Eur Respir J 2001; 18: 228–242
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

ERS TASK FORCE

European Respiratory Society Guidelines on the use of nebulizers

Guidelines prepared by a European Respiratory Society Task Force on the use of nebulizers

Co-Chairmen of the Task Force: J. Boe*, J.H. Dennis# and B.R. O'Driscoll¶

Members of Task Force: T.T. Bauer+, M. Carone§, B. Dautzenbergƒ, P. Diot**, K. Heslop##, L. Lannefors¶¶

The European Respiratory Society (ERS) recognizes that there are an increasing number of national and international guidelines for the management of asthma, chronic obstructive pulmonary disease (COPD) and other chest diseases. Some of these guidelines recommend nebulizer use in specific circumstances, using either a jet nebulizer or an ultrasonic nebulizer to administer a drug to the airways or lungs in the form of an aerosolized mist of fine droplets. Although many patients with severe chest disease are given nebulized treatment both in hospitals and in their own homes, it is recognized that much of this practice may not be evidence-based. Some present practice may be ineffective or even harmful. The manufacturers of hand-held inhalers are obliged to meet exacting standards such as dose-to-dose reproducibility. However, nebulizer devices are sold separately from nebulized drugs and the dose delivered to the lung can be increased 10-fold or more by changing from an inefficient nebulizer system to a highly efficient one. For these reasons, the ERS commissioned a Task Force to review the scientific and clinical principles of nebulized therapy and to produce a set of guidelines (evidence-based whenever possible) for users of nebulized treatment in Europe.

Aims of the European Respiratory Society Nebulizer Guidelines and target audience

It is hoped that the guidelines will improve clinical practice in the use of nebulized therapy throughout Europe. The most important considerations should be efficacy and patient safety. The guidelines will also serve as an educational and scientific resource for clinicians and scientists with an interest in inhaled therapy. These guidelines are aimed at a wide group of healthcare professionals practising in very different healthcare systems throughout Europe. The immediate target audience for the guidelines will be pulmonary physicians, but it is hoped that the messages will be communicated to all healthcare workers who are involved in treating patients with nebulized medication (doctors, nurses, pharmacists, paramedics, physiotherapists *etc.*). The ERS Guidelines will provide recommendations based on scientific and clinical evidence, as described in the next section, and they will provide practical advice for the majority of nebulizer users. The guidelines will also identify areas of ignorance where present practise is based on tradition or opinion rather than scientific evidence. It is also hoped that by identifying these gaps in present knowledge, the guidelines will spur on clinical scientists to undertake new trials to guide future practice.

The aims are summarized as: 1) to improve clinical practice; 2) to enhance the safety and efficacy of nebulizer use; 3) to serve as an educational and scientific resource for healthcare professionals; and 4) to stimulate future research by identifying areas of ignorance and uncertainty.

Format and development of European Respiratory Society Nebulizer Guidelines

The ERS commissioned a Task Force to oversee the production of these guidelines. The membership of the Task Force is indicated above. The methodology of producing the guidelines is described in a series of detailed papers in the *European Respiratory Review* [1, 2]. These papers will serve as the scientific and clinical background for the ERS Nebulizer Guidelines. They also describe the levels of evidence on which the guidelines are based.

Evidence and recommendations have been graded in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) and the Agency for Health Care Policy and Research (AHCPR) scoring system

*Rikshospitalet, Oslo, Norway. #University of Bradford, Bradford, UK. ¶Hope Hospital, Salford, Manchester, UK. +Bergmannsheil-Universitatsklinik, Bochum, Germany. §Salvatore Maugeri Foundation, Veruno, Italy. ƒHopital de la Salpetriere, Paris, France. **CHU Bretonneau, Tours, France. ##Royal Victoria Infirmary, Newcastle Upon Tyne, UK. ¶¶Lund University Hospital, Lund, Sweden.

