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ERS/ISAM TASK FORCE CONSENSUS STATEMENT

What the Pulmonary Specialist Should Know about the New Inhalation Therapies

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ABSTRACT

A collaboration of multidisciplinary experts on the delivery of pharmaceutical aerosols has been facilitated by the European Respiratory Society (ERS) and the International Society for Aerosols in Medicine (ISAM), in order to draw up a Consensus Statement with clear, up-to-date recommendations that enable the pulmonary physician to choose the type of aerosol delivery device that is most suitable for their patients. The focus of the Consensus Statement was the patient-use aspects of specific aerosol delivery devices that are currently available. The subject was divided into different topics, which were in turn assigned to at least two experts. The authors searched the literature according to their own strategies, with no central literature review being performed. To achieve consensus, draft reports and recommendations were reviewed and voted on by the entire panel. Specific recommendations for use of the devices are found throughout the statement. Healthcare providers should ensure that their patients can and will use these devices correctly. This requires that the clinician is aware of the devices that are currently available to

deliver the prescribed drugs, knows the various techniques that are appropriate for each device, is able to evaluate the patient's inhalation technique to be sure they are using the devices properly and to make sure that the inhalation method is appropriate for each patient.

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INTRODUCTION

A joint task force of multidisciplinary experts on the delivery of pharmaceutical aerosols was approved by the European Respiratory Society (ERS) and the International Society for Aerosols in Medicine (ISAM) in order to draw up clear, up-to-date recommendations that enable the pulmonary physician to choose the type of aerosol delivery device that is most suitable for their patients at home and in hospital.

Many drugs are currently delivered directly to the lungs as an aerosol. These include short-acting (SABA) and long-acting (LABA) $beta_2$-adrenergic agonists, anticholinergics, corticosteroids (ICS), non-steroidal anti-inflammatories, antibiotics, and mucolytics. Other drugs are under development for aerosol delivery. These include insulin to treat diabetes, gene therapy vectors to treat CF, vaccines for measles and papilloma virus, chemotherapy agents for lung cancer, new formulations for antibiotics, anti-proteases to treat CF and $alpha_1$-antitrypsin (AAT) deficiency, morphine to relieve pain and ergotamine to relieve headaches.

Devices that are available to deliver these drugs include pressurized metered-dose inhalers (pMDIs), used either alone or attached to spacers or valved holding chambers (VHCs), breath-actuated pMDIs (BA-pMDIs), dry powder inhalers (DPIs), nebulizers and soft mist inhalers.

Treatment guidelines for the management of asthma (1) and COPD (2) are both well established. Both recommend inhaled therapy as the primary route to administer medication. A comprehensive comparison of the dose equivalence of inhaled steroids has been presented (3). Treatment guidelines for cystic fibrosis also include inhalation of aerosolized medications (4-5).

Meta-analysis reports indicate that when patients use the inhalation technique recommended by the manufacturer, all inhalers are effective and can achieve the same therapeutic effect, although different doses may be required (6-7). However many patients do not use the correct technique when using their inhalers (8), either because they have never been taught, or because they have modified the technique following instruction. As is the case with most therapeutic areas, poor adherence with the optimal treatment regimen is common (9). For this reason, treatment guidelines state that a patient's inhaler technique and their level of adherence should be determined before a change is made to a patient's prescription. They also indicate that inhaler technique should always be taught and assessed by competent healthcare professionals.

In this consensus statement, we focus on the patient-use aspects of specific aerosol delivery devices that are currently available, so that prescribers understand what inhalation methods are needed for these devices and can make an informed choice on the type of device that is most suitable for their patients' use at home and in hospital. Devices under development were not included in this review because they are not currently available to the physician.

METHODS

The task force was composed of 11 invited participants who were identified on the basis of their expertise in the area of pulmonary aerosol delivery. The subject was divided into different topics, which were in turn assigned to at least two experts. Topic-writers searched the literature according to their own strategies and determined their own databases. No attempt was made to grade evidence, or recommendations. The literature search ended in December of 2009.

Draft reports written by the experts on each topic were distributed to the entire expert panel and comments solicited in advance of meetings that were held at the 2009 ISAM Congress and the 2009 ERS Congress, as well as a small group meeting at the 2009 ERS School on Medical Aerosols. During these meetings, the recommendations and the evidence supporting the recommendations were reviewed and discussed by the entire panel. Approval of the recommendations required consensus, which was defined as a majority approval. Differences of opinion were accommodated by revising the recommendations until consensus was reached. Despite differences between guidelines and the availability of drugs and devices, the task force tried its utmost to develop a consensus statement that is valid all over the world.

PULMONARY AEROSOL DELIVERY: OVERVIEW

Unlike oral or I.V. therapies, aerosolized therapy delivers drugs directly to the internal lumen of the airways and onto the therapeutic sites. For this reason, the systemic dose of most aerosolized drugs is reduced compared to oral and I.V. treatments. Direct delivery to the lungs also permits a more rapid bronchodilation in response to $beta_2$-adrenergic agonists and anticholinergics and with some LABAs the duration of the effect is enhanced compared to oral treatments.

a) Limitations to Aerosol Therapy

Not all inhalation devices are appropriate for all patients. This is because of differences in the way the devices perform and the need to master specific inhalation techniques that require varying levels of cognitive ability depending on the device. Reviews of randomized controlled trials comparing different inhalers have concluded that they are all equivalent (6-7). However patients in randomized controlled trials receive more inhaler technique training and counseling on the importance of adherence than patients who are seen as part of a routine clinical practice. For this reason, the GINA and BTS guidelines recommend that inhaler technique and the degree of adherence with dose regimens should be assessed before changing a patient's inhalation therapy (1-3).

Based on a real life setting, it has been reported that 76% of patients using a pMDI and between 49-54% of those using a BA-MDI make at least one error when using their inhaler (10). In addition, between 4 and 94% of patients using a DPI do not use it correctly and 25% have never received inhaler technique training (11). Failure to exhale to functional residual capacity before inhaling through their DPI device and failure to use a forceful, deep inhalation were two of the most common problems with DPIs (11). With a pMDI the most common problems were lack of actuation-inhalation coordination and stopping inhalation due to the cold freon effect (12). Despite these errors, 50%, 66% and 70-80% of general practitioners report that their patients inhale the right dose when they use a pMDI, BA-MDI and a DPI, respectively (10).

When patients inhale a short-acting bronchodilator, they inhale another dose if they do not get a sufficient response from the first dose. As a result of this feedback, they can overcome poor technique and potentially poor disease control by increasing their dose. Patients do not get this feedback from other inhaled therapies. For those drugs, it is important that patients use their

device in an optimal manner and this requirement often requires a specific and relatively complex inhalation maneuver that is tailored to the patient's needs and preferences (8).

b) Particle- and Patient-Related Factors that Influence Aerosol Deposition

Table 1 provides the definitions of commonly used terms that describe an aerosol. These terms are derived from *in vitro* measurements of particle-related characteristics and include dose and aerodynamic diameter. In terms of dose, physicians should be particularly aware that some countries label the inhaler with the *nominal* dose (which is the dose that is metered), while others use the *emitted* dose (which is the dose that comes out of the actuator and is available for inhalation at the mouth). For example, beclomethasone pMDI (HFA formulation, QVAR®) is labelled as 100 mcg (the nominal dose) in Europe and as 80 mcg (the emitted dose) in the U.S. Although these two references to dose are not the same, the dose that the patient receives is the same.

Drug delivery via the respiratory tract is more complex than oral therapy. Successful therapy requires a delivery system that generates drug particles of an appropriate size such that they penetrate beyond the oropharynx and larynx and deposit in the lungs (13). Aerodynamic diameter is generally thought to be the most important particle-related factor that affects aerosol deposition. **Figure 1** shows the relationship between aerodynamic diameter and lung deposition (14). Upon entering the oral cavity, particles will deposit by impaction, sedimentation and Brownian motion depending on their size. Particles greater than 5 microns are most likely to deposit by impaction in the oropharynx and be swallowed (13). This is partially the result of the inertia associated with the particle's mass, which reduces its ability to follow the airstream when it changes direction toward the lower airways. It is important to minimize corticosteroid

deposition in the oropharynx because it can give rise to local side effects such as hoarseness and oral candidiasis with ICS (15).

Figure 1 also shows that particles that are smaller than 5 microns have the greatest potential for deposition in the lungs. The proportion of particles within an aerosol that are less than 5 microns is often referred to as the fine particle fraction (FPF), or the fine particle dose (FPD), if expressed in absolute mass of drug in particles less than 5 microns (**Table 1**). Aerosols with high FPFs have a high probability of penetrating beyond the upper airways and depositing in the lungs. Thus, it is not surprising that current devices generate aerosols with a significant proportion of their particles in the 1-5 micron range. The optimal particle size range for aerosols delivered to children is not known. It is likely that it is smaller than what is optimal for adults, due to narrower airway diameters and higher intraluminal flows.

Figure 1 shows that particles between 4 and 5 microns deposit primarily in the bronchial/conducting airways, whereas smaller particles remain in the airstream and are carried into the peripheral airways and the alveolar region. In the periphery of the lung, air flow rate is reduced and particles deposit predominantly by sedimentation, with gravity causing them to 'rain out' and deposit. Most particles between 0.1 and 1microns diffuse by Brownian motion and deposit when they collide with the airway wall. The longer the residence time in the smaller, peripheral airways, the greater the deposition from sedimentation and Brownian motion processes (16). It is recommended that patients hold their breath after inhalation of an aerosolized medication because the breath hold increases the residence time and this enhances deposition in the peripheral airways. Inhaled particles that do not deposit are exhaled (13).

Important patient-related factors include the morphology of the oropharynx and larynx and the patient's inspiratory volume and flow rate. The patient's inspiratory flow rate generally

determines the velocity of the airborne particle and this, in turn, also affects the probability of its impaction in the oropharynx and larynx (17). To minimize deposition in the upper airways and enhance delivery of drug to the lungs when using a pMDI with or without a spacer, or a BA-pMDI, patients should inhale slowly. “Slowly” translates into inhaling fully over 2-3 seconds in a child and 4-5 seconds in an adult after a deep exhalation. This will ensure that flows are approximately 30 L/min, which is the ideal flow when using a pMDI (18). With DPIs, the patient has to inhale as deeply and as hard as they can to overcome the internal resistance to flow and generate the aerosol for inhalation. DPIs also require turbulent energy to deaggregate their formulations and produce a fine particle dose during the inhalation maneuver. The greater the energy imparted by the patient’s inspiratory flow rate, the more effective is the particle deaggregation.

c) Lung Disease and Deposition

The degree of lung disease at the time of inhalation significantly influences the pattern of drug deposition within the lungs. Several studies have shown that central airway deposition is enhanced as mucus plugging, turbulent airflow and airway obstruction increases (19-23). This means that in the face of severe lung disease, little or no drug may deposit in the lung periphery. This may not be clinically important for bronchodilators, but could be for corticosteroids.

d) Drug Receptors

Receptors for inhaled bronchodilators are distributed throughout the lungs (24-25), but they have their greatest effect on receptors in smooth muscle located in the conducting airways. By targeting these receptors, bronchodilators open up (dilate) the larger airways.

