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Nebuliser therapy in childhood

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Jet and ultrasonic nebulisers continue to be of value in childhood. Nebulised therapy provides a portal of entry for systemic drug treatment as well as for the direct treatment of respiratory diseases.

A number of problems arise in evaluating nebulised therapy in children including anatomical and physiological variations due to age, compliance, problems with drug delivery and drug delivery devices, and difficulty in knowing the dose received by the patient. Doses used have largely evolved empirically and delivery methods have been adapted from adult practice. Nominal drug doses used for infants are often similar to those used in older children or adults. The purpose of this review is to describe differences between adults and children which may be of importance for nebulised therapy, to discuss the clinical uses of nebulisers in childhood, and to give practical guidelines for the choice and use of nebulisers.

Anatomical and physiological differences between children and adults

NOSE BREATHING AND UPPER AIRWAY

Although most young children nose breath at rest, their mode of breathing during nebulisation is unclear. Nasal breathing reduces lung deposition of nebulised drugs in adults by about 50%.[1] Little is known of this in children. The upper airway in infants is larger with respect to body size than in adulthood. This, together with the absence of nasal hair in the preadolescent, may make nasal breathing less of a problem than might be expected. Nasal obstruction during upper respiratory tract obstruction may also affect lung deposition when the child is nose breathing.

Another problem with nasal breathing was highlighted in older children breathing through the mouthpiece of a spacer device, where therapeutic failures were attributed to inappropriate inhalation through the nose rather than the mouthpiece.[2] Inhalation training is necessary for all children prescribed a nebuliser.

BREATHING PATTERN[3 4]

Deposition of nebulised drugs within the lung is affected by the breathing pattern. Studies with spacer devices suggest that the ideal pattern is deep slow inhalations[5] accompanied by breath holding. During larger breaths aerosol is likely to penetrate further into the lung, increasing peripheral deposition. Conversely, at the higher flows of deep or fast breathing turbulence is more likely to occur and inertial deposition in the upper airway and major bronchi increases. Even when well, young children usually breathe tidally when given nebulised medications and this may reduce the deposition of the drug in the periphery of the lungs. The effect of crying on aerosol deposition is not known.

Work by Collis has focused attention on the total amount of nebulised drug inhaled by young children.[6] He showed that the quantity of nebulised aerosol that may be inspired, including that deposited in the nose and upper airways, may be independent of the size of the child after six months of age (fig 1). Young children with small tidal volumes will inhale pure aerosol from a nebuliser. As children grow their peak inspiratory flow exceeds the nebuliser output and they entrain surrounding air not containing aerosol. Thus, for a typical nebuliser, older children will inspire the same dose as adults once their inspiratory flow exceeds nebuliser flow and the entire nebuliser output is inhaled. Only infants will inspire with a lower flow than that of the nebuliser output, and only then will the dose received be affected by the child's size. The importance of this observation has been highlighted in relation to bronchoprovocation studies in infants and young children.[7]

Stick and colleagues[8] investigated airways responsiveness to histamine and concluded that infants aged one month responded to a much lower concentration than did older children (median 10 years). However, when they later took into account the nebuliser gas flow in

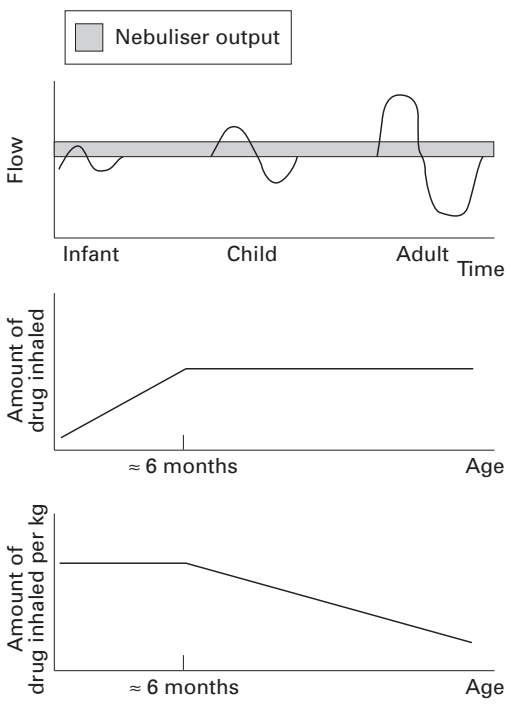

Figure 1 Postulated effect of breathing pattern on drug inhaled. Adapted from reference 6.

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calculating the concentration of histamine inspired there was no difference in responsiveness. Thus, the apparent age related decline in airways responsiveness of children may be an artefact and there may be a need to correct agonist doses for patient size in such studies.

Data from Salmon *et al*[9] suggested that up to 1.5% of a dose of nebulised sodium cromoglycate will be deposited in the lungs of children aged 6–36 months. Assuming approximately 10% of a nebulised dose is deposited in the lungs of an adult, the dose/kg body weight can be calculated. For example, a 70 kg adult will receive 0.14%/kg (10%/70) whereas, using Salmon's data, young children will receive up to 0.15%/kg (1.5% in a 10 kg infant). This suggests that, although there may be poor drug deposition in infant lungs, this is compensated for by their small size so that the final dose/kg body weight reaching the lungs may be very similar to that of an adult.