Correspondence: J. Boe, Dept of Thoracic Medicine, Rikshospitalet, University of Oslo, Norway. Fax: 47 223073917

[3, 4]. The background papers in the *European Respiratory Review* have reviewed each topic in detail and the evidence for each statement or recommendation is graded from I-IV as described in the AHCPR publications. The Task Force has used this evidence and the AHCPR scoring system to grade the recommendations contained in these guidelines as follows. 1) Grade A requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency, addressing the specific recommendation (AHCPR levels Ia and Ib). 2) Grade B requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (levels IIa, IIb and III). 3) Grade C requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities (including opinions of the ERS Nebulizer Task Force). It indicates absence of directly applicable studies of good quality (level IV).

Problems with the scientific background of clinical nebulizer use

Shortage of clinical trials

Trials of nebulized treatment may be especially difficult to initiate because of funding difficulties. Most nebulizer trials involve existing licensed medicines (frequently off patent) and existing devices so they are unlikely to attract funding from the pharmaceutical industry or from large medical charities. Furthermore, large-scale randomized clinical trials of long-term nebulized therapy are extremely costly. This may explain why so many nebulizer trials involve single doses or short treatment periods. It is hoped that the guidelines will stimulate research (and funding for research) into this important area.

Quality of reporting of published trials which involved nebulizer use

The Task Force had difficulty in finding good quality randomized clinical trial evidence to support large areas of present clinical practice. Furthermore, in many cases, authors of published papers have provided little detail about the nebulizer systems which were used in their studies. Important details such as the nebulizer fill volume, nebulization time or the flow rate of the driving gas were frequently omitted. This makes it difficult to reproduce clinical trials or to extrapolate clinical practice from one study to another. One aim of the present guidelines is to alert clinical scientists and journal editors to this issue.

It is recommended that journal editors and reviewers of research protocols should encourage authors to use a single standardized nebulizer system within each research study, and the authors should be obliged to describe this "nebulizer protocol" or "standardized operating procedure" fully in any publication. In some international studies, it may be necessary to use different nebulizer systems in each country but this should be stated clearly in the paper.

It is recommended that the minimum information required to describe a nebulized treatment in a scientific publication should be: drug preparation and dispensed dose; nebulizer device (including details of accessories such as mouthpiece or mask); Comité European de Normalisation (CEN) specification for the device (if available); driving gas source or compressor type and flow rate; fill volume; nebulization time or other end-point (*e.g.* nebulization to dryness); special characteristics of the system or its use, *e.g.* continuously nebulizing, venturi effect only during inspiration, manually operated, breath activated, *etc.*; patients instructed in proper use of nebulizer device.

Responsibilities of manufacturers

In most countries, the purchase of medical equipment such as nebulizers is not regulated as tightly as the purchase of pharmaceuticals and patients may purchase nebulizer equipment without medical advice. Furthermore, many nebulizer chambers are presently sold with little or no printed information regarding their use. It is hoped that the new European Standard will resolve this problem.

It is recommended that all nebulizer chambers or nebulizer systems should be sold with full instructions regarding their use, maintenance and cleaning.

Responsibilities of prescribers

It is recognized that many different types of doctor may initiate nebulized therapy or be asked by a patient to supply medication for use in a nebulizer system which has been purchased by the patient or by a patient's relative without medical advice.

It is recommended that the person who prescribes a nebulized medication should accept responsibility for ensuring that the use of nebulized drugs is appropriate and that the patient is given appropriate advice.

This may, in many cases, include referral to the local nebulizer assessment service or advice to undertake a formal assessment of nebulized therapy as described in these guidelines.

Technical aspects of nebulizer use

What is a nebulizer?

Within these guidelines, a nebulizer is a device that can convert a liquid into aerosol droplets suitable for patient inhalation. To avoid confusion between nebulizers and an expanding range of hand-held metered-dose inhalers, these guidelines will discuss only nebulizer devices in which the end-user must load the medication into the device prior to each treatment. Air-jet nebulizers are the most widely used, although ultrasonic nebulizers are becoming more common. Because air-jet nebulizers are more commonly used throughout Europe, they will form the basis of the technical aspects of nebulizer operation, although it should not be forgotten that new nebulizer designs are becoming available and ultrasonic nebulizers may become increasingly popular for home use.

What is a nebulizer system?