Corticosteroid receptors are also present throughout the airways (26) and inflammation has been shown to exist in all regions of the lungs in asthma (26) and COPD (27). For these reasons,

uniform distribution of an ICS throughout the airways, following inhalation, may be preferable. Further studies are needed to confirm this before recommendations can be made. Furthermore, there is doubt about the effectiveness, or role, of ICS in COPD (28), as reflected in the GOLD guidelines (2).

e) Nasal versus Oral Inhalation

The nose is a more effective filter than the mouth. Thus, inhalation through the mouth is the preferred route for aerosol delivery to the lungs. This is a potential issue when treating infants and toddlers. For example, when children are treated with nebulizers, or pMDIs with spacers or holding chambers, they frequently breathe through their noses using a facemask. While absolute efficiency in terms of lung dose is low during nose-breathing, compared to mouth-breathing (29), the total inhaled dose per kilogram of body weight is relatively higher in the nose-breathing children, compared to older patients using mouthpieces. Therefore, the dose to the lungs per kilogram body weight in nose-breathing infants is probably similar to that achieved by mouth-breathing adults (29).

f) Patient Behavior and Deposition

For inhaled therapy to be effective, the patient must use a device effectively and adhere to a regular treatment regimen (8). Adherence to treatment regimens is known to be frequently poor in all therapeutic areas and is probably not significantly worse with inhaled as compared with oral therapy. However, even if a patient is fully adherent with a treatment regimen, inhaled therapy may be ineffective if poor inhalation technique limits the amount of drug available for lung deposition. Studies have shown that a very high proportion of patients do not have the competence to use their device effectively, either because they have never been shown, or because they have forgotten what they were taught. (8, 30). This is a particular problem in the

elderly, but affects all age groups. Furthermore many patients soon forget how to use the correct technique that they have been trained to use (31). In addition, many of those who are able to demonstrate a good technique in the clinic will contrive to use the device ineffectively in routine use. The most common example of contrivance is spacer disuse (e.g. patient's failure to use a spacer at home).

Data regarding the impact of education on regimen adherence is at best mixed and it is very difficult to influence this aspect of patient behavior. Having a good rapport with the patient has been shown to improve regimen adherence after a consultation, but this effect may be as transient as one week (31). Patients may be more adherent with an inhaler that combines two drugs (i.e. LABA and ICS) in the same dose, compared to using two separate inhalers (32). Although this may simplify the regimen, the effect is far from universal. While education per se probably does not have a significant impact on regimen adherence, patient feedback (33) in terms of regimen adherence and automated reminders appear to influence this aspect of behavior and are likely to become more frequently employed in clinical practice in the future.

Health care providers have a particular duty to ensure that a patient is able to use the inhaler effectively (8). Hence, physicians must ensure that a suitable device is prescribed, that the patient is competent to use it and that the patient understands that little, or no drug, may reach the lungs if the device is not used according to the specified instructions. Competence and contrivance are amenable to educational interventions, though it is important to review these issues with the patient on a regular basis. Once a patient is familiar and stabilized on one type of inhaler, they should not be switched to new devices without their involvement and without follow-up education on how to use the device properly.

g) Choice of Delivery Device

The choice of device to deliver a particular drug is determined by the devices that are available for the prescribed drug and whether the patient can and will use it effectively. **Table 2** provides a summary of the devices that are currently available for delivery of the most commonly prescribed brand-name drugs by pMDIs, BA-pMDIs, nebulizers, soft mist inhalers and DPIs. A pMDI requires good actuation-inhalation coordination, whereas a DPI requires sufficient inspiratory flow, for optimal lung deposition. **Tables 3A** and **3B** provide information for choosing the right aerosol delivery device for patients with good versus poor actuation-inhalation coordination and sufficient inspiratory flow (34). Patients with poor actuation-inhalation coordination include children and elderly patients. Where possible, patients should use one type of device for all their inhaled therapies (1, 3). However this is not always possible. For example, in the U.S. there is no salbutamol DPI. Therefore, those patients may have to use both a pMDI for their beta$_2$-adrenergic agonist and a DPI for their other prescribed medications. Although previous publications have provided general recommendations for inhalation techniques for inhalers (7, 35), **Table 4** provides more detailed instructions on how to use pMDIs, BA-pMDIs, pMDIs with spacers, DPIs, nebulizers and soft mist inhalers. Major advantages and disadvantages for pMDIs with and without spacers, BA-pMDIs, nebulizers and DPIs are summarized in **Table 5** (9).

h) Regulation of Delivery Devices

In Europe, aerosol devices are regulated by the European Medicines Agency (EMA) (http://www.ema.europa.eu). In the U.S., the regulatory agency is the Food and Drug Administration (FDA). (http://www.fda.gov).

i) Recommendations: Prescribers should

- Know the types of devices that are available to deliver specific drugs and classes of drugs (Refer to **Table 2**).
- Appreciate the advantages and disadvantages of each device (Refer to **Table 5**).
- Choose devices that the patient can and will use effectively (Refer to **Tables 3A and 3B**).
- Choose devices that have been approved by the appropriate authorities. (Refer to **Table 2**).
- Train patients about the correct inhalation maneuver that is appropriate for the device being prescribed (Refer to **Table 4**)
- Check the patient's inhaler technique regularly.
- Review the patient's adherence to treatment at each visit.
- Not switch to a new device without the patient's involvement and without follow-up education on how to use the device properly.

AEROSOL DEVICE OPTIONS

a) Pressurized Metered Dose Inhalers (pMDIs)

1. Transition to HFA Products

The pMDI was introduced in the 1950s as the first portable, multidose delivery system for bronchodilators. It is still the most widely prescribed inhalation device. Until recently, the drugs delivered by pMDIs were formulated with chlorofluorocarbon (CFC) propellant and small amounts of excipients (such as valve lubricants). But CFCs are now being replaced by hydrofluoroalkanes (HFAs) due to a ban on CFCs. At present, there are only a few pMDIs that still contain CFCs. In most European countries, CFC-pMDIs have been totally replaced by non-CFC inhalers. After 2013, CFC-pMDIs will no longer be available in the U.S.

(http://latimesblogs.latimes.com/booster_shots/2010/04/the-fda-phasing-out-certain-asthma-inhalers.html). See **Table 2** for drugs that are delivered by HFA- versus CFC-pMDIs.

There are some differences between the CFC and HFA products. Two of the major differences are that the plume released from many HFA-pMDIs has a slower velocity and it is warmer (36). These changes partially overcome the 'cold-Freon' effect that caused some patients to stop inhaling their CFC-pMDIs (12). Another difference is that many HFA-pMDI formulations contain a small amount of ethanol. This affects the taste and further increases the temperature and decreases the velocity of the aerosol. Exceptions to the alcohol content and slower plume velocity are salbutamol (Ventolin®), fluticasone and salmeterol pMDIs and pMDIs with the combination of fluticasone and salmeterol (Seretide®; GlaxoSmithKline, UK) and budesonide (Pulmicort®; AstraZeneca, Sweden). As HFA pMDIs become more widely used, patient feedback regarding the perception of differences between them and CFC pMDIs is diminishing. Nevertheless, when physicians prescribe HFA formulations in place of CFC versions for the first time, they should inform their patients about the differences in taste and sensation.

Cleaning instructions have not been altered for HFA pMDIs. Each HFA-pMDI product provides information on its use and maintenance in its patient information leaflet (**PIL**). Patients should be encouraged to follow those cleaning instructions. The patient should also be instructed that on first use, and after several days, or weeks of disuse, the pMDI should be primed. Priming the pMDI involves discharging 2-4 doses into the surrounding air (away from the patient). Patients should be encouraged to follow the priming instructions described in the PIL.

2. Bronchodilators

Salbutamol, formoterol and salmeterol are all available as pMDIs with HFA propellants (Refer to **Table 2**). In Europe, generic formulations of salbutamol are available both with CFC and with HFA propellants. At the moment, there is no generic salbutamol available in the U.S.

All HFA formulations of formoterol have to be stored at 0-4° C prior to dispensing to prolong the shelf life. Since it cannot be guaranteed that patients will store these products in a cool place, the dispensed label states that they should not be used 12 weeks after the date of dispensing.

Terbutaline is no longer available as a pMDI. Ipratropium bromide is available with HFA propellant. Tiotropium bromide is available in a soft mist inhaler and in a DPI. At present, the combination of salbutamol sulphate and ipatropium bromide is available with CFC propellant.

3. Inhaled Corticosteroids (ICS)

The change over from CFC to HFA propellant was seamless for budesonide and fluticasone, such that the new and old formulations have similar aerosol properties and no change in dose is recommended. However, the reformulation of beclomethasone has not been as straight forward and has led to formulations with different aerosol characteristics and doses, thereby generating some confusion among prescribers. The two currently available HFA pMDIs for beclomethasone, QVAR® HFA-pMDI (Teva Pharmaceuticals, Israel) and Clenil® (Chiesi Farmaceutici, Italy) are both solution aerosols. Solutions are comprised of drug dissolved in a carrier liquid. Nevertheless, these two products are not dose equivalent. Thus, in countries where both products are available, Regulatory Authorities require prescribers to name the brand rather than simply prescribe beclomethasone HFA-pMDI.

QVAR® aerosol particles are much smaller than particles emitted from the CFC suspension product. The MMAD of QVAR® is 1.1 μm, which makes the particles extrafine. Extrafine

particles are sometimes also referred to as ultrafine particles. Because of its extrafine particles and greater FPD, inhalation of QVAR® beclomethasone leads to more efficient lung deposition and lower oropharyngeal deposition than the CFC-formulation (37-38). In addition, clinical trials have demonstrated that one dose of extra-fine HFA-beclomethasone is clinically equivalent to 2.6 times the dose of CFC-beclomethasone (39). In practice guidelines (GINA, BTS), it is now recommended that 100 mcg of beclomethasone in a QVAR® HFA-pMDI is equivalent to 200 mcg in a beclomethasone CFC formulated pMDI. Equivalence data is based on mean data and does not necessarily apply to individuals. Healthcare providers should be aware that regulatory agencies in many countries have approved this new dosing.

Another advantage to inhaling extrafine beclomethasone is that the timing of actuation and inhalation is not as critical (40) and, due to the extrafine particles, lung deposition is less affected by inhalation flow rate (17). Thus, the problems patients have with coordination and inhalation are relatively less important. It also does not appear to be important that approximately 10% of the dose is exhaled (due to the extrafine particles), since the lung deposition is above 50% (38). Finally, deposition of QVAR® appears evenly distributed in the different lung regions. Whether this increase in deposition uniformity improves treatment of inflammation in peripheral lung regions warrants investigation.