LOWER AIRWAYS

Nebulised aerosols are unevenly distributed with more central deposition in adult subjects with bronchoconstriction than in those with normal lung function.[10 11] Similar results have been found in children (discussed below).[12–15] The lower airways of infants are narrow and, as airways resistance is inversely related to the fourth power of the airway radius, a small amount of airway narrowing due to bronchospasm, inflammation or secretions may result in a considerable increase in resistance which encourages central airways deposition. This suggests that the optimum particle size for inhaled therapy in children is smaller than adults, and smaller still for children with bronchoconstriction. Producing aerosols with smaller droplets will mean alterations to nebuliser design and lengthening nebulisation times – issues which are discussed in the paper on pp S31–44. However, it may not be practical to nebulise some medications in small enough particles to produce a therapeutic effect.[16]

RECEPTORS

Nebulised β_2 agonists block the bronchoconstricting activity of histamine[17] and nebulised water,[18] suggesting that β_2 receptors are present within the infant lung. However, several clinical studies have failed to show a response to nebulised bronchodilators in infancy. Although this may be because the underlying cause is mucosal oedema and inflammation rather than bronchoconstriction, failure to deliver the drug in sufficient quantity to the airway may also be important. Turner *et al*[19] found an inverse relationship between age and response to salbutamol in young children and some nebulised drugs have caused paradoxical bronchoconstriction and desaturation when given to infants with a history of wheeze.[20–22] For many drugs we do not know their optimum site of action in the lungs. Steroid therapy for asthma, for instance, may be best delivered to the airways while antibiotics in cystic fibrosis may be best delivered to the distal airways and alveoli. Clearly, different nebuliser systems are needed in each case.

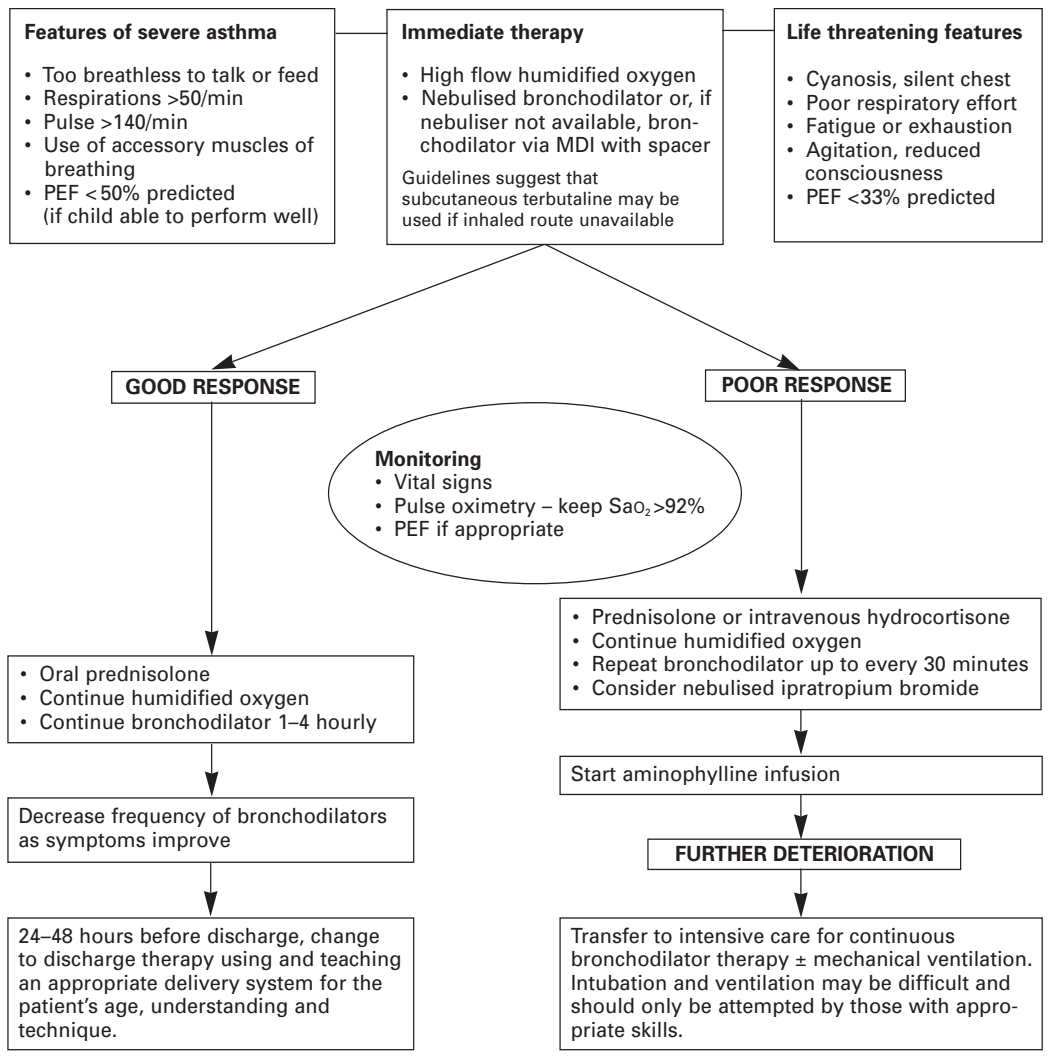
DEPOSITION

Several models have been proposed to calculate the deposition of particles within the respiratory tract of children. These make a number of assumptions about breathing pattern and the structure of the upper and lower respiratory tracts. Thomas[23] assumed nasal breathing at rest, estimated nasal dimensions from the tracheal cross sectional area (assuming the infant nose to be a scaled down adult one), and made assumptions about age related tidal volume and respiratory rate. He predicted that nasal deposition would rise with age so that 0.2% of particles of 2 μm diameter would deposit in the nose at one month, rising to 37.8% at 10 years. Xu and Yu,[24] making different assumptions, predicted the opposite trend with oral deposition and estimated that 6% of particles of 2 μm diameter would deposit in the mouth at one month, falling to 0% at 10 years. To improve these models, age related measurements of upper airways dimensions, the relative amounts of nasal and oral breathing at different ages, and the effect of airways obstruction on particle deposition in the upper airways and lungs are needed.

