol. We have anecdotal experiences of situations where a relatively stable child with severe asthma has deteriorated secondary to vomiting or seizures following the introduction of aminophylline to the asthma treatment. There has been a head-to-head trial of intravenous salbutamol versus intravenous aminophylline in children showing a benefit of aminophylline with a reduced length of hospital stay when compared to salbutamol. However, this compared a single bolus of salbutamol (15 μg/kg over 20 min, which equates to an infusion rate of only 0.75 μg/kg/min) with a bolus followed by infusion of aminophylline (5 mg/kg followed by 0.9 mg/kg/h) and no effects were seen in the first 2 h of the infusion.

**Magnesium**

Intravenous magnesium sulphate is a safe and established treatment for acute asthma in adults. However, there is only limited experience of its use in childhood. There is mounting evidence that intravenous magnesium can provide additional bronchodilation when given in conjunction with standard bronchodilating agents and corticosteroids. A recent meta-analysis identified five small randomised controlled trials with 182 participants. However, its place in the treatment of acute severe asthma remains unclear and certainly it is too soon to conclude with any authority that intravenous magnesium is a safe treatment in children. Doses of up to 75 mg/kg/day have been used for asthma in the emergency department.

Our own experience with intravenous magnesium is limited. Although the evidence suggests that early treatment with intravenous magnesium improves lung function and reduces the rate of hospital admission, it is not our practice to insert an intravenous line early in the course of management. The effectiveness of intravenous magnesium as a “rescue” therapy for asthma failing to respond to more conventional treatment remains unknown. Whilst magnesium sulphate can also be nebulised, there are only limited data regarding its efficacy. Initial studies have demonstrated some promise with an improvement in lung function in severe asthmatics (SMD 0.55, 95% CI 0.12 to 0.98). It is likely that a very large study over many centres will be required to demonstrate the additional benefit of nebulised magnesium. To this end a multi-centre clinical trial of nebulised magnesium in children with acute severe asthma within the UK is about to commence.

**Epinephrine (adrenaline)**

There are several studies which have examined the benefit of nebulised epinephrine in adults and children with acute asthma, but meta-analysis shows no statistically significant advantage of nebulised epinephrine when compared to salbutamol or terbutaline. Further analysis did however demonstrate that 2 mg of epinephrine was required to have a similar efficacy to a single 5 mg nebulisation of salbutamol. The limited data available suggest that the bronchodilator effects of epinephrine are not additional to those seen with more selective β2 agonists. Nonetheless, the authors are aware of at least one case of fatal anaphylaxis which was initially presumed to be acute severe asthma. Prompt recognition of an allergic reaction and treatment with intramuscular epinephrine in these circumstances may be life saving.

**Levalbuterol versus salbutamol**

Acute asthma is usually treated with salbutamol. This is a racemic mixture of (R)-salbutamol and (S)-salbutamol, but the bronchodilator effects of salbutamol are mediated predominantly by the (R)-salbutamol isomer, levalbuterol. Observational studies in adults have suggested that levalbuterol may be effective in reducing hospital admissions. A randomised controlled trial in children, however, comparing levalbuterol to combined treatment with racemic mixture salbutamol and ipratropium bromide showed no benefit in terms of hospital admissions or respiratory distress.

**Leukotriene receptor antagonists in acute asthma**

Cysteinyl leukotrienes have been shown to be mediators of inflammation and bronchoconstriction in patients with asthma and marked elevations of these compounds occur during acute asthma episodes. Evidence supports the use of leukotriene-modifying drugs in the treatment of chronic asthma in all age groups. There have been only two randomised placebo controlled trials of leukotriene receptor antagonists in acute asthma in adult asthmatics and one in the paediatric age range.

The first of the adult studies evaluated 194 patients admitted to hospital with acute asthma. Intravenous montelukast 7 mg or 14 mg, in addition to standard treatment, gave a more rapid recovery in FEV1 over a 2 h period than did placebo (p = 0.007). Montelukast treated patients also needed less β2 agonist and fewer treatment failures occurred compared to placebo. In a second adult study, Silverman showed that addition of oral zafirlukast (20 mg twice daily for a month) to the standard care of adult patients with acute asthma reduced the risk of relapse over 1 month compared to placebo (p = 0.047). Higher doses of oral zafirlukast acutely (160 mg) had a non-significant (p = 0.052, relative reduction 34%) effect in reducing the number of adults who had to stay beyond 4 h.
Oral montelukast (4 mg) has been shown to be more effective than placebo in children between 2 and 5 years of age with mild to moderate acute asthma, significantly reducing respiratory distress during the first 4 h and non-significantly reducing the need for oral steroids. However, its role in more severe asthma or in addition to oral steroids remains unknown.

CASE 2 CONTINUED
The patient continues to require high flow oxygen 4 h after admission, and continues to require salbutamol nebulisers every 20 min. His salbutamol infusion has been reduced to 1 µg/kg/min. Chest x ray reveals no pneumothorax or signs of consolidation or collapse. It is now midnight and your patient is looking tired. The nearest a paediatric intensive care unit is 30 min away by road.

Fortunately, the latter scenario is relatively uncommon. Nonetheless, maintaining control of this situation can be difficult. Arterial blood gas sampling is distressing, painful and almost certainly less useful in this situation than review by experienced clinicians. Carbon dioxide can remain normal or low even in patients in extremis. Experience in adult patients suggests that some of these may benefit from non-invasive ventilation. However, there is no substantive evidence to support its use in children.

In our experience in children who are beginning to tire, becoming confused or who are failing to oxygenate, adequate control of the acute episode may be re-established with mechanical ventilation. It would be foolhardy to consider transferring this patient without an endotracheal tube and transfer to a paediatric intensive care unit is almost always preferable to shared management on an adult intensive care unit. Intubation is best done by an experienced anaesthetist, but there are some important aspects to consider immediately prior to and following intubation which are worthy of discussion with anaesthetic colleagues. Firstly, ketamine (1–2 mg/kg) may be useful in this setting as it is a bronchodilator. However, despite considerable anecdotal evidence suggesting benefit with higher doses in ventilated children with severe asthma (2 mg/kg followed by infusion rates of 0.6–2.7 mg/kg/h), a randomised controlled trial of ketamine at lower doses (0.2 mg/kg bolus followed by 0.5 mg/kg/h) did not result in improvements in clinical status in conscious children with moderate to severe asthma. Secondly, ventilation is likely to be difficult and the largest possible endotracheal tube should be inserted. Following intubation, slow rates and long inspiratory periods are usually the most successful ventilator strategies.

SUMMARY
Although asthma remains the most common reason for emergency admission to paediatric wards in the UK, the majority of children improve rapidly following treatment with oral steroids and inhaled β2 agonists. Nonetheless, a small number of patients either fail to respond or continue to deteriorate. In these situations there is no substitute for clinical experience and the calming influence that this brings to parents and children. Intravenous therapy with salbutamol or aminophylline should bring about improvements when inhaled therapy has failed. However, there remains controversy about which of these medicines offers the most benefit (or causes the least harm). Although intravenous magnesium seems very likely to be safe, its absolute efficacy as a rescue therapy in childhood asthma remains unknown. The value of nebulised magnesium, oral montelukast and nebulised levalbuterol are yet to be fully established in childhood, although each of these treatments shows promise. Our experience suggests that the most important factor in the management of this group of patients is close clinical observation (on a high-dependency unit if possible) and an ability to remain in control of the situation – this remains part of the art rather than the science of medicine. On rare occasions this includes the need to safely and strategically institute mechanical ventilation in some patients prior to transfer to a paediatric intensive care unit.

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