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Nebulised drug therapy may be less e ective in patients undergoing mechanical ventilation than in those spontaneously breathing for two main reasons – firstly, ventilated patients often have severe lung disease associated with airway plugging and collapsed segments which limit the spread of aerosols to a ected areas, and secondly, aerosol deposition from nebulisers and metered dose inhalers is reduced during mechanical ventilation compared with spontaneous breathing.[1] This is due to a number of factors including the site of the nebuliser in the ventilator circuit, the ventilator settings, the method of triggering of the nebuliser, and the size of the endotracheal tube. The indications for nebuliser therapy in mechanically ventilated patients are given in table 1.

In ventilated patients compliance is not a problem and it is not necessary for nebulised treatments to be completed rapidly. Indeed, continuous nebulisation may be appropriate for some conditions so nebulisers need not be selected on the basis of rapid output characteristics.

Jet nebulisers tend to leak around their joining parts, especially when used in conjunction with a ventilator. The back pressure necessary to cause leaks should be documented by the manufacturer and users should be encouraged to use systems which do not leak. There is also a need to determine the nebuliser outputs and the particle size produced when attached to short inspiratory triggered nebulisation.

Nebulisers used in ventilator circuits should not be left permanently in line and should be cleaned and changed between nebulisations to avoid small particle bacterial aerosols.[13] Suitable filters should be placed between the ventilator circuit and the inspiratory and expiratory ports of the ventilator to protect the valves in the ventilator from the e ects of deposited aerosol.

Methods of aerosol administration

Bronchodilators and steroids can be delivered during mechanical ventilation using metered dose inhalers, rather than nebulisers.[14] These are attached to an adapter in the ventilator circuit and actuated during lung inflation. The method is simple and treatments can be administered rapidly. The amount of drug reaching the lungs has been estimated as 1.5–2% in infants[12 15] and 3.9–5.6% in adults.[16 17] Administration using a metered dose inhaler is increased by using an aerosol holding chamber[17] and this method may be more e cient than using an inspiratory phase activated jet nebuliser.[16] Arnon *et al*[18] found that the use of a metered dose inhaler and an Aerochamber (MV15, Trudell Medical, Canada), attached between the Y piece and the endotracheal tube, delivered larger amounts of budesonide to a filter in an in vitro ventilator circuit than either an MAD2 nebuliser or an Ultravent nebuliser. Another study in ventilated patients with airways obstruction has shown that a 270 μg dose of salbutamol given via a metered dose inhaler produces a similar increase in passive expiratory flow rate to that produced by a 2.5 mg dose given by a jet (Upmist) nebuliser.[19]

The factors which appear to increase aerosol delivery to the mechanically ventilated patient from metered dose inhalers are the use of a holding chamber,[17 18 20] locating the metered dose inhaler adapter on the inspiratory limb of the circuit rather than immediately adjacent to the endotracheal tube,[17 20] the absence of humidification,[21 22] activation during lung inflation,[23] the use of larger bore endotracheal tubes,[23] and a reduced lung inflation rate.[23]

Table 1 Indication for use of nebulisers in patients receiving mechanical ventilation

Indication	*Drug type*
Of probable value	
Bronchospasm/asthma [B]	β_2 agonists (salbutamol, terbutaline, etc.)[2–4] Anticholinergic drugs (ipratropium bromide)[2 5]
Of possible value	
Respiratory syncytial virus infection in infants [C]	Tribavirin (ribavirin)[6]
Bronchopulmonary dysplasia in infants [C]	Corticosteroids[7]
Adult and infant respiratory distress syndrome [C]	Surfactants (beractant, colfosceril palmitate, poractant alfa, pumactant)[8–10]
Pulmonary infection [C]	Antibiotics[11]
Pulmonary hypertension [C]	Prostacyclin[12]

[B] and [C] indicate strength of evidence in terms of scientific validity (see Appendix 4 on page S22).

Jet nebulisers can be used during pressure limited or volume cycled ventilation. During volume cycled ventilation the ventilator can only be driven during lung inflation. As the gas used to drive the nebuliser forms a proportion of the patient's tidal volume, its volume and oxygen content must be appropriate for each individual. During pressure limited ventilation the nebuliser can be driven continuously. Jet nebulisers are widely available and cheap, but many are not designed for use during ventilation and leak, particularly at high inflation pressures. During pressure support ventilation the use of a continuously running jet nebuliser may prevent a patient from being able to initiate a ventilator breath as the nebuliser interferes with the achievement of the negative pressure required.[24]

Aerosol deposition from jet nebulisers has been measured in vivo as 1.2–3.0% in adults.[16 25–27] In vivo data are lacking in infants. For tribavirin administration the continuous use of the small particle aerosol generator (SPAG), consisting of a jet nebuliser and par-

ticle drying tube, is clinically proven although deposition associated with this apparatus is unknown and delivery in vitro is poor.