These guidelines recognize the influence of all components attached to the nebulizer which affect performance, including not just characteristics of the nebulizer itself, but also: flow/pressure characteristics of the compressed air (or other power source), connection tubing, patient interface including mouthpiece or face mask, *etc.* If one component of the "nebulizer system" is changed, the performance and overall efficiency of the drug delivery also changes and it is then necessary to redefine the nebulizer system.

Drug solutions versus *suspensions*

Most nebulized drugs fall into two physicochemical categories. Drug solutions contain a drug that is dissolved in saline or occasionally in other liquids (cyclosporine, for example, is dissolved in alcohol). Drug suspensions contain a drug that is not soluble in water or other respirable liquids, they exist as a mixture of small drug particles suspended in liquid. Drug suspensions are inherently more complicated to describe as they are a mass of suspended particles which may or may not be present within the droplets which is clinically important, whereas with solutions, it is assumed that all the drug is homogeneously dispersed throughout all droplets. For example, conventional ultrasonic nebulizers cannot be used to administer suspensions such as nebulized budesonide.

Respiratory tract deposition of nebulized drugs

The three main factors which determine where in the respiratory tract a nebulized drug droplet will deposit are: droplet size, pattern of breath inhalation and age/condition of the lung. Amongst these, the easiest to control is the size of the droplets. On entering the lung, nebulized droplets may deposit by three main mechanisms. Larger droplets can deposit by impaction on airway bifurcations, while smaller aerosols deposit more by sedimentation and diffusion in the smaller airways and alveoli. Figure 1 presents the general relationship between droplet size and deposition in the respiratory tract for tidal-breath inhalation within a healthy adult lung. It is clear from this figure that there is no single area in the respiratory tract where a droplet of a given size (*e.g.* 1 μm) will definitely deposit, although the figure does demonstrate that it is more likely that a 1 μm droplet will deposit in the peripheral lung than in the upper respiratory tract.

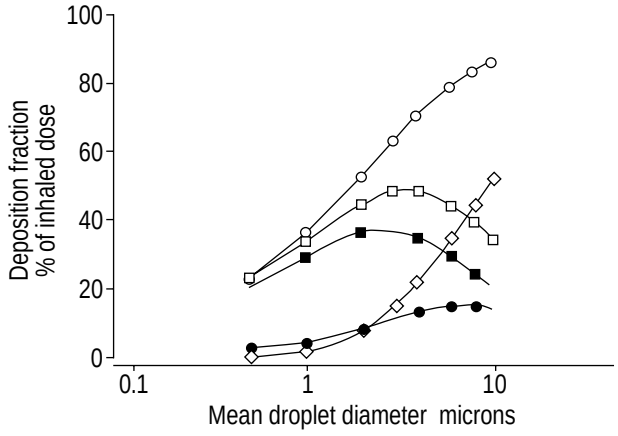

Fig. 1. – Relationship between aerosol aerodynamic diameter and deposition in the healthy adult lung (based on *in vitro* models). ○: total body; □: total lung; ◇: oropharyngeal; ●: central airways; ■: peripheral airways. Reproduced with permission [5].

Nebulizers, like hand-held inhalers, do not emit droplets of only one size (*i.e.* monodisperse). Rather, droplet size present a distribution usually encompassing a 10-fold range from which various descriptors may be derived. Perhaps the most simple, widespread and useful single measure of droplet size is the mass median aerodynamic diameter (MMAD) which is independent of the distribution (lognormal or skewed). Half of the "mass" of nebulized aerosol is contained in droplets which are larger than the MMAD and half smaller. Comparing a nebulizer's MMAD to the deposition curves in figure 1 will generally indicate where in the respiratory tract the droplets will deposit. It may also be valuable to measure the standard deviation (geometric) of the MMAD because this is a useful measure of the spread of droplet size within the distribution. The speed of inhalation is also an important factor in determining where a droplet of a specific size impacts, the faster the inhalation speed, the more likely the droplet is to impact in the upper airways. The age of the patient as well as the condition of the respiratory tract further influence the site of deposition. Despite these complications, the measure of aerosol size, often expressed as MMAD, is the single most useful parameter in predicting the site of deposition.

