Inhalation therapy is a term which is used to describe a variety of treatment techniques, including the delivery of a variety of drugs that may be administered via inhalation, targeting lung tissue, airway secretion and micro-organisms in upper, central and/or peripheral airways. However, studies to date have typically been carried out on drugs targeting systemic effects which are administered through inhalation, aiming at deposition in the alveoli where the drug can be rapidly absorbed and distributed. There are three different kinds of inhalation device – dry powder inhaler (DPI), spray (pressurised metered dose inhaler, pMDI), or nebuliser systems. Each kind of device comes in several different models and brands, and the market is growing rapidly. A nebuliser system can be based on one of three different techniques – jet, ultrasonic and vibrating membrane; all are available as different models. Choosing the optimal device for a patient is essential to ensure the effectiveness of the therapy. However, the choice is dependent on several different factors and there is no single device that is best for all patients in all situations: individual solutions are necessary. Inhalation technique and handling of the device is essential for the effective treatment. Patients must be carefully instructed and taught how to use and take care of their device. The instructions must be reinforced on a regular basis, and the choice of device must be similarly re-assessed. To achieve effective inhalation therapy for patients, personnel must be aware of current developments.

**Keywords:** Inhalation, nebulisation, aerosols, drug therapy

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**Choice of device**

Many drugs may be administered either as a powder, a spray, or a nebulised aerosol. Even though the formulation is the same, the more common drugs are available in different inhaler device brands, or as a solution/suspension to aerosolise in a nebuliser system with unspecified characteristics. What formulation and type of inhalation device to choose is dependent upon factors such as type of drug, patient age, physical and mental capacities, and in what situation the drug is to be inhaled. Typically, the therapist is faced with a choice between a variety of alternatives. Optimally, a spray (pMDI) with a spacer should be used for delivering steroids to avoid a high bioavailability of drug deposited in the oropharynx, and to reduce simultaneously the occurrence of *Candida* spp. in the mouth. Otherwise, if drugs come...
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in different formulations, the over-riding consideration for long-term basic care in Europe is often a dry powder inhaler (DPI). Several studies have shown that DPIs are at least as effective as pMDIs with a spacer in most patients. If not produced as a powder, if patients are too young or cannot take instructions, or due to muscular dysfunction and/or pulmonary condition cannot generate an inspiratory flow through the device sufficient to mobilise the powder, a DPI is not suitable. This is because the drug output and size distribution of the aerosol from DPIs are more or less dependent on the flow rate through the device. A DPI requires a powerful deep inspiration, whereas the pMDI requires slow inspiration; if a spacer is used with the pMDI, an appropriate dosage can be inhaled across more than one inspiration.

The second option to consider is a pMDI with (or without) a spacer. However, in doing so, the clinician (whether as prescriber, instructor, or assessor) should be aware of the clinical relevance of the technical characteristics associated with the different spacers available, including the size of the apparatus and its effects on the aerosol, the manufacturing material and the effects of static electricity, the function of different valves, the relevance of the use of different shape and quality of mouthpieces and masks, and the dead volume in the spacer. If, however, the prescribed drug is produced only as a solution or suspension for nebulisation, or if there are other specific reasons like expecting a better deposition pattern using a nebuliser, the third option is the use of a nebuliser system. The rationale underlying this order is primarily based upon the feasibility of treatment in terms of the patient’s everyday life. Administering a dosage through a nebuliser system and the handling/cleaning of the nebuliser requires a lot of time; furthermore, nebulisers are often bulky and/or complex, inconvenient, and inefficient delivery systems.