There have been few deposition studies of nebulised aerosols in children. Alderson *et al*[12] used a DeVilbiss 900 ultrasonic nebuliser and face mask to study radiolabelled aerosols in 11 children with cystic fibrosis aged from 18 months to 17 years and found large extrathoracic deposition in the younger children and increased lung deposition with age. Those with normal ventilation scans had uniform deposition of labelled aerosol, whereas those with areas of reduced ventilation had corresponding areas of reduced deposition. The mode of inhalation was not noted, but nose breathing by the younger children may explain the differences.

O'Doherty and colleagues[13] found total lung deposition of pentamidine to be similar (2.5% of the nominal dose) in a group of eight children aged 8–13 years inhaling technetium-99m labelled albumin from a Respirgard nebuliser and mouthpiece to a group of adults. There was no relationship between age and total deposition, but the children had more central deposition than the adults.

Conversely, Mukhopadhyay and colleagues[14] failed to show a significant relationship between indices of pulmonary damage and total lung deposition of radiolabelled tobramycin inhaled via a mouthpiece in a group of 27 children and young adults aged 4–23 with cystic fibrosis, although higher Crispin-Norman scores and lower values of forced expiratory volume in one second (FEV_1) were associated with reduced peripheral deposition. The mean dose delivered to the lungs was 8 mg (6.7% of a nominal 120 mg placed in the nebuliser) and there was wide variation between patients. The authors also failed to show any relationship between age and lung deposition. Chua *et al*[15] also



Drug dosages:
The following dosages have been suggested in published guidelines:

Salbutamol – *Nebulised*, 5 mg or 0.15 mg/kg.
MDI + Spacer, 100 μg, one actuation then inhale, repeat up to 20 times.

Terbutaline – *Nebulised*, 10 mg or 0.3 mg/kg.
MDI + Spacer, 250 μg, one actuation then inhale, repeat up to 20 times.
Subcutaneous, 2.5 mg.

Steroids – Prednisolone 2 mg/kg/day for three days, max 40 mg/day, or hydrocortisone 100 mg six hourly IV.

Aminophylline – *Intravenous infusion*, Loading dose, omit if already on theophylline, 5 mg/kg over 20 minutes, then 1 mg/kg/hour.

Ipratropium – *Nebulised*, 250 μg six hourly.

Figure 2 Treatment of severe acute asthma in childhood.

found a median lung deposition of 6% in eight children with cystic fibrosis aged 6–18 years during mouth breathing. Nose breathing in the same group reduced lung deposition to 2.7%, while the median deposition in infants aged 0.3–1.4 years, who breathed nasally during quiet sleep, was 1.3%.

Measuring aerosol delivery

There are a number of problems in measuring the aerosol that is delivered to infants and young children due to difficulty in measuring baseline respiratory function and controlling inhalation in an often uncooperative age group. The administration of radiolabelled drugs to young children and infants has tended to be restricted to those with serious underlying respiratory problems. Although the total radioactive dose in these studies is small, impaction theory and work with other aerosols suggest that high central deposition may occur and "hot spots" of deposition may be found over a small area at airway bifurcations.[25] The impact

of uneven deposition and hot spots on the calculated risk of radioisotope administration has received little attention.[26]

Lung deposition may also be estimated using a pharmacokinetic approach[27 28] (see also the review on pp S31–44).

Clinical use of nebulisers in childhood

ASTHMA

Nebulisers are used most commonly in acute severe asthma and in children too young to use other devices. There is considerable variation in nebuliser usage in Europe with a more than eight fold difference between countries in the number of physicians prescribing nebulised steroids to children.[29] Nebulisers are bulky, expensive, and inconvenient and, where possible, metered dose inhalers with spacer devices or dry powder inhalers are the preferred method of drug delivery.[30]

Status asthmaticus

It is important to use oxygen to drive nebulisers wherever possible. Nebulised salbutamol is beneficial in the treatment of severe acute asthma in adults prior to admission to hospital,[31] and high dose inhaled β_2 agonists given by nebuliser or metered dose inhaler and spacer (see below) are recommended in the immediate treatment of severe asthma (fig 2).

A recent advance in the management of acute childhood asthma has been the use of frequent and repeated nebulisation of β_2 agonists. Frequent nebulisation (every 20 minutes) of a β_2 agonist led to a smoother increase in FEV_1 and an earlier and better maintained peak response than hourly treatment.[32] A dose of 0.15 mg/kg salbutamol (to a maximum of 5 mg) given every 20 minutes appears to be more effective than lower doses.[33]