To complicate the area further, there exist many different methods of measuring nebulized aerosol size and each produces different results which makes it difficult for both the lay person and expert to interpret them. To simplify interpretation of nebulized droplet size, these guidelines have adopted the measure of aerosol size defined by a European Standard (prEN13544-1) and recommend that this methodology be used as the primary means of establishing nebulized droplet size. This will facilitate a more meaningful comparison of droplet size data between different nebulizer systems. Figure 2 presents a schematic of how droplet size is measured using the European Standard. Table 1 provides a summary of the nebulized aerosol droplet size that may be best suited for common clinical applications.

Ten-fold differences in nebulizer system performance!

The inherent differences in delivered aerosol between nebulizer systems currently available throughout Europe are significant. These differences can be ⩾10-fold. Important factors influencing the total dose delivered to a patient's airways include the initial volume fill, the efficiency by which nebulized aerosol is made available for patient inhalation, and

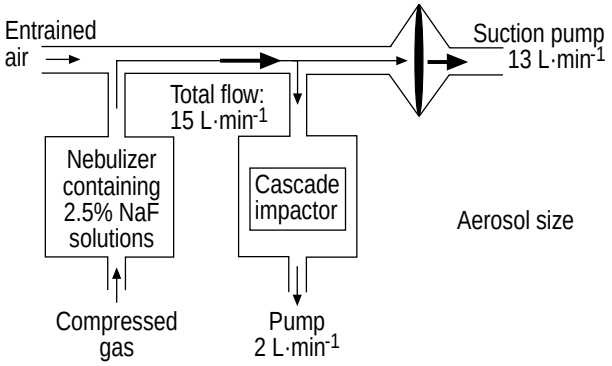

Fig. 2. – Schematic of Comité European de Normalisation methodology to measure nebulized aerosol droplet size. A constant inhalation of 15 L·min^{-1} is drawn over (or through) the nebulizer. Nebulized aerosol containing a NaF solute tracer mixes with the entrained air. A low flow cascade impactor (Marple Series 296/8X) samples aerosol at 2 L·min^{-1} from this flow, and impacted aerosol can be subsequently desorbed and analysed from each size fraction from which the droplet size distribution can be determined (not to scale).

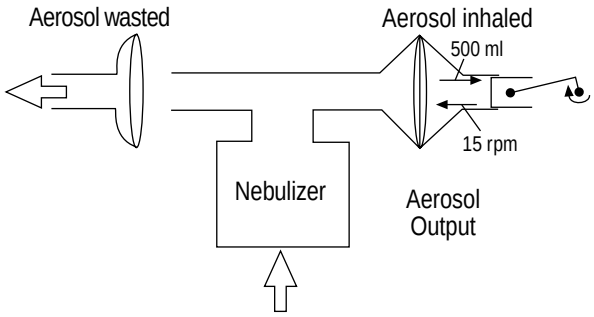

Fig. 3. – Schematic of Comité European de Normalisation methodology to measure nebulized aerosol output. "Inhaled" aerosol output is subject to sinus flow breath simulation and aerosol is collected onto low resistance electrostatic filters. Aerosol contains trace concentrations of sodium fluoride which can be subsequently desorbed and quantified electrochemically (not to scale). rpm: revolutions per minute.

the amount of residual or "dead" volume left in the nebulizer on cessation of operation. Aerosol dose is a vague concept in nebulized drug therapy. It is not common practice to prescribe a "dose delivered to lung", but prescribers usually specify the amount of drug to be dispensed in a particular volume of nebulizer solution. Prescriptions do not usually specify the nebulizer system. The choice of nebulizer varies and is often selected by a person other than the prescriber (*e.g.* hospital supplies dept). Nebulization therapy usually continues until the volume left in the nebulizer is so low that the nebulizer ceases to function continuously and begins to "sputter". This volume is typically ~1 mL, but may be as low as 0.5 mL or as high as 1.5 mL. The amount left is very high compared to a typical volume fill (*e.g.* 2.5 mL). Thus, treatment time becomes critically dependent not only on the rate of aerosol output and volume fill, but also on the minimum volume a nebulizer system requires to operate. Lung delivery of nebulized drugs will also be increased greatly when breath-activated nebulizers are used (at present, half of the nebulizer output is wasted during expiration).