It has been suggested that prescribers should consider drug and device as single entity; however, for patients prescribed several different drugs for inhalation, this may be a problem. For example, consider the case of a 12-year-old girl with cystic fibrosis who had been prescribed a bronchodilator combined with saline (x3), a diluted mucolytic agent (x1), and an antibiotic (x2), and who was taught to use three different nebuliser systems to administer these drugs. Handling and cleaning the devices every day was too time-consuming, and this regimen meant that there was too much equipment and material to carry when going away for the week-end. On the other hand, patients who have been prescribed one drug that is

Fig. 1. Schematically illustrated lung volumes and ventilation distribution in healthy and obstructive with a progressing disease. TLC, total lung capacity; TV, tidal volume; FRC, functional residual capacity; RV, residual volume.
produced only for nebulisation are sometimes prescribed other drugs for inhalation (e.g. bronchodilators) in a formulation to be used with the same device. However, this must be regarded as unnecessarily time-consuming for the patient, if this combination of drugs is not specifically needed or desired; in such cases, these patients may very well use a DPI for the bronchodilator. There are patients who get confused and more often perform inhalation errors if prescribed more than one type of inhaler device for parallel use. So, individual solutions must be considered the best options for individual patients.

Several studies published mainly during the last 15 years have shown that administrating a drug through a nebuliser system in asthma is not more effective than through other inhaler devices. The use of nebuliser systems for maintenance asthma therapy and acute wheezing episodes in all ages is decreasing, even for small children in emergency departments; instead, pMDIs with spacers are being used in a more restricted capacity for the smallest children and in emergency departments. DPI devices are being used for older children and in adults for maintenance therapy; with appropriate individual training, using a DPI is possible from the age of 4–5 years.

This notwithstanding, there are still patients who prefer to use a nebuliser system. It is important to remember that the aerosol is transported by the inspired air only to the ventilated parts of the lungs. As obstructions worsen, the ventilation distribution declines, and the lung volumes and breathing patterns change, making inhalation therapy less effective (Fig. 1). Theoretically, severely obstructed patients may benefit from inhaling one dosage across more than one inspiration, in an attempt to improve the intrapulmonary deposition pattern. This might be of specific interest when administering suspensions that are not easily absorbed and further transported by the local circulation, or for drugs directed at anaemic targets such as mucus or microorganisms in the airways. If the obstructed patient can accept a somewhat complicated regime, more than one breath per dosage may allow them to reach parts of the lungs that otherwise do not participate in ventilation. This can be achieved by inhaling from different lung volumes, and by using the known effects that gravity has on regional ventilation in different positions. This may, theoretically, be possible by splitting up a dosage of, for example, 400 µg into four inspirations carrying 100 µg each, to be administered as: the first inspiration from functional residual capacity (FRC) in sitting, the second inspiration from residual volume (RV) in sitting, the third from FRC in left-side lying, and the fourth from FRC in right-side lying. Inhaling a dosage through four inspirations via a DPI or pMDI with spacer is still time-effective compared to nebulising the dosage, and again, may theoretically improve the deposition pattern compared to administering the whole dosage through one inspiration only.

**Nebulisation therapy**

Inhaling with the help of a nebuliser system is based on the expectation that the nebuliser system will aerosolise all types of drugs to provide a good aerosol quality which can then be effectively delivered in any situation, from mechanically ventilated patients to basic every-day home-care, in neonates as well as in adults, and with all degrees of lung disease and adapted breathing patterns. How much do we know about the aerosolised drug, and the fraction of the nominal dosage that actually reaches the lungs? The common assumption that the majority of the drug placed in the nebuliser is delivered to the target area does not encourage therapists to examine critically what actually happens: maybe it is like Dennis said: ‘The current situation is near anarchy’. The fraction of the nominal dosage that is deposited intrapulmonarily in patients with obstructive pulmonary disease has been shown to range from about 1% of the loaded dosage in infants to 63% in adults. It should be noted, however, that the range of these figures was very large in both studies. A common solution to this problem is to increase the nominal dosage; despite this, such a solution is not acceptable since it has the consequence that more of the drug may be deposited in the mouth and oropharynx, which will mainly increase the side-effects associated with treatment. Furthermore, future medications may not have a large safety margin. To overcome the problem of low aerosol deposition at the target area and the large inter- and intrapatient variability, we must understand and be aware of the variables that affect deposition. An increased co-operation between the medical devices and pharmaceutical industries, and the medical personnel and instructors working with nebulisation therapy is desirable when developing new systems. As we have come to understand the limitations and potentials of existing and developing technology better, it is clear that we can substantially improve the efficiency of nebulisation therapy.