Continuous nebulisation in non-intubated children with severe asthma in intensive care is becoming more common. Moler *et al*[34] studied 19 children and found continuous nebulisation of terbutaline (4 mg/hour) to be effective in improving clinical scores and decreasing arterial carbon dioxide tension ($PaCO_2$). No significant toxicity was recorded during treatment lasting up to 37 hours. Portnoy *et al*[35] found that 12 patients treated with continuous nebulised terbutaline (1–12 mg/hour for 1–24 hours) showed improvement in gas exchange and respiratory rate within an average of eight hours. No significant toxicity was noted and all 12 were discharged from the intensive care unit within 24 hours. In a further 26 children[36] with severe exacerbations of asthma unresponsive to systemic theophylline, methylprednisolone and intermittent β_2 agonist inhalation, continuously nebulised terbutaline administered at doses of 1–12 mg/hour for a mean duration of 7–8 hours (range 1–24) caused clinical scores to improve rapidly and all patients showed marked improvement in pH and $PaCO_2$ during the first two hours. Improvement in oxygenation was more variable and tended to be delayed. If nebulisation was interrupted even for a few minutes during the acute phase of treatment the wheezing and respiratory rate increased. Surprisingly few toxic effects occurred. These included transient unifocal premature ventricular contractions, hyperglycaemia, muscle cramps, and tremor. Transiently raised creatine phosphokinase levels may occur in children receiving high dose continuous salbutamol[37] but its significance is not clear. Moler[38] compared plasma concentrations and cardiac side effects of terbutaline in 16 children with "stable asthma" given 16 mg terbutaline either continuously or as four doses of 4 mg over 20 minutes in a randomised double blind trial. Continuous nebulisation produced similar plasma concentrations and cardiovascular effects to intermittent therapy. Increased creatine phosphokinase levels were not seen.

Side effects may be dose related. Portnoy *et al*[35] have suggested that continuous terbutaline should be given at a dose of 1–3 mg/hour since this dose is efficacious and causes few side effects. Singh and Kumar[39] have confirmed these findings with salbutamol at a dose of 0.15 mg/kg/hour.

In a prospective randomised study Papo[40] treated 17 children with either continuous or intermittently nebulised salbutamol (0.3 mg/kg/hour or 0.3 mg/kg over 20 minutes every hour). As judged by the clinical score and blood gas values, the children treated continuously improved faster and spent less time in hospital than those receiving intermittent treatment. No side effects were seen.

The International Paediatric Asthma Consensus Group[41] have suggested that inhaled β_2 agonists can be used in far higher doses and for longer periods than have hitherto been recommended, including continuous administration of full strength respirator solutions of salbutamol and terbutaline, although only in a hospital intensive care unit. Typical equipment used for the continuous administration of nebulised treatment is shown in fig 3.

Many children under the age of 18 months recover spontaneously from wheeze without treatment. Indeed, under the age of 12 months an argument could be made for observing infants with mild to moderate wheeze, especially as treatment with nebulised bronchodilators may be associated with transient drops in oxygen saturation and short term paradoxical bronchoconstriction.[19 21] In practice a therapeutic trial is usually undertaken. Nebulised salbutamol, given in two doses one hour apart, relieved clinical signs of respiratory distress in wheezy children less than two years of age more effectively than placebo,[42] and nebulised ipratropium bromide was effective in 40% of wheezy infants admitted to hospital.[43]

Nebulisers are sometimes recommended for home treatment. In one survey 20% of parents gave a second dose of nebulised bronchodilator rather than seeking help when their child did not improve.[44] Clear written and verbal instructions need to be given. Mild attacks characterised by the absence of severe or life threatening features (fig 2) may be treated with nebulised bronchodilator therapy every 4–6 hours providing the child responds well to each

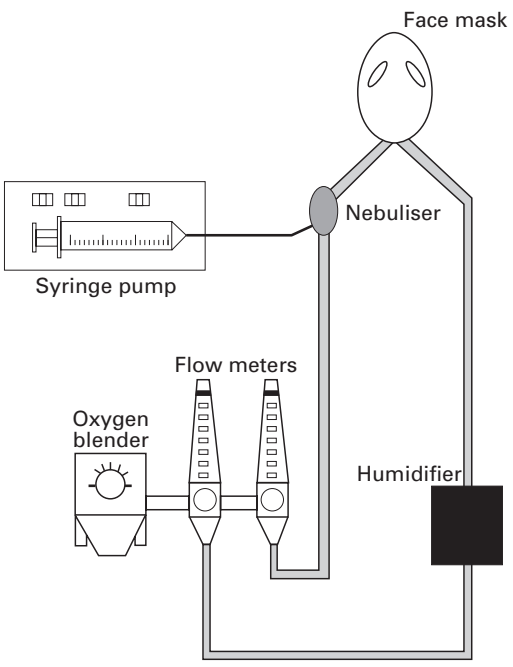


Figure 3 Possible equipment for continuous nebulisation. Humidified oxygen is used to drive the nebuliser at flows of 6–8 l/min. Additional oxygen is supplied by the other limb and should be adjusted to maintain normal oxygen saturation. The syringe driver constantly refills the nebuliser as aerosol is produced. The syringe rate and concentration of drug used will need to be adjusted for the individual patient and type of nebuliser.

dose and there is a steady improvement. A "good response" may include a reduction in dyspnoea and in the use of accessory muscles of respiration, a decrease in respiratory rate and audible wheeze, and a resumption of normal activities such as playing and feeding. If the response is poor with worsening of the above features, or lasts less than four hours, or if the child is becoming worse, the family doctor should be consulted with regard to possible hospital admission and oral corticosteroid therapy (prednisolone 2 mg/kg). Prophylaxis should be considered in children requiring nebulised bronchodilator therapy on a regular basis.[30]

Several studies have shown that a β_2 agonist delivered by a metered dose inhaler and large volume spacer device is as effective as a nebuliser for rapidly achieving maximum possible bronchodilation in severe exacerbations of asthma.[45]

Nebulisers compared with metered dose inhalers

In chronic asthma: terbutaline delivered by a metered dose inhaler and Nebuhaler spacer provided similar clinical benefit to nebulised terbutaline in the long term management of children and adults with stable airflow obstruction.[46] A dose response study of inhaled terbutaline administered via a large volume spacer or nebuliser in asthmatic children also found that they were equivalent in children who were not in acute respiratory difficulty.[47] In a randomised double blind crossover study fenoterol was given by nebuliser or by metered dose inhaler, with or without a large volume spacer, to 10 children with asthma.[48] All three methods of drug delivery produced significant changes in lung function compared with placebo, but the increase in FEV_1, FVC, and peak flow were greatest with the metered dose inhaler and spacer.