As with droplet size, these guidelines recommend that methods embodied in the European Standard are used to determine the: 1) rate of aerosol output; 2) total emitted aerosol dose from a particular nebulizer system; and 3) minimum volume required for effective nebulization. The latter is particularly important as it is mainly this that defines "treatment time" and nebulizer efficiency defined by the proportion of initial volume fill that is eventually delivered to the patient. Figure 3 illustrates how such measurements are performed using European Standard methods incorporating a simulated breathing pattern.

Type testing using the European Standard

In the near future, nebulizer manufacturers will be required to test each of their nebulizer systems with a

Table 1. – Site of action of commonly nebulized drug aerosol therapies and the droplet size thought ideal for maximum clinical benefit

Drug	Target airway site	Special considerations
β_2-agonists acute Adults and children	Central-peripheral	Use O_2 as driving gas unless there are concerns about CO_2 retention
β_2-agonists chronic Adults and children	Central-peripheral	Reduce nebulization time for treatment compliance
Anti-cholinergic Adults and children	Central	Mouthpiece (preferable) or tight sealing face mask (Mouthpiece for glaucoma patients)
Corticosteroid Children and adults	Central-peripheral	Minimize skin and eye exposure Mouthpiece (preferably) (or tightly sealed face mask)
Amino-glycosides or Colomycin Adults	Central-peripheral	Mouthpiece Filter or exhaust exhaled gases Pretreat with β-agonist when necessary
Pentamidine Adults	Peripheral	Mouthpiece Pretreat with nebulized β-agonist Filter or exhaust exhaled gases
Amphotericin Adults	Central	Dilute with water not saline Filter or exhaust exhaled gases
rhDNase	Central	Mouthpiece

O_2: oxygen; CO_2: carbon dioxide; rhDNase: recombinant human deoxyribonuclease.

reference solution according to the European Standard (prEN13544-1). This will result in standardized information being supplied with every nebulizer. This information will include the following. 1) Description of the nebulizer system which includes the flow rates and volume fills at which tests were made. 2) Rate of aerosol output and total aerosol output. 3) The droplet size distribution curve from which the median size (MMAD) and spread (goblet size deposition (GSD)), and per cent aerosol mass within any given range can be obtained (*i.e.* >5 μm, 2–5 μm, ⩽2 μm).

The methods on which the European Standard is based are designed to reflect clinical conditions as closely as possible. The consistency of methods to obtain this *in vitro* information through the European Standard will essentially provide a type test of each nebulizer system. This will allow for a meaningful comparison of relative performances of different nebulizer systems, and this in turn can be used to guide the optimal use of nebulizers in clinical practice.

There are some important limitations in interpreting test data supplied by manufacturers complying with the European Standard. The first is that data supplied by manufacturers relate only to drug solutions that have properties similar to saline. Test data cannot be readily extended to suspensions (*e.g.* budesonide) or to solutions that have a significantly greater viscosity than saline (*e.g.* some antibiotics). The second is that the rates and amounts of aerosol delivery have been obtained using a simulated adult healthy breathing pattern and these cannot be readily transferred to paediatric applications or to diseased adults. The test methods adopted within the European Standard are sufficiently flexible to accommodate additional test configurations.

It is recommended that where applicable, suppliers should be asked for additional data on specific drug solutions and suspensions, and alternative breathing patterns.

Characteristics of good and bad nebulizer systems

Nebulizer systems offer a great range of performance and how good or bad an individual system is depends on what it is intended to do. For example, if a system was required to deliver the maximum amount of "useful" aerosol (droplets 0.5–5 μm) in the minimum amount of time, with a minimum of inconvenience, then the characteristics of a "good" system would include the following. 1) Fast rate of nebulization, implying that the maximum amount of nebulized aerosol is potentially available to the patient over any given time. 2) Minimum waste of drug aerosol, implying that the maximum amount of aerosol released is delivered to the patient and not emitted into the environment. 3) Low residual volume, implying that more of the volume fill will be delivered to the patient as aerosol. 4) Well-defined droplet size distribution. If, however, the same system was required to deliver only a modest volume of drug aerosol, then the system described earlier becomes "bad" because such an efficient system of delivery will deliver an unnecessarily large aerosol dose with possible increased local and systemic side-effects.