Several factors may improve aerosol delivery to the mechanically ventilated subject from jet nebulisers. Placing the nebuliser in the inspiratory limb of the ventilator circuit rather than at the catheter mount connection or on the expiratory limb increases delivery.[28 29] However, placing the nebuliser too far from the patient (>30 cm) may increase deposition on the circuit and reduce delivery.[30] Delivery is also increased by inspiratory triggered nebulisation,[29] increasing the fill in the nebuliser,[27] interrupting humidification during nebulisation,[22 31] and attaching the nebuliser to a spacer in the inspiratory limb.[25 27 28] Alteration of the ventilator settings also a ects deposition which is increased by decreasing the respiratory rate, increasing the inspiratory time, and by decreasing minute ventilation.[25 27 28] In spontaneously breathing subjects the use of positive end-expiratory pressure (PEEP) can increase the improvements in lung function provided by inhaled salbutamol,[32] but use during mechanical ventilation will increase peak airways pressure and may also worsen air trapping associated with severe bronchospasm.[33] Small particles are associated with increased penetration of endotracheal tubes[34] and nebulisers which produce these may be associated with higher pulmonary deposition.[35]

Ultrasonic nebulisers can be used during all types of mechanical ventilation. They are simpler to use than jet nebulisers as no gas flow is required and many have large capacities. Disadvantages are that in theory some drugs might not be stable during ultrasonic nebulisation and the process may produce erroneous automated measurements of tidal volume. Pulmonary aerosol deposition in vivo associated with ultrasonic nebulisers has been estimated as 1.3% in infants using the Pentasonic. In vivo data are lacking in adults but in vitro data indicate that delivery through an endotracheal tube during volume cycled ventilation can be as high as 22% using the Samsonic ultrasonic nebuliser, an 18 ml fill volume, and an aerosol storage chamber.[36] Under similar conditions the system 22 Acorn jet nebuliser delivers 10%.[28]

The factors that appear to improve aerosol delivery using ultrasonic nebulisers include placing the nebuliser in the inspiratory limb of the ventilator circuit rather than at the catheter mount connection or on the expiratory limb,[26] increasing the fill in the nebuliser,[28 36] attaching the nebuliser to a spacer in the inspiratory limb,[28 36] and alteration of the ventilator settings – for example, decreasing the respiratory rate, increasing the inspiratory time, or decreasing the minute ventilation.[36] Drugs have to be shown to be stable during ultrasonic nebulisation.

Recommended practice

Any of the following three methods of aerosol administration currently appear to be appropriate for mechanically ventilated patients:

1. Administration by metered dose inhaler into a spacer connected to the inspiratory limb of the ventilator circuit with actuation at the onset of lung inflation. Humidification should be interrupted for a few minutes before administration.
2. Use of an inspiratory phase activated jet nebuliser connected to an aerosol holding chamber placed on the inspiratory limb of the circuit, or at least connected by a T piece in the inspiratory tubing no more than 30 cm from the Y piece. A high nebuliser gas flow should be used and the drug solution should be diluted to fill the nebuliser to capacity. Humidification should be discontinued for a few minutes before and throughout nebulisation.
3. Use of an ultrasonic nebuliser connected to the inspiratory limb of the circuit. The drug solution should be diluted to fill the nebuliser to capacity and humidification should be discontinued for a few minutes before and throughout nebulisation.

Clinical evidence of benefit from drug aerosols

Evidence that can be used in assessing the potential value of nebulised therapy in ventilated patients, in order of importance, is as follows:[37] (1) clinical trials using clinically relevant end points such as survival, length of stay in ITU, length of stay in hospital; (2) clinical trials using physiological measurements such as changes in airway resistance or lung compliance; (3) aerosol deposition and deposition measurements in vivo in man using radiolabelled aerosols; (4) aerosol deposition measurements in animals (these are particularly appropriate for paediatric studies although not all lung conditions a ecting infants can be mimicked in the lungs of healthy animals and, furthermore, the airway structure of animals di ers from that of human infants and therefore the distribution of aerosol may be di erent); (5) aerosol delivery measurements made in vivo by measuring urinary excretion of nebulised drugs although measurements may be a ected by other factors such as renal or liver function; (6) aerosol delivery measurements made in vitro or using combined in vivo/in vitro methods using radiolabelled or fluorescent aerosols. These are inevitably overestimates of in vivo lung deposition.

An ideal approach is a combination of these methods. In vitro studies can select those nebulisers worthy of consideration for delivering a particular drug, and then deposition and clinical outcome can be demonstrated in a particular clinical situation. The amount of drug deposited is estimated to prove that su cient drug is being deposited for clinical benefit.