Clenil® (Chiesi Farmaceutici, Italy) is an HFA-beclomethasone product that was developed with the intention of providing dose and particle size characteristics similar to the beclomethasone CFC-pMDI product. It is a solution that was formulated with glycerol to make the particles larger, so the particles are not extrafine. No dose change is recommended when converting from CFC-beclomethasone to HFA-Clenil®.

A beclomethasone-formoterol combination has also been introduced as an HFA-pMDI solution (Foster®; Chiesi Farmaceutici, Italy). Aerosol particles for both drugs in this product are extrafine (MMAD for beclomethasone = 1.3 μm and for formoterol = 1.4 μm) (41). In different countries, this product is also known as Fostair®, Fostex®, or Innovair®. Studies have demonstrated that two inhalations of the beclomethasone/formoterol 100/6 HFA-pMDI product twice daily is clinically equivalent to two inhalations of fluticasone/salmeterol 125/25 twice daily (Seretide®; GSK, UK) (42) and to two inhalations of budesonide/formoterol 200/6 from a Turbuhaler® twice daily (43).

Another corticosteroid, ciclesonide (Alvesco®; Nycomed; CH), is available as an HFA-pMDI product. It was also formulated as a solution and has a lung deposition profile that is similar to extrafine beclomethasone pMDIs. It is equivalent to other ICS therapies at similar nominal doses. In Europe, it is recommended for once daily dosing. In the U.S., it is recommended for twice daily dosing. It also has the same inhalation technique advantages as described above for QVAR®. Flunisolide is also available in some countries as an HFA-pMDI (Aerospan®; Acton Pharmaceuticals, Marlborough, MA).

4. Recommendations: Prescribers should

- Know the devices that deliver drugs by HFA- versus CFC-pMDIs (refer to **Table 2**).
- Know the differences between the HFA-beclomethasone pMDI formulations and their clinical relevance.
- Specify the brand when prescribing beclomethasone HFA-pMDI, in countries where both Qvar® and Clenil® are available

- Know that the equivalence guidance is based on mean data and does not necessarily apply to individuals. Whenever a change is made in an ICS device, titration to the lowest effective ICS dose should be performed.
- Instruct patients to adhere to the cleaning and priming instructions in the PIL.
- Ensure that patients follow the inhalation techniques for pMDIs as recommended in **Table 4.**
- Instruct patients that they may not always sense or taste drug entering their mouth from some of the new pMDI products. Nevertheless, if they follow the instructions, they should receive the appropriate dose of drug.

b) Breath-Actuated pMDIs (BA-pMDIs)

BA-pMDIs that are currently available are the Autohaler® and Easi-Breathe®. They were developed to overcome the commonly encountered problem of poor actuation-inhalation coordination with standard pMDIs (44). The Autohaler® automatically actuates at inspiratory flow rates of approximately 30 L min^{-1} and the Easi-Breathe® actuates at 20 L min^{-1}. In one study, less than 5% of patients were unable to achieve the threshold inspiratory flow rate required for actuation of the Autohaler® (45) and there were fewer errors, compared to using conventional pMDIs (10). **Table 2** shows that salbutamol and beclomethasone are available as BA-pMDIs in Europe. In the U.S., only pirbuterol is available. For patients with poor actuation-inhalation coordination, BA-pMDIs may improve lung deposition, compared to pMDIs alone (44).

1. Recommendations: Prescribers should

- Know that breath-actuated pMDIs may be useful for patients who have actuation-inhalation coordination difficulty.

- Instruct patients to be sure that they have triggered the dose during the inhalation. This is noticed by taste, or sensation, or a noise that confirms dose emission. The noise from the Easi-Breathe® is quiet and resembles a 'whoosh'.
- Ensure that patients follow the inhalation techniques for BA-pMDIs as recommended in **Table 4.**
- Recognize that some oropharyngeal deposition still occurs with extrafine QVAR® BA-pMDI and instruct patients to rinse out their mouths after inhaling.

c) Spacers and Valved Holding Chambers (VHCs)

Table 6 lists the most commonly used spacers. Spacers are accessory devices to be used with pMDIs. They can be simple extension devices that increase the distance between the pMDI and oropharynx, thereby reducing orophayngeal deposition, or they can be more elaborate. Spacers that incorporate a one-way-valve are called valved holding chambers (VHCs). They allow patients to inhale a static cloud. VHCs overcome the issue of coordinating actuation with inhalation and increase pulmonary deposition in those subjects who do not have optimal coordination when actuating a pMDI (46-49). Spacers and VHCs should not be used with BA-pMDIs.

Due to the reduced impaction in the oropharynx, spacers and VHCs are recommended for use with ICS. Impaction in the oropharynx is also reduced by using Qvar® HFA-pMDI (without a spacer) (37). Nevertheless, since some oropharyngeal deposition may still occur, patients are advised to rinse out their mouths after inhaling an ICS with any of these devices. Changing the spacer in effect represents a change in the delivery system. With a change in spacer device, regular monitoring and titration of the ICS dose to the lowest effective dose is advised.

Although the shape and volume of spacers can vary greatly, they are generally grouped into two categories (a) small volume (130-300 ml) and (b) large volume (600-800 ml). Some spacers incorporate a whistle that makes a sound if inspiratory flow is too fast. Training subjects to ensure that the whistle does not sound assists with developing an optimal inhalation technique. Some spacers incorporate a reverse-flow design to enhance small particle delivery to the patient. In these spacers, the flow of aerosolized medication is directed away from the patient's mouth upon actuation and then is directed back towards the mouth during inhalation.

Some pMDIs are licensed with a specific spacer. For example, HFA Seretide® is licensed with the Volumatic®, or Aerochamber®. Clenil® is licensed with the Volumatic® in the UK and with the Aerochamber® in the rest of Europe. Qvar®-HFA and Alvesco® are licensed for use with the Aerochamber®.

A major disadvantage to spacers is that they are generally more bulky and less portable than a pMDI and this often results in patients using the pMDI alone. Spacers also reduce the dose output from a pMDI to a variable extent. An additional source of variability in drug delivery with spacers is due to accumulation of an electrostatic charge on the plastic walls. Laboratory studies indicate that this electrostatic charge reduces spacer performance, such that the aerosol dose available for inhalation is reduced. This effect is most marked in newly purchased devices. The effect of electrostatic charge on clinical outcome of an aerosolized medication is less clear and may affect some formulations more than others (50).

A number of 'non-static' spacers have been developed. At present, there is a gradual country-by-country transition to the use of an Aerochamber® made of a non-static plastic material. Another option is the Vortex® (PARI, GmbH, Germany), which has an extremely thin metal

layer on the inner surface of a plastic spacer that reduces static charge. The non-static metal Nebuchamber® (Astra Zeneca, Sweden) is currently off the market.

Because spacers are generally used for many months, they require periodic cleaning to prevent deterioration in the function of the valve and for hygienic reasons (51-52). The general advice for both newly purchased and previously used devices is to clean them by washing them with a low concentration of dishwashing liquid and allowing them to drip dry (53). In this way, the plastic is coated with detergent, which reduces the electrostatic charge, decreases drug losses on spacer walls and promotes lung deposition (54).

The PIL's of the different spacers are not consistent in terms of how often a spacer should be cleaned. It ranges in general from once a week to once a month. One study suggests the effect of detergent coating on electrostatic charge diminishes within one week. (55). But it is not clear if this applies to all devices, so the recommendation is to follow the guidelines for cleaning found in the PIL for individual spacers. There is no consensus on whether spacers should be rinsed after cleaning with dishwashing liquid. Therefore, it is important to follow the recommendation found in the PIL for each spacer in terms of whether to rinse after washing or not.

Only one dose should be actuated into the spacer prior to each inhalation because multiple inhalations increase drug losses within the spacer as a result of increased turbulence (56). Also, the dose should be inhaled immediately after a dose is introduced into the spacer. Time delays reduce the emitted dose because particles have more time to deposit within the spacer (56).

1. Recommendations: Prescribers should

- Ensure that VHCs are used with pMDIs by infants and children and by patients with poor coordination, or inhaler technique.
- Ensure that spacers, or VHCs, are used when prescribing corticosteroids by pMDI

to reduce oropharyngeal side-affects and absorption via the gut.

- Advise patients to rinse out their mouths after inhaling a corticosteroid, even when using a spacer, VHC, or Qvar® HFA-pMDI (with or without a spacer).
- Know that spacers and VHCs should not be used with BA-pMDIs.
- Ensure that patients follow the inhalation instructions for spacers as recommended in **Table 4**.
- Instruct patients and caregivers to clean and use spacers according to the PILs.
- Instruct patients and caregivers not to actuate more than once into a spacer prior to each inhalation and to inhale immediately after actuation with no time delay.
- Know that with a change in spacer device, regular monitoring and titration of the ICS dose to the lowest effective dose is advised.

d) Dry Powder Inhalers (DPIs)

DPIs that are currently available are small and portable and are breath-actuated, so patients do not have to coordinate actuation with inhalation. There are two basic types of DPIs: (1) multidose DPIs that contain many doses inside the device; and (2) single dose capsule DPIs. There are also two versions of the multidose type: (1) those that contain a bulk formulation in a reservoir that is metered by the patient during use; and (2) pre-metered factory dispensed doses packaged inside blisters within the device. **Table 2** shows that most DPIs are of the reservoir type.

All DPIs require the patient to prepare a dose prior to inhalation and these are described in the PIL. Patients who do not perform these procedures correctly may receive no dose, irrespective of the inhalation maneuver they subsequently adopt and this type of critical error

occurs frequently (57). A few studies suggest that some patients have more problems using single dose DPIs than multidose devices (58-59).

Patients should be instructed to exhale into the room to functional residual capacity before inhaling through their DPI device. They should not exhale into the device, since that will result in blowing the dose out of the device. Failure to perform the proper exhalation maneuver before inhalation was the most common mistake made by DPI users (11). Also, studies have shown that dose emission is reduced when the DPI is exposed to extremely low and high temperature and humidity (60). Therefore, DPIs should be stored in a cool dry place.

To ensure good powder flow during manufacture and consistency during dose metering, all DPIs are formulated with their drug particles attached to either a carrier, or as agglomerates in the form of pellets. To facilitate lung deposition, drug particles are deagglomerated during inhalation. This is achieved by the creation of turbulent energy inside the DPI. The turbulent energy is the product of the patient's inhalation flow multiplied by the DPI's resistance. For this reason, all DPIs that are currently available are classified as passive devices. Increasing the inspiratory flow is generally associated with improved performance for a given device (61).