The use of spacer devices with face mask attachments – for example, the Aerochamber, the Volumatic with Laerdal face mask, the Nebuhaler with McCarthy mask, and the Babyhaler – are becoming increasingly popular. Treatment of asthmatic infants with inhaled steroids via such devices has been particularly successful in a group that is otherwise difficult to treat.[49 50] Less drug is deposited in the mouth and oropharynx than with nebulisation and treatment time is shorter.

In acute severe asthma: randomised trials[51–58] comparing nebulisers and metered dose inhalers in the treatment of acute severe childhood asthma are outlined in table 1. In two of the studies[57 58] the spacer was less effective in some of the younger children and patients with severe airways obstruction, possibly because they could not produce sufficient flow rates to trigger the valve.

A recent analysis of trials comparing metered dose inhalers with nebulisers in the emergency treatment of acute severe asthma[45] concluded that there was no significant difference between the two delivery methods. The minority of studies that claim nebulisers to be superior have compared the bronchodilator response in acute exacerbations using lower doses of β_2 agonists from metered dose inhalers than from nebulisers or, where numerical dose equivalence has been maintained,[59] the spacer has been used in such a way that most of the dose administered is not available for inhalation.[60]

The use of a spacer and metered dose inhaler is cheaper than a nebuliser.[61] Newhouse has commented[62] that in several studies aerosols generated by metered dose inhalers have been 50–75% less expensive than equivalent nebuliser therapy, although this estimate includes the cost of respiratory therapists who are not generally used in UK hospitals. Spacers and metered dose inhalers may easily be used in acute asthma and should be administered by giving one puff every few seconds until improvement occurs (up to 20 puffs).[30]

Prophylaxis of asthma

Sodium cromoglycate remains a safe prophylactic treatment for childhood asthma.[63 64] It reduces symptoms when given four times a day,[65] although it may not do so in younger children when given three times a day.[66 67] Sodium cromoglycate compares favourably with oral theophylline in controlling symptoms and the absence of side effects.[68] If asthma symptoms are not controlled by sodium cromoglycate then inhaled steroids are usually considered. The nebuliser suspension of beclomethasone dipropionate has been discontinued. Clinical trials using this nebulised formulation showed little benefit[69] as only a

Table 1 Randomised trials of nebulisers versus metered dose inhalers used with spacers in the treatment of acute severe childhood asthma

Reference	*No. of patients*	*Age (years)*	*Study design*	*Drug regime*	*Primary outcome measures*	*Results*	*Comments*
Freelander[57]	28	3–13	R, NB	Terbutaline 2.5 or 5 mg by NEB, 1.25 or 2.5 mg by MDI + Nebuhaler	Symptom score, PEF	NEB = MDI	Nebuliser group older
Prendergast[58]	27	3–6	R, NB	Terbutaline 0.2 mg/kg NEB + face mask, 0.05 or 0.1 mg/kg MDI + Nebuhaler	Symptom score	NEB = MDI	
Fuglsang[51]	21	7–14	R, DB	Terbutaline 0.1 mg/kg NEB or MDI + Nebuhaler, then crossover	FEV_1	NEB < MDI	
Lin[52]	111	5–16	R, NB	Terbutaline 2.5 mg NEB + mouthpiece, 0.75 mg MDI + Aerochamber	FEV_1/PEF/ FVC, Sao_2, symptom score	NEB < MDI	Neb < MDI for Sao_2, PEF and FEV_1. Desaturation occurred with nebuliser use
Parkin[53]	60	1–5	R, NB	Salbutamol 0.15 mg/kg + ipratropium bromide 125 μg by NEB + face mask, salbutamol 4–600 μg + ipratropium bromide 40 μg by MDI + Aerochamber	Symptom score at 12 hours	NEB = MDI	Nine subjects crossed over from Aerochamber to nebuliser
Kerem[54]	33	6–14	R, DB	Salbutamol 0.15 mg/kg by NEB + face mask (max 5 mg) 600–1000 μg by MDI + Volumatic	FEV_1, Sao_2, symptom score	NEB = MDI	Multiple actuations of MDI into spacer
Vazquez Cordero[55]	18	?	R, NB	Salbutamol, repeated doses at 20 minute intervals to max 0.15 mg/kg (or 5 mg) by NEB + face mask or MDI + Volumatic	FEV_1	NEB = MDI	
Chou[56]	152	2–? Median 8.8 yrs	R, NB	Salbutamol 0.15 mg/kg by NEB + face mask (max 5 mg), 270 μg by MDI + Aerochamber	PEF, symptom score, Sao_2	NEB = MDI	Number of treatments determined by attending physician. MDI group had shorter treatment times in ER