There are few published studies proving the e cacy of aerosol drug treatments in ventilated patients and it is often necessary to make clinical judgements on the need for aerosol therapy using clinical trial data from spontaneously breathing subjects. This information is used, together with lung deposition or delivery data from patients receiving mechanical ventilation,

Table 2 Nebulisers for which there are research data on deposition achieved with nebulised saline, water, or drug solutions

Nebuliser	*Manufacturer*	*Reference*
Acorn jet nebuliser	System 22, Medic-Aid, Pagham, Sussex, UK	25, 27, 28
Samsonic	DP Medical, Meylan, France	36
DP100	DP Medical, Meylan, France	36
Aerotech II	CIS-US. Bedford, MA, USA	22
Twin-jet	Puritan-Bennet, Carlsbad, CA, USA	16, 22
Respirgard II	Marquest, Englewood, CO, USA	22
Power mist	Hospitak, Lindenhurst, NY, USA	22
Whisper	Marquest, Englewood, CO, USA	6
UltraNeb	DeVilbiss, UK	36
Ultravent	Mallinckrodt, St Louis, MO, USA	18, 35
Low flow nebuliser	Baxter Healthcare, McGaw Park, IL, USA	9
MAD2	Astra Meditec, Lund, Sweden	18

to try and predict the usefulness of treatment. Apparatus for which there are research data on delivery or lung deposition during mechanical ventilation are shown in table 2.

Nebulised β_2 agonists are e ective for acute severe asthma in spontaneously breathing patients[38] and their use during mechanical ventilation can also improve measurements of pulmonary function (respiratory system resistance, compliance) in adults[1 2 39] and infants[3] with acute asthma, although not all studies have shown this.[40] Pulmonary function can also be improved in adults with chronic obstructive pulmonary disease.[39 41] No clinical trials have been performed to compare di erent bronchodilators or methods of aerosol administration. In some patients delivery of aerosol to peripheral bronchioles may be particularly poor because of intense bronchospasm and it may often be appropriate to use intravenous as well as inhaled bronchodilators in patients with severe disease.

Ipratropium bromide also improves pulmonary function in mechanically ventilated patients with COPD.[1 4 42]

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Clinical trials have been performed in infants with respiratory failure associated with RSV infection, evaluating the e cacy of continuous nebulisation of tribavirin (20 mg/ml) using the SPAG.[43] This consists of a jet nebuliser coupled to a particle drying tube. In one study[5] infants treated with nebulised tribavirin had reduced durations of mechanical ventilation, oxygen treatment, and hospital stay compared with infants treated with nebulised water. In a second study[44] infants treated with nebulised tribavirin had small reductions in the duration of mechanical ventilation, supplemental oxygen use, and hospital stay compared with those receiving nebulised saline. However, the di erences were not statistically significant, although a clinically relevant drug e ect may have been missed because of reduced study power. Other possible explanations for the apparent di erences in the findings of these studies are that the nebulised water used as a placebo in the first study may have had a deleterious e ect on lung function. Alternatively, treatment with tribavirin may have been commenced too late for maximum benefit in the second study. Neither study included patients with apnoea and the e ects of nebulised tribavirin in this group have not been assessed. Further studies using larger patient numbers, di erent doses, and di erent methods of administration will be needed to clarify the role of nebulised tribavirin in severe RSV infection. This topic is discussed further in the chapter on nebuliser treatment in childhood on pages S78–88.

The SPAG, as well as being cumbersome to use, is an ine cient method for delivering aerosol (0.1 µl/min) compared with other methods and its particle size output is comparatively large (mass median aerodynamic diameter (MMAD) 6.8 µm).[45] Other devices may be better for delivering tribavirin but this has yet to be proved.

Tribavirin may deposit in ventilator circuits and block the expiratory valve, leading to expiratory pressures and barotrauma. This should be avoided by appropriate use of filters to protect the ventilator from the e ects of the aerosol.

Nebulised beclomethasone 50 µg eight hourly for 28 days reduced airways resistance and increased dynamic compliance in infants with bronchopulmonary dysplasia.[6] Beclomethasone was administered using a Whisper (Marquest Medical Products, Englewood, Colorado, USA) jet nebuliser on the inspiratory limb of the circuit and running at 4–8 l/min of humidified gas. Pulmonary deposition was not measured. Beclomethasone dipropionate nebuliser solution is no longer produced but it is to be expected that beclomethasone delivered by metered dose inhaler or an alternative nebulised steroid such as budesonide should provide similar benefit. Further studies confirming the value of this form of treatment are needed.

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Preliminary evidence suggests that nebulised colfosceril palmitate (40–80 mg) given continuously over five days may improve the alveolar-arterial oxygen tension gradient (A–aD $_2$) and fractional inspired oxygen (F $_2$) and reduce mortality in adults with sepsis-induced ARDS.[9] Weg *et al*[8] also used nebulised colfosceril palmitate in a group of patients with ARDS for 12 or 24 hours per day and found a trend towards improvement in mortality compared with no treatment.

Nebulised orciprenaline (metaproterenol) has been shown to reduce airways resistance in patients with ARDS.[46]

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