Different DPIs do not have the same internal resistance to airflow and range from low to high resistance (61-62). This resistance means that patients have to use a deep and forceful inhalation when using a DPI to receive the correct dose. Failure to use this type of inhalation is another common error when patients use their DPIs (11). The resistance of a DPI can be classified with respect to the inhalation flow required to produce a pressure drop of 4kPa. This value was chosen because it is the one recommended by Pharmacopoeias for the *in-vitro* characterization of the dose emitted from a DPI. A device that is characterized as having a low resistance requires an inspiratory flow of more than 90 L min^{-1} to produce this pressure drop. A medium resistance

device requires 60-90 L min^{-1}. A medium/high resistance device requires 50-60 L min^{-1} and a high resistance device requires <50 L min^{-1} (61-62). **Table 2** shows resistances for most DPI devices (61-62). Patients will inhale faster through a low resistance device (62). However, because the internal energy in a DPI will be the same whether a patient inhales slowly through a DPI with a high resistance, or inhales fast through a DPI with a low resistance, deaggregation of the powder will also be the same (62). For this reason, it is not valid to compare devices or classify them with respect to flow (61, 62). DPIs with a high resistance tend to produce greater lung deposition than those with a lower resistance (61-62), but the clinical significance of this is not known. Furthermore as the inhalation flow increases, deposition in the central airways will increase and distribution uniformity throughout the airways will decrease (17).

Figure 2 shows two possible patient inhalation profiles (63). Both of the profiles attain the same peak inhalation flow, but one starts with a fast inhalation (i.e. fast acceleration rate) and the other gradually speeds up its flow (i.e. slow acceleration rate). It has been shown that deagglomeration of particles takes place inside the device before the metered dose leaves the DPI and is increased if the acceleration is fast at the start of inhalation (64). Thus, the fine particle dose will be greater and the MMAD smaller when the initial acceleration rate of the inhalation flow is fast (64-65). Hence patients should be instructed to inhale forcefully from the beginning of their inhalation.

Superimposed onto the two inhalation profiles in **Figure 2** are representations of when the dose is emitted from a capsule-DPI and from a reservoir- or blister type-DPI. Clearly, the dose is emitted earlier during inhalation from the reservoir- or blister type-DPI, compared to the capsule-DPI. For this reason, inhalation volume becomes important for patients using DPIs with capsules and they should repeat the inhalation to ensure that they receive the full dose.

Each DPI has a minimum threshold energy below which deagglomeration is inefficient, resulting in a reduced emitted dose with a high MMAD and small FDP. Below the minimum threshold energy, the patient will receive no, or very little, therapeutic effect from the drug. For example, it has been shown that the Turbuhaler® provides some clinical effect at low flows (66), but the minimum flow is around 30 L min^{-1} and the optimal flow for this device is around 60 L min^{-1}. The Novolizer is designed not to release its dose below an inspiratory flow rate of 35 L min^{-1} (67). Another dose cannot be metered until this thresh hold has been overcome. The Easyhaler® (68) and Clickhaler® (69) have both been shown to be effective at low inhalation flows. For the Diskus® (70) and Handihaler® (71), the minimum inhalation flow is probably 30 L min^{-1}. For the Aerolizer®, it is probably >60 L min^{-1} (72).

Studies have shown that young (pre-school) children with asthma (73) and patients with COPD (74) may have problems achieving minimum flows through some DPIs and inhalation flow is reduced during acute exacerbations (75). No manufacturer has stated the minimum flow for their DPI, although it is clear that this information is needed.

1. Recommendations: Prescribers should

- Refer to the inhalation instructions in the PIL and as described in **Table 4.**
- Ensure that the patient is aware of the dose preparation instructions in the PIL.
- Ensure that the patient understands that they should exhale into the room to functional residual capacity before inhaling from their DPI.
- Instruct the patient that they should not exhale into the DPI device before inhalation.
- Instruct the patient to inhale forcefully from the beginning. They should not gradually increase their speed of inhalation.

- Instruct the patient to inhale each dose as deeply as they can and to continue to inhale for as long as possible.
- Instruct the patient that for single-dose capsule DPIs, they should perform two separate inhalations for each dose.

e) Nebulizers

Nebulizers convert solutions and suspensions into small droplets. Solutions are comprised of drug dissolved in a carrier liquid, whereas suspensions are comprised of solid drug particles suspended in the carrier liquid. The advantage to using nebulizers includes their ability to aerosolize high doses of drugs that are not available with DPIs or pMDIs. In addition, many nebulizers come with facemasks so they can be used by patients less than 2 years old, the elderly and those with severe respiratory distress.

1. Pneumatic or Jet Nebulizers

Pneumatic or jet nebulizers use compressed gas flow to entrain liquid from a reservoir and break the liquid into small droplets by means of baffles. The particle size distribution of the aerosol leaving the device is determined by the design of the baffle and the flow through the device. These nebulizers are relatively inefficient, compared to newer devices described below. Despite their inefficiency, they are still widely used. For a detailed description of these systems refer to the ERS Guidelines on nebulizers published in 2001 (76).

When these nebulizers are employed in the home, their performance is dependent on the choice of compressor that is used to drive the nebulizer (77-78). Some nebulizer manufacturers specify the compressors that have been tested with their product.

2. Breath-Enhanced Jet Nebulizers

Breath-enhanced jet nebulizers (e.g. the LC Plus®, PARI; Ventstream®, Philips Healthcare, NL; NL9M, DTF, France) increase output by increasing airflow through the device during inhalation. Breath-enhanced nebulizers are relatively more efficient and deliver drug faster than traditional jet nebulizers.

3. Dosimetric Jet Nebulizers

Dosimetric jet nebulizers are also more efficient than traditional jet nebulizers. The breath-actuated AeroEclipse® (Trudell Medical International, Canada) generates aerosol during inhalation only, eliminating waste during exhalation. The AKITA® system (Activaero, Germany) controls the entire inhalation maneuver of the patient by applying a positive pressure delivered with a computer-controlled compressor. It can be used with conventional jet nebulizers and has been shown to improve aerosol delivery efficiency, with up to 60% deposition in the lung periphery of patients with chronic obstructive pulmonary disease (COPD) (79). Such computer-controlled systems cost significantly more than traditional nebulizer delivery systems alone.

The newer breath-enhanced jet nebulizers and dosimetric jet nebulizers are more efficient and reduce the time it takes for delivery of aerosolized medications, compared to traditional jet nebulizers. However, like traditional jet nebulizers, it is difficult to know when dosing is completed with these newer nebulizers. The only indication that treatment should be stopped with any of these nebulizers is when the nebulizer starts sputtering.

4. Ultrasonic nebulizers

Ultrasonic nebulizers transmit sound waves generated by vibrating a piezoelectric crystal at high frequency (>1 MHz) to the surface of the drug solution to be nebulized where the droplets are formed. Although ultrasonic nebulizers can nebulize solutions more quickly than pneumatic

jet nebulizers, they are not suitable for suspensions and the piezoelectric crystal can heat and inactivate protein drugs such as dornase alfa (80-81).

5. Vibrating Mesh Nebulizers

Vibrating mesh devices are either active or passive systems. In active devices (e.g. Aeroneb® Go and Pro devices, Aerogen, Ireland; eFlow®, PARI), the aperture plate vibrates at a high frequency and draws the solution through the apertures in the plate. In passively vibrating mesh devices (e.g.,MicroAir®, Omron Healthcare, Japan; I-neb®Adaptive Aerosol System (AAD), Philips Healthcare), the mesh is attached to a transducer horn and vibrations of the piezoelectric crystal that are transmitted via the transducer horn force the solution through the mesh to create an aerosol.

The eFlow® is designed to be used with either a very low residual volume to reduce drug waste, or with a relatively large residual volume, so that it can be used instead of conventional jet nebulizers with the same fill volume.

The I-neb® AAD pulses medication delivery into 50 to 80 percent of each inspiration, based on an average of the last three breaths (82). This device provides feedback to the patient regarding dose delivery and also incorporates software that can be used to monitor patient adherence.

Vibrating mesh devices have a number of advantages over other nebulizer systems. They are very efficient and quiet and are generally portable, since they operate as effectively when using batteries, or electricity. However, they also are currently significantly more expensive than other types of nebulizers, require a significant amount of maintenance and cleaning after each use to prevent build up of deposit and blockage of the apertures, especially when suspensions are aerosolized, and to prevent colonization by pathogens. They are currently most widely used for

the treatment of patients with cystic fibrosis. However, they are being developed for other uses such as delivery of vaccines and they can also nebulize liposomal formulations (83-85) and proteins (86).

The performance of various nebulizers can vary substantially. These differences may not be clinically significant when used to deliver bronchodilators, since these drugs have a wide therapeutic index. However, when delivering drugs with narrow therapeutic indices, it is important to choose a device that has been shown to be clinically effective. For this reason, new nebulized medications are increasingly being licensed with clear recommendations as to use with specific nebulizers. Licensing drugs for delivery with specific nebulizers should reduce the potential for substantial variation in delivered dose due to alterations in the delivery system.

6. Facemasks and Mouthpieces

Generally, mouthpieces are employed during nebulizer delivery. However, facemasks may be necessary for treatment of acutely dyspnoeic, or uncooperative patients such as infants and toddlers. The facemask is not just a connector between the device and the patient. Principles of mask design are different depending on the device. For example, a VHC with facemask must have a tight seal to achieve optimal lung deposition (87). On the other hand, the facemask for a nebulizer should not incorporate a tight seal, but should have vent holes to reduce deposition on the face and in the eyes (88-89). Improvements in facemask design provide greater inhaled mass while reducing facial and ocular deposition (90).

Many times when a patient does not tolerate the facemask, practitioners employ the “blow-by” technique, which simply directs the aerosol towards the nose and mouth with the mouthpiece. However, there is no data to indicate that this is an effective method for delivering

aerosol to the lungs and an NIH Expert Panel recently indicated that the use of this technique is not appropriate (91).

7. Recommendations: Prescribers should

- Choose a nebulizer based on the recommendation found in the PIL for the drug that is being prescribed.
- Choose a compressor that has been tested with the prescribed nebulizer brand.
- Know that a jet nebulizer treatment should be stopped once the nebulizer starts sputtering.
- Use an appropriate facemask when a mouthpiece is unsuitable.
- Not use the "blow-by" technique.
- Instruct patients that they need to clean their nebulizers after each use according to manufacturer's directions.
- Instruct patients that they should be careful not to touch the mesh when cleaning vibrating mesh nebulizers, as this could damage the unit.
- Instruct patients that they should follow the manufacturer's recommendations for when to purchase a new nebulizer.

f) Soft Mist Inhalers

Currently, there is only one commercially available soft mist inhaler: The RespimatSoft Mist® Inhaler (Boehringer Ingelheim, Germany). This inhaler is available in Germany for the delivery of fenoterol 50µg/ipratropium bromide, 20µg per puff. In Germany and many other countries, it is available for the delivery of tiotropium bromide, 2.5µg per puff. The Respimat® atomizes the drug solution using mechanical energy imparted by a spring. When the spring is released, the solution is forced through an extremely fine nozzle system (92-93). This produces a

fine mist that is slow-moving, leading to lower deposition in the mouth and throat and relatively high lung deposition (i.e. about 39%) (94-96).