R = randomised; NB = not blinded; DB = double blind; NEB = nebuliser; MDI = metered dose inhaler; PEF = peak expiratory flow; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; Sao_2 = oxygen saturation; ER = emergency room; NEB = MDI = no difference in outcome between nebuliser and metered dose inhaler groups; NEB < MDI = outcome measures significantly better in the metered dose inhaler group.

small amount of drug exited nebulisers in particles small enough to enter the lungs.[16] Budesonide suspension appears to give a therapeutic dose of drug contained in respirable particles[70 71] and may reduce the need for oral therapy in adults[72] and children[73] with severe chronic asthma. Nebulised budesonide reduced the need for other maintenance treatment in 47 of 56 infants and preschool children with severe chronic asthma in one study[74] but not in another.[75]

The use of a mouthpiece improves lung deposition and reduces deposition on the face. However, young children may not use the mouthpiece properly, inhaling through the nose, blocking the mouthpiece with the tongue, or simply blowing through the mouthpiece. The best delivery method should be individually determined. If a face mask is used for nebulised corticosteroids the eyes and face should be washed after each treatment and a drink given. Holes in the mask should be covered if the drugs in the aerosol are potentially harmful to the eyes. If a child complains of a sore throat or is reluctant to feed, oral candidiasis should be looked for.

PAEDIATRIC AND NEONATAL INTENSIVE CARE

Most non-elective admissions to intensive care are related to respiratory disease or failure,[76] making the inhaled route particularly logical for treatment. Compared with instillation into the trachea, nebulisation results in a much more homogenous distribution of drug in the lung. There is, however, a paucity of information concerning nebuliser use in paediatric intensive care.

Mechanical ventilation

Nebulised aerosol therapy during mechanical ventilation, also discussed by O'Doherty and Thomas on pp S56–59, is affected by the type of nebuliser, the volume fill, the treatment time, the inspiratory time, and the presence of a humidification device. Some studies have shown an effect of the size of the endotracheal tube on drug delivery in vitro,[77] while others have not.[78 79] There is considerable variation in the amount of drug delivered from different nebulisers[80 81] and from the same nebuliser to different patients.[82 83] Evaluating five different nebulisers in a neonatal circuit with a pressure limited ventilator and 3.5 mm endotracheal tube without additional humidification, Cameron *et al*[80] found that deposition of an aerosol of aminophylline onto a filter varied by a factor of 10. Furthermore, there were considerable differences between the ability of the different nebulisers to deliver a suspension. In vitro nebulisers producing small, sub-micronic particles appear to deliver more drug,[77] but in clinical practice many of these tiny particles may be exhaled and, when suspensions are being nebulised, the aerosol produced may not contain any drug particles.

Animal and in vitro studies have shown that lung deposition of aerosol may be improved by increasing the volume fill,[81 84] increasing the proportion of the respiratory cycle spent in inhalation,[81 84] and increasing tidal volume and aerosol residence time within the lung.[85] Humidification during jet nebulisation is provided by the nebuliser and additional humidification decreases lung deposition.[77 78] When nebulisers are used as the source of driving gas in ventilator circuits, significant changes may need to be made to the ventilator settings. Aerosol flow in the ventilator circuit may lead to excessive drug deposition on ventilator parts leading to valve malfunction.[85] The use of in line filters on the expiratory limb is recommended.

Nebulisers may run continuously during ventilation or may be phased to operate only during inspiration. This, however, does not necessarily improve drug delivery, presumably because there is a delay between nebuliser actuation and aerosol production which occurs towards the end of the inspiratory phase.[82] With continuous nebulisation considerable amounts of aerosol tend to be expelled with the waste

gases or are deposited in the ventilator tubing.

Lung deposition of nebulised aerosol is 1–5% of the initial dose in most studies. Although this appears small, it is in fact extremely large when expressed per kg body weight. One study in adults[83] in which all the factors outlined above were optimal delivered over 15% of the dose of radiolabelled albumin placed in a nebuliser. Like some of the other studies quoted above, delivery of aerosol was through a tracheostomy tube. It remains to be seen if these high levels of drug delivery can be repeated in children using nasotracheal or orotracheal tubes and different nebulisers and types of ventilator.

Several papers have described the in vitro administration of aerosols to the mechanically ventilated model lung by use of a metered dose inhaler and intratracheal catheter,[86–88] with deliveries in excess of 90% of the dose, much of it in particles smaller than 5 μm. A subsequent report[89] which described epithelial airway lesions in rabbits treated by this method means that it cannot be recommended and emphasises the need for drug delivery methods to be fully evaluated.

An alternative to nebuliser therapy is the use of a metered dose inhaler and in-line spacer. These are effective in improving drug delivery to intubated patients and may be cheaper.[90] The spacer allows high velocity particles from the metered dose inhaler to decelerate and propellants to evaporate, reducing particle size. This reduces impaction of drug on the tubing and improves drug delivery. Spacer size is important[79] but the optimum size is not known.

Grigg and colleagues[91] evaluated the delivery of sodium cromoglycate to ventilated neonates via either an ultrasonic nebuliser or a metered dose inhaler with spacer. They first instilled a known amount of drug into the trachea and measured the fraction excreted in the urine over the ensuing 24 hours. They then administered sodium cromoglycate by one of the two systems studied and, by measuring the urinary excretion, extrapolated the dose delivered to the lungs. Despite a 2–3 fold variation in dose delivered between the infants within each group, the metered dose inhaler and spacer delivered a much higher dose/kg than the nebuliser (234 μg/kg vs 107 μg/kg). In a parallel study this group compared their in vivo findings with different in vitro methods of measuring drug delivery from ventilators and found good agreement with a filter and test lung, suggesting that this may be the method of choice for further in vitro work in this field.

