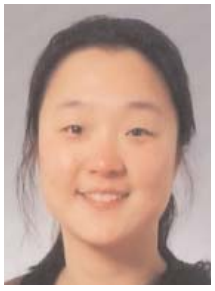

Paediatric indications for aerosol therapy in hospital: what is the evidence?

Hettie M Janssens, MD, PhD

Paediatric respiratory conditions provide the hospital caretaker with multiple challenges when trying to decide the best medication and route of administration. Choosing the proper aerosol therapy using evidence-based medicine can reduce the length of stay and decrease overall cost of treatment.

Asthma is the most common condition treated with aerosols in the hospital setting. However, there are several other paediatric respiratory diseases such as cystic fibrosis, bronchiolitis, croup and others in which aerosol therapy is used. Unfortunately, the evidence for clinical efficacy is often lacking or conflicting for many of these conditions. This review presents the evidence found in current literature for treating paediatric respiratory diseases with aerosol therapy in hospital.

Asthma

Asthma is characterised by broncho-obstruction and airway hyperreactivity caused by airway inflammation, bronchospasm and hypersecretion. Evidence-based treatment of asthma includes anti-inflammatory drugs, such as inhaled corticosteroids and leucotriene-antagonists, and bronchodilators, such as beta-2-agonists and anticholinergics. For maintenance treatment at home, it is recommended to choose a pressurised metered dose inhaler (pMDI) combined with spacer or a dry powder inhaler (DPI) as aerosol delivery device. Children presenting in the emergency room (ER) with an acute asthma exacerbation receive inhaled bronchodilators. Traditionally, this is administered via a jet nebuliser. The advantages are that oxygen can be given during the inhalation and a large dose can be administered at once. A disadvantage is that nebulising is time consuming and that personnel are unnecessarily exposed to inhaled drugs. However, a recent meta-analysis concluded that the pMDI with a spacer produced outcomes that were at least equivalent to nebuliser delivery [1]. In addition, the length of stay in the ER was significantly shorter when a pMDI/spacer was used. Although in most hospitals the nebuliser is still the first choice [2], this evidence has led to the implementation of pMDI/spacers being the preferred method of administration for bronchodilators in a few hospitals. A recent study showed a better cost-effectiveness ratio after the pMDI/spacer was introduced in the ER, which was largely due to lower labour costs [3].

Cystic fibrosis

Cystic fibrosis (CF) lung disease is characterised by airway obstruction caused by impaired mucociliary clearance, chronic infection and inflammation. Progressive disease results in irreversible lung destruction and decreased life expectancy. Aerosol treatment has become increasingly important in the treatment of pulmonary complications of CF. Inhaled steroids [4], and bronchodilators [5] have not been proven to be effective in improving lung function, but are still widely used. Current aerosol treatment focuses on two areas, mucolytics and antibiotics.

Mucolytics: The most commonly used inhaled mucolytics are recombinant human DNase (rhDNase), hypertonic saline and N-acetyl cysteine. For the latter there is some evidence that it improves mucociliary clearance, but there is no convincing evidence showing that this provides better outcomes in CF patients. rhDNase is a relatively new inhaled mucolytic. rhDNase works by degrading the DNA from decomposed neutrophils found in infected mucus and thereby reduces the viscosity of CF sputum. There is evidence that inhaled rhDNase gives long-term improvement in lung function and a reduction in pulmonary exacerbations in children with CF [6]. rhDNase is recommended by the manufacturer to be nebulised by a jet nebuliser. There are data, although limited, showing that rhDNase can be safely used in mesh nebulisers. Hyperosmotic agents increase the water content of airway mucus. Nebulised hypertonic saline (7% NaCl) has been shown to improve mucociliary clearance. Hypertonic saline has been known to cause cough and bronchospasm. Using a beta-2-agonist before nebulisation may help to avoid this problem [7]. Hypertonic saline for nebulisation has been shown to be safe for use in infants [8].

Inhaled antibiotics: CF patients colonised with *Pseudomonas aeruginosa* (PA) have a more rapid decline in lung function and have a higher rate of morbidity and mortality than patients who are negative for PA [9]. Using an inhaled anti-pseudomonal antibiotic appears to improve lung function and reduce the frequency of infections [10]. PA can be eradicated by using inhaled tobramycin twice daily for four weeks. Other examples of inhaled anti-pseudomonal antibiotics are colistin, azthreonam, gentamicin, ceftazidime and carbenicillin. Inhaled tobramycin and colistin are already licensed for use in children, with azthreonam currently being evaluated

for its safety and efficacy [11]. The current evidence is limited for all the other inhaled antibiotics and at this time they are not recommended for routine use in children who have CF.

Caution with nebulisers

Preferably, use the type of nebuliser that the pharmaceutical company recommends. The choice of nebuliser is based on clinical studies in which efficacy and safety have been proven for that specific drug-device combination. If a different nebuliser needs to be used the healthcare provider should monitor the efficacy and safety of the product carefully. Some medicines are broken down into inactive substances when exposed to the heat from ultrasonic nebulisers.