CHOICE OF DRUG-DEVICE COMBINATIONS TO USE AT HOME

Device options and drugs for treating asthma and COPD at home are summarized in **Table 2**. Drugs include bronchodilators, corticosteroids and combination formulations. The effectiveness of these drugs has been reviewed in detail (1-3, 91, 97). These drugs can be administered by pMDIs, BA-pMDIs, DPIs, nebulizers, or soft mist inhalers. In large part, the choice of delivery system is dependent on the class of drug chosen and by the capabilities of the patient. It is important to prescribe a device that the patient can and will use effectively at home. A spacer should be employed when inhaled corticosteroids are delivered by a pMDI and patients should still be instructed to rinse out their mouth and gargle after each treatment to reduce the occurrence of oropharyngeal candidiasis and to minimize systemic absorption of swallowed drug.

Patients with diseases other than asthma or COPD also utilize inhaled medications during treatment at home. These include patients with pulmonary arterial hypertension (PAH), HIV-infected (AIDS) patients and patients with cystic fibrosis (CF). The most recent developments in drugs and devices to treat these patients are summarized below.

Patients with PAH:

Inhaled iloprost (Ventavis®; Acetelion Pharmaceuticals US, Inc.) is licensed for treatment of PAH with the I-neb® AAD.

HIV-infected (AIDS) or immunocompromised patients:

Inhaled pentamidine solution is an anti-infective agent that helps to treat or prevent pneumonia caused by the organism *Pneumocystis carinii*. The Respirgard II nebulizer (Marquest; Englewood, CO) is licensed to deliver NebuPent® 300mg for oral inhalation.

Patients with CF:

Patients with CF must inhale one or more therapies at home several times per day. A recent review by Flume et al. examined the clinical evidence for each therapy and provides guidance for the prescription of these therapies (4). Aerosolized antibiotics have been advocated for both eradication of the initial infection and for suppression of the chronic infection due to *Pseudomonas aeruginosa* in patients with CF. During nebulization of antibiotics, an expiration filter can be used to prevent contamination of the room and exposure of bystanders to potentially toxic drugs.

Tobramycin inhalation solution is an approved inhaled antibiotic used to treat *Pseudomonas aeruginosa* in patients with CF. TOBI® (Novartis Pharmaceutical, Switzerland) is licensed for inhalation with a PARI LC PLUS™ nebulizer and a DeVilbiss® Pulmo-Aide® air compressor (Sunrise Medical, PA). Bramitob® (Chiesi Farmaceutici, Italy) is licensed for administration with the PARI LC Plus and PARI TURBO Boy compressor. In the summer of 2011, inhaled tobramycin will be licenced as a dry powder formulation for treatment of CF in some countries. Another inhaled antibiotic, inhaled colistin, is also recommended for treatment of CF. Colistin is recommended to be used with an appropiate jet-nebulizer, such as the PARI LC Plus® or LC Star®, with either the PARI Master® or a similar compressor. Inhaled colistin is also licensed for use with the I-neb® AAD in several countries. Similarly, in some countries, aztreonam inhalation solution is licensed for use with the eFlow® nebulizer as Cayston® (Gilead Sciences, Inc.; Foster City, CA).

Nebulised hypertonic saline (7% NaCl) (Hyper-Sal®; PARI) has been shown to improve mucociliary clearance in patients with CF (98) and has been tested primarily with the PARI LC Star® nebulizer and PARI Proneb® compressor combination. MucoClear® (6% NaCl) (PARI) and Hyaneb (7% NaCl) (Praxis Pharmaceutical) are also available for mucociliary clearance. Both manufacturers recommend using a PARI nebulizer for administration.

Recombinant human DNase (rhDNase; dornase alfa) (Pulmozyme®; Genentech; South San Francisco, CA) was developed to degrade free DNA that accumulates within the CF mucus, thereby improving the viscoelastic properties of airway secretions and promoting airway clearance (4). Recommended nebulizer/compressor combinations for delivering rhDNase include the Hudson T Up-draft II® with Pulmo-Aide®, the Marquest Acorn II® with Pulmo-Aide®, the PARI LC Jet® with PARI Proneb® compressor, the PARI BABY® with PARI Proneb®, Durable Sidestream® with Mobilaire® or Porta-Neb®.

A detailed overview of new aerosol delivery devices for treating patients with CF has been written by Kesser and Geller (99).

1. Recommendations: Prescribers should

- Know the many device options for treating patients at home (Refer to **Table 2**).
- Choose the device that the patient can and will use.
- Teach patients how to use the device correctly (Refer to **Table 4** for use of pMDIs, BA-pMDIs, pMDIs with spacers, DPIs and nebulizers).

CHOICE OF DRUG-DEVICE COMBINATIONS TO USE IN THE EMERGENCY ROOM AND IN HOSPITAL

a) pMDIs with Spacers versus Nebulizers to Administer Short-Acting Bronchodilators in the Emergency Room

Until recently, treating asthmatics and patients with COPD in the emergency room usually involved nebulization of short-acting bronchodilators (1-3, 100-101). However, several studies have demonstrated similar efficacy for inhaled bronchodilators using pMDIs with spacers (pMDIs alone are not as effective), compared to nebulizers in emergency rooms in patients with non life-threatening asthma and in patients with COPD with non-severe exacerbations (102-107). To more closely match the dose administered by nebulization, the number of puffs from the MDI should be increased to between 4-10 puffs in the emergency room setting (103). Administrations should be repeated as needed (103). Potential advantages of this approach are cost savings, reduced time of administration and, more importantly, reinforcement of self-management messages.

b) Nebulizers and Severe Asthma and COPD in the Emergency Room

Nebulizers are indicated for patients with asthma and COPD who are undergoing severe exacerbations, especially those with alterations of consciousness. Oxygen is commonly employed as the driving gas for jet nebulizers in patients with severe asthma, or acute exacerbations of COPD. It is advisable to avoid the uncontrolled use of oxygen in patients with severe COPD because of the risk of hypercapnia with high doses of oxygen (108-109). Such patients should be monitored for oxygen saturation and level of consciousness.

c) Recommendations: Prescribers should

- Know that, in non life-threatening asthma and non-severe exacerbations of COPD, aerosolized beta$_2$-adrenergic agonists can be administered effectively using a pMDI with spacer or VHC.

- Use a nebulizer to administer beta$_2$-adrenergic agonists whenever the patient cannot perform the correct inhalation maneuver with the pMDI and spacer.
- Use nebulizers in patients with severe asthma or COPD, especially those with consciousness alterations.
- Use a driving gas flow of 6-8 L min^{-1} for non-portable nebulizers.
- Use oxygen as appropriate for the clinical condition.

d) Nebulizers and Non-CF Diseases in Hospital

Hypertonic saline (3% or 5%) 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 (110).

Nebulized iloprost (Ventavis®) has been approved in many countries for class III NYHA primary pulmonary hypertension. It is licensed for use with the I-neb® AAD.

CHOICE OF DRUG-DEVICE COMBINATIONS TO USE IN SPECIAL POPULATIONS

a) Children

Aerosol therapy is often used for the treatment of pulmonary diseases in children. However, many of the pediatric indications are not evidence-based. A recent ERS Task Force Guideline discusses recommended treatments for pediatric pulmonary diseases (111).

Many of the new devices also are not approved for use in children and few studies are available to show efficacy in this population. However, according to the recently approved EMA guidelines, not all new drug-device combinations need to be tested clinically before approval for use in children is given. Look for the new guidelines on the requirements for clinical

documentation for orally inhaled products at the following link:
(http://www.ema.europa.eu/pdfs/human/ewp/4850108en.pdf)

The choice of device for children is affected by the child's cognitive ability. Children up to approximately 3 years of age are generally unable to adopt specific inhalation techniques and therefore are treated with nebulizers with a facemask (88), or with pMDIs with a VHC and facemask (112). Refer to the inhalation instructions for nebulizers and pMDIs with spacers and facemask in **Table 4**. If the VHC-facemask combination does not achieve a tight fit over the child's nose and mouth, drug delivery to the lungs will be significantly reduced (87). In a struggling child, it is difficult to achieve a good seal with the facemask and the inhaled dose is substantially reduced. If the child is screaming, or crying, most of the inhaled drug deposits in the upper airway, not in the lungs (89).

If a child can be taught to use a mouthpiece, this should be encouraged, since mouthpiece breathing increases lung deposition, compared to facemask breathing (29). Most (but not all) children can be taught to use a mouthpiece from around 3 years of age**.** When a child is inhaling through a mouthpiece attached to a nebulizer, place the mouthpiece in the mouth and instruct the child to close their lips around it. The child should then inhale and exhale using normal (tidal) breaths, with occasional deep breaths, until the nebulizer starts to sputter, or no more aerosol is produced.

There are different ways to inhale from a pMDI/spacer using a mouthpiece. The easiest technique is inhaling from the spacer with normal, quiet breathing and this is useful when working with young and older children. With appropriate instruction, most children over the age of six should be able to perform a "single breath" technique with a pMDI/spacer (48). This technique is described by Roller et al. and appears to improve lung deposition of QVAR®,

compared to normal quiet breathing in older children (48). An experienced individual should instruct the child and caregiver how to perform these techniques and should check to determine if the child is able to perform it correctly. Refer to the inhalation instructions for spacers with a mouthpiece in **Table 4**. If compliance with a pMDI and spacer is an issue for a child over the age of six, most of these children (but not all) should be able to produce the forceful inhalation that is required to use a DPI (11). Refer to the inhalation instructions for DPIs in **Table 4**.

In general, a pMDI-spacer is often the cheapest option for aerosol therapy. However, many school age children will not use the spacer and, therefore, fail to deliver adequate amounts of drug to the lungs. In this context, a DPI may be the best option, although they are not intrinsically 'superior' to the pMDI-spacer and are more expensive.

As mentioned above, nebulizers can be used to deliver aerosols of formulations that cannot be administered as an aerosol with either pMDIs or DPIs. However, the new mesh nebulizers are an expensive option, and cheaper, pneumatic and breath-enhanced devices are more time consuming and therefore less tolerated than a pMDI-spacer combination that incorporates a facemask in young children.

Several studies have demonstrated similar efficacy for inhaled $beta_2$-adrenergic agonists using pMDIs with spacers (pMDIs alone are not as effective), compared to nebulizers in emergency rooms in children with non life-threatening asthma (103, 112). As in the case of adults with asthma, the number of puffs from the MDI should be increased to between 4-10 puffs in the emergency room setting to more closely match the dose administered by nebulization, (112). Administrations should be repeated as needed (103).