A similar proportion of the nominal dose was delivered to the lungs in studies by O'Callaghan[92] using beclomethasone in rabbit studies and in vitro by Everard[93] using sodium cromoglycate. With a 4×11 cm cylindrical chamber connected to the inspiratory limb of the ventilator circuit, Everard[93] found better delivery at higher tidal volumes, with longer inspiratory times, by connecting the spacer as close as possible to the endotracheal tube, and by actuating the metered dose inhaler immediately before the start of the inspiratory phase.

Grigg *et al* subsequently studied the delivery of budesonide from a spacer and metered dose inhaler in a ventilator circuit using the same test lung methodology[94] and reported an encouragingly high percentage of drug delivery (14.2% of the dose). These results imply that different drugs may behave differently within spacers and underline the need for devices to be evaluated with each different drug and formulation.

NEONATOLOGY

Several lung disorders in the newborn may be amenable to inhaled therapy. β_2 agonists and anticholinergic agents are effective in ventilated and spontaneously breathing infants.[95–99] Inhaled steroids may be used in bronchopulmonary dysplasia[100] and there has been recent interest in delivery of pulmonary antioxidants by nebulisation to prevent neonatal lung injury.[101] Delivery of surfactant and pulmonary vasodilators directly to the lung raises exciting possibilities for the treatment of neonatal lung disease. However, little is known of the effect of inhaled medication on the immature lung, and concern has been expressed about the possible effects of high dose steroids[102] and of propellants and surfactants in metered dose inhalers.[103]

Many of the factors affecting lung deposition discussed in previous sections also apply to neonates, but very little pertinent clinical information is available. Many of the questions posed by a 1990 review[102] remain unanswered. Once again, spacer devices may prove to be more efficient and cheaper than nebulisers.[103]

BRONCHIOLITIS

Bronchiolitis is the commonest lower respiratory tract infection of infancy,[104] occurring in winter epidemics each year. The illness generally runs a benign course and, although many infants need admission to hospital, the mortality is less than 1% of these.

Ribavirin may be used in the treatment of acute bronchiolitis and is administered by a small particle aerosol generator (SPAG) which produces particles of drug approximately 1.3 μm in diameter. In infants who were previously well, symptom scores and oxygen saturation improved more rapidly in those treated with the drug, but the length of time in hospital was unchanged.[105 106] There is no evidence that treatment alters long term morbidity. Because of the generally benign course of the illness, and the costs and difficulties of ribavirin administration, it is not usually used for infants who were previously well.[104]

Infants with chronic cardiorespiratory disease such as bronchopulmonary dysplasia are at risk of more severe disease and the mortality may be up to 3.5% of those who are admitted to hospital.[107] There have been few satisfactory controlled studies of ribavirin therapy in this group. It may improve symptom scores and oxygenation, but not mortality or the length of hospital stay.[108]

There have been a number of uncontrolled reports of ribavirin use in infants mechanically ventilated for bronchiolitis caused by respiratory syncytial virus[109] but only two published randomised controlled trials. Smith *et al*[111] studied 28 infants of mean age 1.4 months, seven of whom had underlying disease. They received either ribavirin (20 mg/ml) or sterile water from a SPAG continuously for seven days or until extubated. Those who received ribavirin had significantly shorter duration of mechanical ventilation, use of supplemental oxygen, and hospital stay. This study has been criticised because of the use of nebulised water as a "placebo"[111] which may have provoked bronchoconstriction, although this has been discounted.[112 113] Furthermore, the duration of ventilation in the placebo group was similar to that of untreated historical controls in a previous study.[114]

Meert *et al*[115] randomised 41 children who required mechanical ventilation for bronchiolitis caused by respiratory syncytial virus to receive either ribavirin 20 mg/ml via a SPAG made up with 0.9% saline or 0.9% saline alone. Ribavirin or placebo were given for 18 hours a day for five days or until extubation, whichever was sooner. There was no statistically significant difference between the two groups in the duration of mechanical ventilation, use of supplemental oxygen, and hospital stay.

Ribavirin may precipitate in ventilator circuits causing high expiratory pressures and leading to pneumothoraces.[116] Blockage of the expiratory valve of the ventilator can be avoided by the use of filters in the expiratory limb of the circuit which should be changed regularly.[117] It is currently administered for 12–20 hours per day from a SPAG which releases aerosol into an oxygen tent or hood. High dose therapy of short duration has been shown to reduce the viral load and was well tolerated in one small uncontrolled study.[118] Short duration therapy, if efficacious, would allow improved care of infants and should be further evaluated.

Nebulised bronchodilators[119] and ipratropium bromide[120] have been used in a number of studies with little effect on measures of illness severity or lung function in infants with acute bronchiolitis, and nebulised salbutamol may worsen oxygen saturation.[20]

CYSTIC FIBROSIS

Nebuliser therapy has made a significant contribution to the management of children with cystic fibrosis, delivering antibiotics, anti-inflammatory agents, and bronchodilators to the lungs. Newer treatments to improve sputum clearance are being developed, and the role of nebulisers in this disease is discussed by Spencer on pp S89–91.