Miscellaneous indications

There are many other paediatric respiratory disorders in which aerosol treatment is used. A few are discussed briefly below.

Bronchiolitis is a disorder caused by a viral lower respiratory tract infection that can lead to serious shortness of breath in infants. In the management of bronchiolitis, inhaled bronchodilators and corticosteroids are often used. However, a guideline on the management of bronchiolitis recommends that inhaled bronchodilators and corticosteroids should not be used routinely [12]. rhDNase has been suggested as a way to stimulate mucus clearance in bronchiolitis but it is expensive and has not been shown to shorten the length of stay or even to improve respiratory symptoms. It has however been shown to lengthen the duration of oxygen need [10]. Epinephrine might theoretically have an effect on acute bronchiolitis because it contains alpha adrenergic properties which lead to vasoconstriction and reduction of airway oedema. However, a systematic review showed that nebulised epinephrine for acute bronchiolitis results in a modest short-term improvement in outpatients, but not among inpatients [13]. Nebulised 3% saline seems to be the only agent to be clinically effective in bronchiolitis. It has been shown to significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis [14].

Croup is another common respiratory infectious disease in children aged between six months and six years. It is characterised by a swollen subglottic region, resulting in inspiratory stridor and a characteristic cough. Inhaled steroids in high doses have been shown to be effective. However, there is a preference for oral corticosteroids [15]. Croup is the only indication in which larger particles (of >4 μm) during inhalation are preferable, in order to target the upper respiratory tract.

Atelectasis is the loss of volume of a part of the lung by collapse of alveoli. It is often seen in patients who are ventilated, as the result of a lower respiratory tract infection or after surgical treatment. Several studies have now been published showing the beneficial effects of rhDNase in the management of atelectasis, for both infants and children [16, 17]. There are also some data on N-acetylcysteine showing benefits for this condition [18].

Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) is one of the most common long-term respiratory complications in ventilated pre-term infants [19]. Systemic steroids provide at least a temporary improvement in respiratory function, but are associated with adverse side effects. Two reviews of inhalational versus systemic corticosteroids have shown that there was a slight increase in the incidence of CLD following the use of inhaled compared to systemic steroids in preventing CLD [19]. The conclusion is that inhaled corticosteroids are no more effective than systemic as treatment in established CLD [19]. Presently, there are no long-term outcome data available from studies using inhaled corticosteroids to prevent or treat CLD. The usefulness of beta-2-agonists in treating infants with CLD remains unclear due to conflicting published data [19].

Impaired mucociliary clearance in non-CF disease: Such conditions as primary ciliary dyskinesia, bronchiectasis, tracheobronchomalacia, and neuromuscular diseases with impaired cough function are all examples of disease that can cause recurrent pulmonary infections due to impaired mucociliary clearance or mucus hypersecretion. N-acetylcysteine, rhDNase and hypertonic saline are the muco-active agents of choice that have been studied most frequently. Unfortunately, the studies on the efficacy of these agents have been done mainly in adults and CF patients. Therefore there is limited literature available on the efficacy of muco-active agents in children with non-CF diseases. rhDNase and hypertonic saline seem to be the most promising for use in non-CF disease [18].

Conclusion

In today's hospitals, aerosolised drugs are used to treat many paediatric respiratory diseases. In asthma and CF, aerosol therapy is well established and many of the therapies have been proven effective through evidence-based research. However, there are many other paediatric respiratory diseases in which aerosol therapy is often used, but where there is far less evidence available and occasionally the research has even shown the therapy to be of no benefit. This review has covered the most recent treatment suggestions for several conditions that require aerosol therapy and we hope it is of benefit for hospital pharmacists when advising on these treatments for children.

This article is the second in a 2-part series on aerosol therapy in children. Part 1 was published in EJHP Practice, 2008, Issue 6.

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NEWS FLASH

Revised guidelines on use of ESAs

Adherence to new international guidelines on the use of erythropoiesis stimulating agents (ESAs) in the management of chemotherapy-induced anaemia can improve the quality of life of cancer patients, while minimising the risks of ESA side effects.

Speakers at the Hospira-sponsored symposium at the joint ECCO 15-ESMO 34 Congress in Berlin, Germany, 20–24 September 2009, urged colleagues to stick to the revised haemoglobin thresholds recommended in the guidelines and target ESA treatment at those cancer patients undergoing chemotherapy who have been shown to gain most benefit.

International guidelines now recommend initiating ESA treatment in patients with haemoglobin levels less than 10g/dL and stopping once they have become transfusion independent or when their haemoglobin levels reach 12 g/dL. Speaker Dr Jim Janinis was confident that by following them, lower levels of venous thromboembolic events would be reported.

Sixty-eight percent of delegates attending the symposium reported that their clinics were now using biosimilar ESAs.

Aapro MS, Link H. September 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. The Oncologist. 2008;13 (Suppl 3):33-6.