1) Recommendations: Prescribers should

- Match the device to the patient's capability to perform the specific inhalation maneuvers recommended for the device.
- Choose a device that has performance capability information for the specific age group of the patient.
- Refer to **Table 4** for inhalation instructions.
- Choose a combination nebulizer with a facemask, or a pMDI with a VHC and facemask for children younger than the age of 3 years.
- Maximize cooperation to optimize lung deposition in young children.
- Teach children who are 3-6 years old to breathe tidally from a spacer using a mouthpiece, if they can perform this technique correctly.
- Teach children who are 6 years old or older to adopt a single slow maximal inhalation and breath hold while using a pMDI-spacer with a mouthpiece, if they can perform this technique correctly.
- Know that in the emergency room, $beta_2$-adrenergic agonists can be administered to children with mild and moderate exacerbations of asthma by means of a pMDI-spacer, or nebulizer.

b) The Elderly

Those prescribing aerosol treatment for the elderly face similar problems to those confronted by physicians who treat children. Cognitive decline means that the more complex manuevers may be challenging for many elderly patients. The situation is compounded by dexterity issues. Once again, the clinician is obligated to prescribe a delivery system that a patient can and will use effectively. For many with limited abilities to adopt complex inhalation manuevers, the simplicity of a jet nebulizer may be a necessary compromise.

c) Intubated and Mechanically-Ventilated Patients

Aerosols can be administered to intubated and mechanically-ventilated patients by pMDI and in-line spacer, or by nebulizer. The efficacy of pMDI delivery during mechanical ventilation is dependent on the actuation of the pMDI through a spacer or holding chamber that is tightly inserted in the inspiratory limb side of the ventilator circuit at approximately 15 cm from the endotracheal tube (113-114). In adult patients, a tidal volume ≥ 0.5 L guarantees drug delivery to the lower respiratory tract (115-116).

The rate of aerosol production and the characteristics of the aerosol that is generated by nebulizer differ between devices (117) and depend on ventilator mode (118), pulmonary mechanics (118), inspiratory flow rate (119) and distance from the endotracheal tube (120).

The efficiency of aerosol delivery with both pMDIs and nebulizers is reduced by humidity in the ventilator circuit (121). In contrast, aerosol delivery is increased with both pMDIs and nebulizers when helium-oxygen mixtures are used in place of air, or air-oxygen mixtures to ventilate the patient (122) and both techniques have proven to be clinically effective (123).

Aerosolized albuterol/salbutamol at a dose of 2.5 mg with a nebulizer (124), or 4 puffs (400 μg) with a pMDI and spacer (114), produces significant bronchodilator effects in mechanically ventilated patients with COPD. The albuterol/salbutamol should be repeated every 3-4 hours (113). Nebulized fenoterol at a dose of 0.4 mg was found effective in intubated COPD patients (125). Both pMDIs and jet nebulizers are equally effective for bronchodilator administration in mechanically-ventilated patients, but pMDIs have the advantages of convenience, lower cost, and lesser risk of damaging flow sensors.

In mechanically ventilated ARDS patients, nebulized prostacyclin and prostaglandin E_1 are as effective as nitric oxide in improving oxygenation and hemodynamics (126-127).

Newer generation vibrating mesh nebulizers have been designed specifically for use during mechanical ventilation and have been shown to be efficient for drug delivery in bench studies. These devices are currently under investigation and little clinical information is available.

1) Recommendations: Prescribers should

- Know that aerosols can be administered to intubated and mechanically-ventilated patients by pMDI and in-line spacer, or by a nebulizer designed for use during mechanical ventilation.
- Know that aerosolized albuterol/salbutamol at a dose of 2.5 mg with a nebulizer, or 4 puffs (400 mcg) with an MDI, or nebulized fenoterol at a dose of 0.4 mg have significant bronchodilator effects.
- Know that higher doses produce negligible additional therapeutic advantage.

d) Patients on Non-Invasive Mechanical Ventilation (NIV)

Aerosols can be administered to patients receiving NIV by pMDI and spacer with facemask, or by nebulizer with facemask. Based on the currently available literature (128) the recommended technique for using a pMDI in patients receiving NIV is to: (1) minimize leaks in the mask and or circuit; (2) place cylindrical spacer (volume ~140 ml) between circuit and mask; (3) shake pMDI canister well and place it in the adapter of the spacer chamber; (4) actuate pMDI at the beginning of inspiratory air flow from the ventilator; (5) repeat actuations after an interval of at least 15 seconds; (6) monitor patient and assess clinical response. The recommended technique for nebulizers is to: (1) minimize leaks in the mask and or circuit; (2) fill nebulizer with drug solution up to optimal fill volume (4 to 6 ml); (3) place nebulizer in an upright position between circuit and mask; (4) operate nebulizer with gas flow between 6 to 8 L min-1; (5) tap nebulizer periodically until it begins to sputter or stops producing aerosol; (6) remove nebulizer

form circuit, rinse with sterile water, air dry, and store in a clean space; (7) monitor patient and document clinical response.

The position of the leak port in the circuit influences efficiency of drug delivery from a nebulizer during non-invasive ventilation, but it does not influence the efficiency of drug delivery from pMDIs (129). Nebulizer efficiency is higher with the leak port in the circuit as compared to a leak port in the facemask (130). Furthermore, the findings of Calvert and colleagues (130) suggest that a nebulizer placed between the leak port and facemask (ventilator, leak port, nebulizer, facemask) performs with higher efficiency than placement of the nebulizer between the ventilator and leak port (ventilator, nebulizer, leak port, facemask).

1) Recommendations: Prescribers should

- Know that aerosolized medications can be administered during NIV either by pMDI and a spacer with facemask, or with a nebulizer and facemask.
- Know the proper technique for using a pMDI and spacer, or nebulizer, during NIV.
- Know where to position the nebulizer in relation to the leak port in the circuit.

THE FUTURE

Developments in inhaled therapy will lead to novel drugs using existing delivery systems, existing drugs delivered in novel delivery systems and new drugs in novel delivery systems. The increasingly prescriptive approach of regulators relating to drug device combinations should remove much of the variability that has been evident in the past due to the choice of nebulizers and compressors. Prescribers must continually update their understanding of the strengths and weaknesses of any delivery systems they choose to prescribe. Recommendations for future research in this field are found in Haughney et. al (131).

CONCLUSIONS

The use of an inhaler by a patient has a strong scientific basis that is related to the dose of drug that is deposited into the lungs. Because dose delivered to the lungs is so dependent on the correct use of the delivery system, those who prescribe inhaler devices should ensure that patients can and will use them correctly. This requires that prescribers know the devices that are currently available to deliver the prescribed drugs and the various techniques that are appropriate for each device, are able to evaluate the patient's inhalation technique to be sure they are using the devices properly and make sure that the inhalation method is appropriate for each patient. This Consensus Statement provides considerable information about the correct use of these devices, including detailed information about what drugs are currently available for delivery with specific devices, detailed instructions for how to use specific inhalers, guidelines for how to determine what device is best for your patient at home and in hospital, as well as numerous recommendations for ensuring that your patient understands how to use the device you prescribe.

It should be stressed that once a patient is familiar and stabilized on one type of inhaler, they should not be switched to new devices without their involvement and without follow-up education on how to use the device properly. A recent study has shown that asthma control deteriorates if an inhaler is substituted for a different device at the prescribing, or dispensing stage, without involving the patient (132). Prescribers should be especially vigilant on this point in order to avoid changes to the type of device their patients receive through the pharmacy.

Table 1: Definitions of commonly used terms that describe an aerosol

Term	Definition
*Labeled Dose or Nominal Dose	The mass of drug that is available within the aerosol generator per actuation. This is the dose that is metered.
*Total Emitted Dose or Delivered Dose (TED)	The mass of drug emitted per actuation that is actually available for inhalation at the mouth.
Fine particle dose (FPD)	The mass of particles <5 microns in size within the total emitted dose.
Fine particle fraction (FPF)	The fine particle dose divided by the total emitted dose
	.
Aerodynamic equivalent diameter (d_{ae})	The diameter of a fictitious sphere of unit density (1g cm^{-3}) that has the same gravitational (settling) velocity in the same gas as the actual particle.
Mass Median Aerodynamic Diameter ($d_{ae,mm}$ or MMAD)	The MMAD divides the aerosol size distribution in half. It is the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller.
Geometric Standard Deviation (σ_g or GSD)	The GSD measures the dispersion of particle diameter and is defined as the ratio of the median diameter to the diameter at ± 1 standard deviation (σ) from the median diameter. In a cumulative distribution plot of the aerodynamic diameter and mass of particles, the GSD is calculated as the ratio of the median diameter to the diameter at 15.9% of the probability scale, or the ratio of the diameter at 84.1% on the probability scale to the median diameter. Aerosols with GSD $\geq$ 1.22 are considered polydisperse. Most therapeutic aerosols are polydisperse and have GSDs in the range of 2–3.

*Lung deposition can be presented as a percentage of the nominal or emitted dose. Note that these two parameters are not the same.

Table 2: Devices currently available for delivery of commonly prescribed brand-name drugs by pMDIs, BA-pMDIs, nebulizers, soft mist inhalers and DPIs

Drug class	Drug/Device (brand name) Not all drugs/devices are available in all countries.	Dose available (nominal dose unless *emitted dose); μg unless otherwise stated	Comments For all drugs, patients should be monitored for side effects
2 A: pMDIs and BA-MDIs formulated with HFA propellant unless otherwise stated in the comments column. The dose of reformulated product is the same as the CFC version unless specified. **pMDIs:**			
(a) anticholinergics	ipratropium bromide (Atrovent®)	21	
(b) beta$_2$-adrenergic agonists	formoterol (Atimos® or Foradil®)	12	Atimos emits extrafine particles. Discard Atimos 12 weeks after dispensing.
	salbutamol	100	Airomir®, Proventil® and ProAir® contain a small amount of alcohol. In some countries, Ventolin® has a dose counter. In some countries, some generic versions are formulated with CFC products.
	salmeterol (Serevent®) levalbuterol (r-salbutamol) (Xopenex®)	25 45	 Contains a small amount of alcohol
(c) corticosteroids	beclomethasone (QVAR®)	50 & 100	QVAR® Aerosol Inhaler and Alvesco® inhaler emit extrafine particles. Due to greater lung deposition, the prescribed dose of QVAR is half that of the traditional beclomethasone dose. Licensed with the Aerochamber®, in some countries.
	ciclesonide (Alvesco®)	*40, *80 & *160	

	beclomethasone (Clenil®)	50, 100, 200 & 250	Formulated with HFA-propellants, but has particle size characteristics that are similar to CFC-beclomethasone. Licensed with the Aerochamber®, or the Volumatic®, in some countries.
	beclomethasone (Beclazone®)	50, 100 & 250	Formulated with CFC propellant, but will be discontinued in the near future.
	budesonide (Pulmicort®)	50, 100 & 200	50μg strength is currently formulated with CFC propellants.
	fluticasone (Flixotide®, Flovent®) flunisolide HFA (Aerospan®)	50, 125 & 250 80	
(c) combinations	beclomethasone/formoterol (Foster®). In some countries, this product is known as Fostair®), Fostex®), or Innovair®)	100/6	Beclomethasone and formoterol in this combination product are formulated as extrafine particles.
	budesonide/formoterol (Symbicort®)	*80/4.5, *160/4.5	Should be discarded 12 weeks after dispensing. Has a dose counter.
	fluticasone/salmeterol (Seretide®)	50/25, 125/25 & 250/25	Has a dose counter. Licensed with the Volumatic®, or Aerochamber®, in some countries.
	ipratropium bromide/ salbutamol (Combivent®)	18/100	Formulated with CFC propellant, but will be discontinued in the near future.
(d) cromones	nedocromil sodium (Tilade®)	2mg	Has been discontinued in many countries.
	sodium cromoglycate (Intal®)	1mg and5 mg	Formulated with CFC propellant, but will be discontinued in the near future.
BA-pMDIs:			