LARYNGOTRACHEOBRONCHITIS (CROUP)

Croup is common in infants and young children due to acute obstruction of the laryngeal area, usually secondary to a parainfluenza virus infection. The clinical syndrome consists of inspiratory stridor, a barking cough, hoarseness, and signs of respiratory distress. Nebulised racemic adrenaline has been shown to improve respiratory distress transiently.[121] The effect is noticeable within 30 minutes and usually lasts less than two hours. There is no evidence that the use of adrenaline alters the natural history of the illness, but its use may lead to a decreased need for intubation.[122] Its major use is in children in whom temporary relief is required while facilities are arranged to provide an artificial airway. In certain patients where it is very important to avoid endotracheal intubation – that is, those with subglottic stenosis – nebulised adrenaline has been given at regular intervals, but only in the intensive care unit where facilities for intubation are immediately available. It should not be used in ambulatory patients who are sent home soon after treatment.[123]

Treatment of croup with systemic corticosteroids has been investigated extensively and a meta-analysis of 10 studies concluded that this treatment was effective.[124] Husby *et al*[125] reported that nebulised budesonide (2 ml of 500 μg/ml using a Pari nebuliser with a CR 60 compressor) given twice, 30 minutes apart, resulted in a significant decrease in stridor, cough, recession, dyspnoea, and cyanosis two hours after administration in children with moderate to severe croup compared with a control group given nebulised saline. The authors suggest that the rapid onset of action may be due to α adrenergic vasoconstriction. Unfortunately, there were no data on the condition of patients following the measurements made two hours after drug delivery, and further information is awaited.

Vaccination

Blockage of replication of the measles virus in vivo by maternal antibodies may render immunisation ineffective in a number of very young children. In this age group administration of the vaccine by aerosol has the theoretical advantage that antibodies lining the respiratory epithelium, predominantly IgA, are less likely to be acquired from the mother (and therefore inhibit viral replication and immunisation) than circulating maternally derived antibodies which are predominantly IgG.

In a Mexican study[126] 86% of a group of infants aged five months seroconverted after immunisation by aerosol with the Edmonston-Zagreb strain vaccine. The vaccine was given via a nebuliser chamber driven by a compressor for 30 seconds. In a subsequent study in Gambia[127] 94% of infants aged 4–6 months seroconverted after Edmonston-Zagreb strain vaccine was given by nebulisation into a plastic hood placed over the head and shoulders. Measles infection is probably acquired through the nasal or conjunctival mucosa, and this may also be the preferred site of delivery of the vaccine. This is another example where the optimum site for aerosol delivery is not known. It is not known if vaccine given by aerosol provides protection earlier than if given by the subcutaneous route.

Table 2 Factors to consider when choosing a nebuliser for children (much of this information is unclear or unknown in paediatric practice)

Patient factors:	
Age	Can an alternative more suitable device be used such as a metered dose inhaler and spacer?
	Is a mouthpiece or face mask to be used? A mouthpiece is preferred where it is used properly.
Lifestyle	Are size, weight, and portability important?
Drug factors:	
Suspension or solutions?	Some nebulisers are inappropriate for drug suspensions – for instance, ultrasonic nebulisers and jet nebulisers producing very small particles.
Viscosity	Viscous solutions such as some antibiotics are not nebulised by some nebulisers.
Site of deposition	Smaller particles for alveolar deposition, but are these needed for steroids or β_2 agonists?
Technical factors:	
Drug output	Choose the nebuliser with the highest respirable output in the shortest time. "Breath assisted, open vent" nebulisers have not been fully evaluated in children.
Compliance	What is the optimum nebulisation time with the proposed drug and nebuliser?
Bioavailability	Increasing the dose to the lungs may also increase systemic drug effects.
Optimum compressor	Choice of compressor may vary the output of the nebuliser considerably and should be chosen with a particular drug and nebuliser in mind.
Cost of the nebuliser	
Durability of the nebuliser	

Choice of nebuliser and method of use

In the authors' opinion, nebulisers are overused both in hospital and in the community for the treatment of childhood asthma. They can often be replaced by a metered dose inhaler and spacer. Where nebulisers are recommended, their use should follow recognised guidelines.[30 41]

If children use nebulisers at home, oral and written instructions should be given to the patient or parent on the method of use, the action to be taken in the event of worsening asthma, the cleaning and maintenance of the nebuliser and compressor, and when to attend for follow up. The child should be supervised in a clinic with expertise in the delivery of inhaled medications such as an asthma clinic. Such supervision should include measurement of spirometric values or peak flow, monitoring of prescriptions, and regular servicing of the compressor.

Very little work has been done on the important factors to be considered when choosing a nebuliser for children. Some thoughts are given in table 2, but these are not based on extensive research. The device should conform to British Standard BS7711. The nebuliser/compressor combination proposed must deliver an adequate amount of the prescribed drug in appropriately sized particles to the patient. Ideally this information would be provided by an independent source but, if not, it may be obtained from the manufacturer

Breath assisted open vent nebulisers improve drug delivery but require further evaluation before they can be recommended for infants and young children. Where possible, a mouthpiece should be used with a nebuliser as this increases pulmonary deposition of drug. If a face mask is used it should be closely applied to the face. The patient should be given a maximum time for nebulisation (based where possible on specific studies). This time will depend on the nebuliser and drug being used, but for some medications administered for asthma little drug may be delivered after five minutes.

Conclusions

Nebulised drug therapy has a very important role in paediatric practice. With the development of new drugs such as rhDNase and genetic therapies, indications for using nebulisers will increase. Much more work is needed on the basics of drug delivery by inhalation to this age group to ensure reproducible delivery of adequate drug quantities to the desired site. In the treatment of asthma it is likely that delivery of bronchodilators and prophylactic medications by metered dose inhaler and spacer will become more popular than nebulised therapy, thereby decreasing treatment time and cost.

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