There are many different types of nebuliser system on the market, and the market is growing rapidly. Some nebulisers, although producing good aerosol quality, show a poor ratio between inspiratory drug delivery and expiratory drug loss, even though several technical approaches have improved the ratio. Wastage of drug into the room, into an expiratory filter, or condensed on the patient-side of the aerosolising part in the nebuliser should be a concern with the new generation of very
expensive drugs. Some nebulisers are most efficient at delivering small droplets targeting the peripheral lung, some nebulisers are better suited to deliver larger particles for the upper airways, and (at least in this author’s opinion) other nebulisers are not suited for drug aerosol delivery at all. The inherent differences in delivered aerosol between nebuliser systems currently available can be ≥ 10-fold. The three different nebulisation techniques in current use are the jet, the ultrasonic, and the vibrating membrane. Between and within each group there are marked differences in functional design and construction; there are also differences in terms of capacity characteristics, optimal handling, and ease of use. There are many different brands (for the most part, globally available), and each brand comes in different models with different characteristics. The new brands and models added to the market are most often very well scrutinised, which is not necessarily the case with the older ones still in use. But, it is important to consider how the information about new nebuliser systems was derived since they can be evaluated in many different ways (i.e. defining parameters differently, using various measuring techniques and set-ups). It is important to note that manufacturers’ specifications alone may be poor criteria for device selection for clinical use, because of how and why those specifications are derived, and the potential gap between test methods and the complexity of clinical situations. A common set-up used for testing and evaluating is an assumed ‘mechanical’ patient with a lung function of inspiratory vital capacity (IVC) of 5 l, tidal volume (TV) of 500 ml, and breathing frequency of 12 breaths/min. The clinical relevance of data and specifications obtained under standardised laboratory conditions may be limited when one considers the circumstances of routine hospital use, or the every-day situation for the patient with obstructive pulmonary disease, when simplicity, maintenance and cleaning, and ease of use is important. In these circumstances, different nebuliser systems have both good and bad points, and there is probably no single system that is the best for all patients and all kinds of drugs. As Fink has indicated previously: ‘Optimising aerosol delivery requires knowledge of a number of technical details and caregivers should stay abreast of the continuing advancement of technologies and techniques associated with aerosol delivery, especially in the light of emerging devices and formulations’. For therapists, it is up to us to ask the questions that we need to have answered, not least as the information we are given frequently contains only the favourable parts.

Different nebulisers have different performance, and come with their own specific characteristics and accessories. The most important characteristics are summarised in Table 1.

A jet nebuliser system consists of the driving source and the nebuliser, which must be considered as a unit. Changing the driving source to provide a different capacity or changing the type of nebuliser will have a significant influence on the aerosol quality and/or the output. For many drugs, it is essential that the aerosol reaches the peripheral airways. If desirable, targeting of aerosol to specific sites within the lungs is possible. Droplets < 5 µm are considered respirable in healthy adults, although around 3 µm are preferable, and droplets < 1 µm reach alveoli where they may be absorbed quickly, making the drug systemically available. However, this is not desirable in cases where the target is airway tissue (of any kind), airway secretions, or micro-organisms residing in the airways. The size, weight and speed of the droplets are important factors.