(a) beta$_2$-adrenergic agonists	salbutamol	100	Easibreathe®) Inhaler and Airomir® Autohaler.
	pirbuterol	200	Maxair® Autohaler; will be discontinued after 12/31/10.
(b) corticosteroids	beclomethasone (QVAR®)	50, 100	Qvar Autohaler® and Qvar Easi-Breathe®)Inhaler. beclomethasone formulated as extrafine particles.
2B Nebulizers and Soft Mist Inhalers **Nebulizers:**			
(a) beta$_2$-adrenergic agonists	formoterol fumarate inhalation solution (Perforomist®)	20/2ml	
	sabutamol inhalation solution	0.083% Vials with 1,2 and 5mg/ml	Vials do not require dilution. Add saline until 4ml total for jet nebulizer
	arformoterol tartrate (r-formoterol) inhalation solution	15	
	levalbuterol (r-salbutamol) inhalation solution	0.31mg/3ml, 0.63mg/3ml & 1.25mg/3ml	Store in foil pouch. Once pouch is opened, use vials within 2 weeks.
	metaproterenol sulfate (Alupent®)	0.5%, 0.6% & 5%	
(b) non-steroidal anti-inflammatories	cromolyn sodium	20mg	Can be mixed with salbutamol inhalation solution in nebulizer.

(c) antibiotics	tobramycin inhalation solution	300mg/5 ml (TOBI®)	Licensed for use with PARI LC Plus™ nebulizer and Devilbiss® Pulmo-Aide® compressor
		300mg/4 ml (Bramitob®)	Licensed for use with PARI LC Plus™ and PARI TURBO Boy® compressor
	colistin inhalation solution (Promixin®)	Vial with powder: 1million units (= 80 mg) with water and saline for solution (3 ml)	Licensed for use with jet nebulizer (PARI LC Plus™ or similar nebulizer) with appropriate compressor. Licenced for use with the I-neb® AAD, in some countries.
	aztreonam inhalation solution (Cayston®)	75mg/2 ml	Licensed for use with the eFlow®, in some countries
(d) corticosteroids	budesonide inhalation suspension	0.25mg, 0.5mg & 1mg (Pulmicort Respules®); 0.25mg & 0.5mg (generic)	Licensed for use with jet-nebulizers Not for use with ultrasonic nebulizer.
	Fluticasone inhalation suspension	0.50mg/2 ml; 2mg/2ml (Flixotide®)	

(e) mucolytics	recombinant human DNase (Pulmozyme®) hypertonic saline inhalation solution Hyper-Sal™ MucoClear® Hyaneb™	2.5 mg/2.5 ml 3.5%/4ml &7%/4ml 6%/4ml 7%/5ml	Licensed for use with many nebulizers (see text for details). Should not be used with ultrasonic nebulizers. Fluid should not be diluted or mixed with other drugs. Studied with jet nebulizers and breath-enhanced nebulizers with appropriate compressors Also contains sodium hyaluronate 0.1%	
(f) prostacyclin (g) anticholinergics (h) anti-infective	iloprost (Ventavis®) ipratropium bromide (Atrovent®) pentamidine (NebuPent®)	2.5/ampule & 5/ampule 500/vial 0.02% 300mg	Licensed for use with I-neb® AAD Can be combined with salbutamol, or metaproterenol, solutions Licensed with Respigard II nebulizer	
Soft Mist Inhalers:				
(a) anticholinergics	tiotropium bromide	2.5	Respimat®	
(b) combinations	fenoterol/ipratropium bromide	50/20	Respimat®	
2C: Dry Powder Inhalers (DPIs)				
Device	Drug (brand name)	Dose Available	Type	Resistance

Aerolizer®)	budesonide formoterol	200 12	Capsule	Low
Diskhaler®)	beclomethasone fluticasone salmeterol zanamivir (antiviral)	100, 200 & 400 100, 250 & 500 50 5mg	8 sometimes 4	Low
Diskus (Accuhaler®) in the UK)	fluticasone salbutamol salmeterol fluticasone/salmeterol	50, 100, 250 & 500 200 50 100/50, 250/50 & 500/50	Individual doses in a blister inside the device	Medium
Clickhaler®)	Beclomethasone budesonide formoterol salbutamol	50, 100 & 250 100, 200 & 400 12 114	Multidose Reservoir	Medium/ High
Cyclohaler®)	beclomethasone budesonide salbutamol	100, 200 & 400 200 & 400 200	Capsule	Low
Easyhaler®)	beclomethasone budesonide formoterol salbutamol	100, 200 & 400 100, 200 & 400 12 100 & 200	Multidose reservoir	High
Handihaler®)	tiotropium	18	Capsule	High
Maghaler®)	budesonide	200	Multidose reservoir	
Novolizer®)	budesonide formoterol salbutamol	200 12 100	Multidose reservoir	Medium
Pulvinal®)	beclomethasone salbutamol	100, 200 & 400 200	Multidose reservoir	Medium/ High
Spinhaler®)	sodium cromoglycate	20mg	Capsule	Low
Spiromax®)	budesonide	100, 200 & 400	Multidose reservoir	Medium/ High
Turbuhaler®)	budesonide formoterol terbutaline budesonide/formoterol	100, 200 & 400 90 & 180 (in U.S.) 6 & 12 500 100/6, 200/6 & 400/12	Multidose reservoir	Medium/ High
Twisthaler®)	mometasone	200 & 400 220 & 110 (in U.S.)	Multidose reservoir	High

Table 3A: How to choose the right aerosol delivery device for patients with good actuation-inhalation coordination

Inspiratory Flow	**Inspiratory flow**
***At least 30 L min^{-1}**	***<30 L min^{-1}**
pMDI	pMDI
BA-MDI	
DPI	
Nebulizer	Nebulizer

Table 3B: How to choose the right aerosol delivery device for patients with poor actuation-inhalation coordination

Inspiratory flow	**Inspiratory flow**
***At least 30 L min^{-1}**	***<30 L min^{-1}**
pMDI +spacer	pMDI +spacer
BA-MDI	
DPI	
Nebulizer	Nebulizer

(Adapted from Table 4 reference 34)

*Inspiratory flow rate can be determined from the flow/volume curve generated during spirometry measurements, or by using devices like the IN-Check Dial® (Clement Clarke International).

Table 4: Detailed instructions on how to use pMDIs, BA-pMDIs, pMDIs with spacers, DPIs, nebulizers and soft mist inhalers

pMDIs (For patients with good actuation-inhalation coordination.
1. Shake 4 or 5 times if suspension formulation. 2. Take the cap off. 3. Prime the inhaler (refer to the patient information leaflet (PIL) for specific instructions) 4. Exhale slowly, as far as comfortable (to empty the lungs). 5. Hold the inhaler in an upright position. 6. Immediately place the inhaler in the mouth between the teeth, with the tongue flat under the mouthpiece. 7. Ensure that the lips have formed a good seal with the mouthpiece. 8. Start to inhale slowly, through the mouth and at the same time press the canister to actuate a dose. 9. Maintain a slow and deep inhalation, through the mouth, until the lungs are full of air. This should take an adult 4-5 seconds. 10. At the end of the inhalation, take the inhaler out of the mouth and close the lips. 11. Continue to hold the breath for as long as possible, or up to 10 seconds before breathing out. 12. Breathe normally. 13. If another dose is required, repeat steps 4-12.
BA-pMDIs (For patients ≥6 years old)
1-7. Same as above for pMDIs alone. 8. Start to inhale slowly, through the mouth. The patient should sense that a dose has been released – either by taste, or a noise when the dose is released (the noise is quiet for the Easibreathe). 9. Maintain a slow and deep inhalation, through the mouth, until the lungs are full of air. This should take a primary school child about 2-3 seconds and an adult 4-5 seconds. 10-13. Same as above for pMDIs alone.
pMDI + spacer with facemask (For patients ≤3 years old, or anyone who cannot breathe consciously through the mouth)
1-3. Same as above for pMDIs alone. 4. Insert the mouthpiece of the pMDI into the open end of the spacer and ensure a tight fit. If a reverse flow spacer is used (**Table 6**), insert the valve stem of the pMDI into the port on the mouthpiece of the spacer. 5. Place the facemask over the nose and mouth and be sure the fit is tight to the face. 6. Actuate one dose into the chamber of the spacer. 7. The patient should inhale and exhale normally into the spacer at least 10 times. 8. Take the facemask off the patient's face. 9. If another dose is required, repeat steps 1-8.
pMDI + spacer with mouthpiece (For patients ≥3 years old. Caregiver should determine if child

can perform this technique correctly)
1-4. Same as above for spacer with facemask 5. Place the mouthpiece of the spacer in the patient's mouth with the teeth over the mouthpiece and the lips sealed around it. 6. Actuate one dose into the chamber of the spacer. 7. Instruct the patient to inhale and exhale using normal (tidal) breaths into the spacer at least 5 times. With some spacers, the inhalations and exhalations can be monitored by observing the movement of the valves. 8. If another dose is required, repeat steps 4-7. 9. If ICS are used, rinse mouth afterwards.
pMDI + spacer with mouthpiece (For patients ≥6 years old. Caregiver should determine if child can perform this technique correctly)
1-4. Same as above for spacer with facemask. 5. Insert the mouthpiece of the pMDI into the open end of the spacer and ensure a tight fit. If a reverse flow spacer is used (**Table 6**), insert the valve stem of the pMDI into the port on the mouthpiece of the spacer. 6. Place the mouthpiece of the spacer in the patient's mouth with the teeth over the mouthpiece and the lips sealed around it. 7. Instruct the child to exhale slowly, as far as comfortable, to empty their lungs 8. Actuate one dose into the chamber of the spacer and start to inhale slowly through the mouthpiece. Some spacers will make a whistle noise if inspiration is too fast. 9. Maintain a slow and deep inhalation through the mouth, until the lungs are full of air. This should take a primary school child 2-3 seconds and an adult 5 seconds. 10. At the end of the inhalation take the inhaler out of the mouth and instruct the patient to close their lips. 11. Continue to hold the breath for as long as possible for up to 10 seconds before breathing out. 12. Breathe normally. 13. If another dose is required, repeat steps 1-12. 14. If ICS are used, rinse mouth afterwards.
DPI (For patients ≥5-6 years old. Caregiver should determine if child can perform this technique correctly)
1. Take the cap off (some do not have a cap). 2. Follow the dose preparation instructions in the PIL 3. Do not point the mouthpiece downwards once a dose has been prepared for inhalation because the dose could fall out. 4. Exhale slowly, as far as comfortable to empty the lungs. Do not exhale into the DPI. 5. Start to inhale forcefully through the mouth from the very beginning. Do not gradually build up the speed of your inhalation. 6. Continue inhaling until the lungs are full. 7. At the end of the inhalation take the inhaler out of the mouth and close the lips. Continue to hold the breath for as long as possible, or up to 10 seconds. 8. Breathe normally. 9. If another dose is required, repeat steps 1-8.