### Table 1. The most important characteristics for nebuliser performance

- Adequate aerosol quality within a narrow range, expressed as mass median aerodynamic diameter (MMAD) ± SD (there is no single adequate MMAD for all drugs and situations, adequate quality is to a certain extent dependent on drug and on treatment target, as well as on respiratory condition and lung size)
- High output (ml/min)
- Small residual volume (drug left in the nebuliser loading chamber after treatment, currently 0.5–1.5 ml)
- Little loss of aerosol into the room or into expiratory filter, or condensed on the patient side of the aerosolising part of the nebuliser
- Low aerosol delivery flow rate (if the delivered aerosol flow velocity of a jet nebuliser is too high, deposition in the mouth and oropharynx increases; if the velocity exceeds the inspiratory flow velocity of the infant, then aerosol is lost into the room during inspiration)
- Allows use of a varied, flexible breathing pattern
- Ergonomic mouthpiece, which it is also possible to use in side-lying positions
- Easy to use and to handle (good instructions, few parts, easy to put together and dismantle, ‘foolproof’, stands ‘robust’ treatment, easy to clean, available and cheap spare parts, easy to service and repair)
- Not too big, heavy, or noisy
in deciding where they will be deposited in the airways. Additionally, different drugs may have different properties influencing the nebulising process: the MMAD and/or the output may differ significantly between, for example, a bronchodilator and a mucolytic or antibiotic drug. Weight concentration (osmolality), viscosity, and surface tension of the solution/suspension also influences the mass flow rate and the distribution of aerosol mass by droplet size; mass flow rate decreases as weight concentration increases, but droplet size does not change. The total drug output may differ markedly since the concentration of a strongly nebulised drug may be higher in the residual volume than in the loaded volume. Some drugs are unstable and may change during the aerosolising process; for example, if pH changes as concentration of the drug changes during nebulisation, or if heated as in some ultrasonic nebulisers. Also, proteins foam easily when used with compressed air. This is a complicated area, and there is still much to learn, especially about new, more complicated and expensive, drug formulations.

Inappropriate inhalation technique may result in misuse, systemic overdose, and/or diminished response of the administered drugs – perhaps even in unnecessary repeat hospitalisations. 

Independently of what drug and device is chosen, repeated and thorough tuition of correct use of the inhaler device is essential to produce the desired results. A recent review suggests that each type of inhaler device can deliver an effective dosage of most drugs to most patients when being used properly. After one education session, 57% of the children studied in one report showed correct inhalation technique, after three sessions this rose to 98%. Comprehensive instruction combined with repeated checks in the clinical setting increased good performance from 39% to 93% of the adults studied in another trial. Asking patients to demonstrate their inhalation technique is recommended at each visit to the out-patient clinic, as is ensuring regular opportunities for follow-up and corrections if needed. However, it has been shown that medical personnel responsible for teaching the correct use are frequently lacking in basic knowledge and user skills! In one study, respiratory therapists, primary care physicians, pharmacists and nurses performed 82%, 78%, 58% and 54%, respectively, of all essential items correctly; it would thus appear that training the caregivers should be the essential first intervention.

Important factors in achieving an optimal inhalation technique can be summarised as:

1. Always try to use a mouthpiece first. If using a mask for inhalation therapy, it is impossible to judge whether patients inhale through the nose or the mouth. Inhaling aerosol through a mask via the nose decreased lung deposition by up to 67%, compared with inhaling through a mouthpiece. Many small children and infants can cope very well with the use of a mouthpiece, as they accept that you need to hold an index finger gently to their nostrils.

![Fig. 2. Placing the mouthpiece well into the mouth, the tongue underneath, teeth around and lips shut tightly must be considered optimal.](image)

![Fig. 3. Inhaling with TV from FRC is varied with deep inspirations to TLC and with small breaths at RV level.](image)
2. Optimal placing of the mouthpiece, i.e. into the mouth, tongue underneath, teeth around and lips tight (Fig. 2).

3. Slow inspiratory flow velocity should be maintained.

4. If of benefit, acceptable and/or possible: (i) use variable lung volumes (Fig. 3); and (ii) use more than one position (Fig. 4).

Droplets deposit mainly by impaction in the central airways, where inspiratory flow velocity is up to 1000 times higher than in the most peripheral airways. In the periphery, droplets deposit mainly by sedimentation, due to the very low flow rate; however, sedimentation takes time. A long breathing cycle is, therefore, desirable but is progressively more difficult the more dyspnoeic the patient. Small inner airway diameters causes higher inspiratory flow rates, which give rise to turbulence and whirls that increase the impaction in the central airways. The smaller the inner airway diameter, the easier turbulence occurs; therefore, a slow laminar inspiratory flow rate is favourable, and a small MMAD is necessary in situations like this. This is of course essential to consider when treating chronic airway obstruction, cysts and bronchiectasis, emergency episodes in asthma, and with small children. Laube et al.11 showed that in cystic fibrosis patients, an aerosol quality of MMAD 1 µm and a low inspiratory flow rate (18 l/min in this study) reached the more peripheral airways, and deposited a more even pattern than MMAD 3.7 µm and a flow rate of 38 l/min (the inhaled volume and the inhalation time was the same). Crying has been shown to reduce the deposition to almost zero in infants.22 A slow, controlled, breathing frequency was found to increase the proportion of the pulmonary deposition significantly.23

Cleaning of nebulisers is another area of interest; this includes getting rid of sticky or dried drug residuals, micro-organisms, and getting the component parts dry again as soon as possible (especially within any recesses, which should be as limited as possible). There is no standard method of cleaning: each clinic or company endorses their own particular recommendations with respect to their regimen or product. In such cases, a pragmatic approach is important. The more complicated the recommendations, the less likely the adherence; rather, recommendations adapted to the situation are preferable. Devices used repeatedly by many patients in hospital settings should be cleaned with great accuracy and safety; in contrast, devices used by one individual at home should be cleaned adequately to obtain optimal results, but without being a too great a burden in the everyday life of the patient. However, a study showed that only 41% of the respiratory therapists taught their patients to disinfect the nebuliser, and many patients and respiratory therapists overused ‘single use’ devices that cannot be properly cleaned.24 To make sure the nebuliser systems function optimally, they need regular maintenance and certain delicate parts should be replaced. Replacement annually or bi-annually is recommended, depending on the level of use.

One common question that arises when using nebuliser systems is when to stop the inhalation. ‘When no more aerosol is produced’ used to be a common answer with the jet nebuliser systems. However, contemporary nebuliser systems developed over the last several years have confused prescribers and users, since such devices often end up with very large residual volumes after treatment. As a practical option for advising patients and therapists, maybe the dosage should be specified as a fixed period of delivery (x min), depending on indication, patient size, as well as what drug and device is being used? We need more specific information about respirable fraction of nominal dosage in the different nebuliser systems that are currently available, and we also need to know more about how to specify the dosage for the different drugs that are now on the market. The cornerstone

Fig. 4. Ventilation distribution in sitting and in bilateral side-lying in (A) healthy and in (B) small children and severely obstructed patients.
for successful therapy over time is probably frequent contacts between patient and medical personnel, with regular check-ups and re-assessments of adherence and inhalation technique. To underpin this, a high level of communication between medical personnel and the patient is, of course, essential.

REFERENCES

3 Dolovich MB. Assessing nebulizer performance. Respir Care 2002;47:1290–301
13 Fink JB. Devices and equipment evaluations. Respir Care 2004;49:1157–64
14 Fink JB. Aerosol device selection: evidence to practice. Respir Care 2000;45:874–85
16 Rubin BK. Nebulizer therapy for children: the device-patient interface. Respir Care 2002;47:1314–9
24 Lester MK, Plume PA, Gray SL, Anderson D, Bowman CM. Nebulizer use and maintenance by cystic fibrosis patients: a survey study. Respir Care 2004;49:1504–8

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