Jet nebulizers (For patients of any age who cannot use a pMDI with a valved holding chamber, with or without a facemask, or if the drug is only available as nebulizer liquid)
1. Assemble tubing, nebulizer cup, and mouthpiece (or mask). 2. Pour the medication solution into the nebulizer cup. 3. Do not exceed the fill volume recommended by the manufacturer. 4. Connect to power source; flow of 6-8 L/min, or compressor. 5. Place mouthpiece in the mouth and close the lips around it (or cover the nose and mouth with an appropriate facemask). 6. Keep nebulizer vertical during treatment. 7. Inhale and exhale using normal (tidal) breaths, with occasional deep breaths, until the nebulizer starts to sputter, or no more aerosol is produced. 8. If the treatment must be interrupted, turn off the unit to avoid waste. 9. At the completion of the treatment, take the mouthpiece out of the mouth. 10. Dismantle and clean nebulizer following manufacturer's instructions. 11. With technology that differs from that of a traditional jet nebulizer, clinicians should thoroughly review operating instructions prior to patient use and instruction.
Mesh nebulizers (for use with drugs licensed with this type of nebulizer)
1. Assemble the device according to the manufacturer's instructions. 2. Follow manufacturer's instructions to test the nebulizer function prior to the first use of a new device and after each cleaning to verify proper operation. 3. Pour the medication solution into the medication reservoir. Do not exceed the volume recommended by the manufacturer. 4. Turn on the power. 5. Hold the nebulizer in the position recommended by the manufacturer. 6. Put the mouthpiece into the mouth and close the lips around it. 7. Inhale and exhale using normal (tidal) breaths, with occasional deep breaths. 8. At the completion of the treatment, take the mouthpiece out of the mouth. 9. Clean nebulizer following manufacturer's instructions.
Soft mist inhalers
Assemble and use the device according to the manufacturer's instructions.

Table 5: Advantages and disadvantages to pMDIs, pMDIs with spacers, BA-pMDIs, nebulizers and DPIs

Type	Advantages	Disadvantages
HFA-pMDIs (Both suspension and solution pMDIs)	Portable and compact	Coordination of actuation and inhalation needed.
	Short treatment time	Most patients inhale too fast.
	No contamination risk.	Low lung deposition and high oropharyngeal deposition.
	High reproducibility between doses.	Important to prime before use if new or not used in some time.
		Must be kept upright during inhalation.
		With most devices, the number of doses remaining is difficult to determine. Only one $beta_2$-adrenergic agonist device has a dose counter (Ventolin®) and it is available only in the USA. Seretide® and Symbicort® (combination drug devices) have dose counters. Symbicort® is only available in the USA.
		Few drugs available as breath-actuated pMDIs.
HFA-pMDIs that emit extrafine particles	Same as items 1-4 for pMDIs above.	Important to prime before use if new, or not used in some time.
	Higher lung deposition and lower oropharyngeal deposition, compared to pMDIs that are used alone.	
	Good for inhaled corticosteroids. When using QVAR®, the corticosteroid dose can be half of what is prescribed for patients using traditional corticosteroid pMDI products.	Only two corticosteroid products available (Qvar® and Alvesco®). Only one combination product available (Foster®).

pMDI-Spacers	Less need for coordination of actuation and inhalation compared to a pMDI alone.	More expensive and less portable than pMDI alone.
	Reduced oropharyngeal deposition compared to pMDI alone.	Prone to reduced or inconsistent dosing because of electrostatic charge associated with plastic spacers.
	Improves lung deposition if poor with pMDI alone.	Special washing instructions.
	Useful for maintaining efficient drug delivery during acute exacerbations.	Steps in administering drug with a spacer are crucial. Mistakes can lead to reduced, or no drug, being inhaled (i.e. multiple actuations into spacer before inhalation and delay of inhalation after actuation).
	Can use tidal breathing if the spacer has a valve.	
	Some spacers make a noise to indicate that the inhalation flow is too fast.	Some children like to make the noise and if they do they will be inhaling too fast.
BA-pMDIs		
DPIs	May be useful for patients who cannot coordinate inhalation and actuation; may be useful for elderly.	Patients sometimes stop inhaling once actuation occurs.
	Should not be used with a spacer or VHC.	
		Breath-actuation does not control inspiratory flow rate, so patients need to be instructed to inhale slowly.
		Can only be used with drug that is dispensed with device; no substitutions.
	Portable and compact. Many are multi-dose.	
	Some are single-dose with doses kept separately in sealed packages.	Single-dose devices require repeat loading, which can lead to error. Two separate inhalations are required for each dose.
	Breath-actuated, so no outside energy source, or propellant, is needed. No propellant needed, thus avoids possible damaging effects to earth's ozone layer from CFCs. Also, there is no need to coordinate actuation and inhalation, which is needed with a pMDI.	DPI delivery can result in high oropharyngeal deposition because a forceful inhalation is needed to aerosolize the particles.

		Flow dependent dose emission for some designs. Poor quality (or no) dose emitted if inspiratory flow is too slow.
		Patients need to exhale into the room to functional residual capacity before inhaling from the DPI. Patients should not exhale into the device once the dose has been prepared for inhalation, or the dose could be blown out of the device.
	Most multi-dose devices have a dose counter.	Patients need to inhale forcefully from the beginning. They should not gradually increase their speed of inhalation.
	Short treatment time.	Uncertain of emitted dose during acute exacerbations.
		More expensive than pMDIs
		Must be upright when preparing the dose for inhalation. Must be kept upright or turned horizontally during inhalation.
		Need to be stored in a cool and dry place.

Nebulizers		
	May be used at any age. Vibrating mesh nebulizers are portable and do not require an outside energy source.	Pneumatic jet devices require an outside energy source and compressor.
	Patient coordination not required.	Treatment times can be long.
	May be used to dispense drugs that are not available for delivery by pMDI or DPI.	Suspensions do not nebulize well.

	No propellant needed. Breath-enhanced nebulizers, dosimetric nebulizers and vibrating mesh nebulizers are much less wasteful of drug than pneumatic jet nebulizers. Dosimetric nebulizers deliver aerosol during inhalation only, over a proscribed time period, and turn off when dosing is complete.	Performance (i.e. emitted dose and particle size) varies significantly between devices. With pneumatic jet nebulizers, drug can be lost to the surrounding environment during exhalation, exposing caregivers and other personnel to the drug. Many pneumatic jet nebulizers are wasteful since a certain volume of solution cannot be aerosolized (i.e. dead volume). There may be a risk of bacterial contamination if the device is not properly cleaned.
		Newer devices (i.e. vibrating mesh nebulizers) are expensive.

(Adapted from reference 9)

Table 6: Characteristics of commonly used spacers

Spacer **Not all devices are available in every country**	**Type**	**Valved**	**Anti-static**
Aerochamber Plus®	Small volume	Yes	No
Aerochamber Max®	Small volume	Yes	Yes
Optichamber® (Breathatec® in Australia)	Small volume	Yes	No
Vortex®	Small Volume	Yes	Yes
Volumatic®	Large volume	Yes	No
Babyhaler®	Large Volume	Yes	No
Ace®	Large Volume/reverse flow	Yes	No
Optihaler®	Large volume/reverse flow	No	No
InspirEase®	Opaque reservoir/reverse flow	No	No
Microspacer®	Extension device	No	No
Synchro-Breathe®	Extension device	No	No

FIGURE LEGENDS

Figure 1: The International Commission on Radiological Protection model showing the relationship between aerodynamic diameter and lung deposition (Adapted from reference 14).

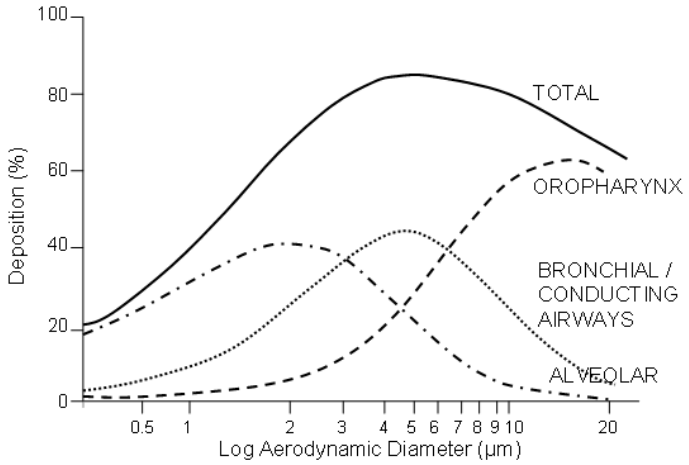
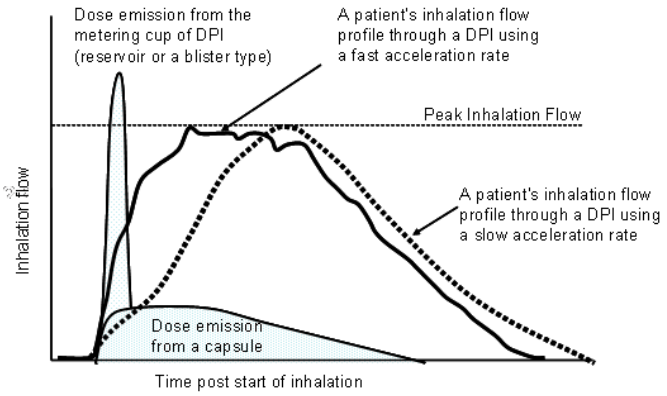


Figure 2: The relationship between dose emission from a DPI and the patient's inhalation (Adapted from reference 63).



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