These guidelines recognize that consideration must be given to matching nebulized drug delivery to the performance of nebulizer systems. This requirement will vary according to the needs of different patient groups or stages of the disease. The two main factors to take into account are: 1) how much nebulized drug is ideally required for delivery to the patient; and 2) the aerosol size required to deliver nebulized droplets to the site of action. Small aerosols (<5 μm) will deposit peripherally, whereas droplets ~5 μm will mainly deposit in airways that are more central.

The guidelines recognize that little clinical evidence exists to answer these questions and it is therefore difficult to choose the ideal nebulizer system for a given application. This being the case, these guidelines recommend that a scheme is developed to define the best available nebulizer system for various therapies, in order to reduce variability in nebulized dose delivery and thereby improve clinical practice.

Choice of nebulizer system

For bronchodilator drugs, any nebulizer system that complies with the CEN standards could be used in accordance with the manufacturers instructions. However, end-users and purchasers should avoid using inefficient systems that may waste most of the drug dose. It is suggested that a system with a good CEN performance (output and droplet size) should be chosen. Such a system would require lower doses of medication, or shorter treatment times, that may be more convenient for patients and also yield savings in overall treatment costs.

Although a face mask may theoretically deliver less medication to the lungs, two clinical studies have shown equivalence between face masks and mouthpieces for bronchodilator effects, possibly due to the tendency of breathless patients to mouth-breathe (Grade B). A face mask should ideally be avoided if a nebulized steroid is administered (to avoid steroid administration to the facial skin and eyes) (Grade C). It should also be avoided or sealed very tightly if anticholinergic agents are to be administered to patients with glaucoma (Grade C).

How to select the optimal system for a given patient or usage

All healthcare systems throughout Europe currently have some system by which nebulized drugs are prescribed for each clinical application. In addition, all prescribers and users of nebulized therapy will commonly have experience using one (or more) nebulizer system for each clinical application. Local practices may differ greatly, possibly within institutions. It is recommended that a standard operating practice (SOP) be adopted for each nebulizer system in use (Grade C). This will provide a baseline in determining the clinical effectiveness of that nebulizer system for each given application. This can then be

Table 2. – Parameters to be standardized in the use of nebulizer systems

Nebulizer type
Choice of driving gas
Driving gas pressure
Driving gas flow rate
Drug and formulation
Nebulizer fill volume (as recommended by manufacturer)
Time of nebulization
Accessories (Mouthpiece/face mask *etc.*)
Residual solute volume (amount of drug left in chamber)

used to assess potential improvements to the nebulizer system, as outlined in the three steps discussed later.

Implementation and use of standard operating practices as a means of improving the efficacy of nebulized drug therapy

Step 0: standardize the way current nebulizer systems are used. If health practitioners can agree an SOP for the way in which nebulizer systems are used locally, they can be sure that future clinical outcomes are patient specific, rather than due to a significant change in drug output from the nebulizer. Parameters to consider are listed in table 2. Nebulizer manufacturers can provide advice on the optimum operating parameters for a particular nebulizer.

Step 1: assess drug output from the current nebulizer system. The scarcity of useful *in vitro* data describing nebulizer system performance has perhaps contributed to an arbitrary choice of nebulizer system. However, the standardization of nebulizer aerosol output and size made possible through the European Standard allows any given SOP to be re-assessed. For a specific clinical application, the SOP can be used in conjunction with data from the manufacturer to allow the dose delivered using this SOP to be derived. This dose can be the total output or can be modified by the fraction of the aerosol in the optimal size range (table 1), to give a "useful" dose. If appropriate, the potential systemic exposure arising from drug not in the "useful" range, either: 1) by being too large, being swallowed and subsequently orally available; or 2) by depositing in an inappropriate region of the lung, and being directly absorbed into the systemic circulation with minimal local efficacy should also be considered. Based on this approach, potential modifications to the existing SOP can be assessed to see whether drug delivery can be further optimized by a change in one of the operating parameters, *e.g.* gas-flow rate.

Step 2: evaluate alternative nebulizer systems. This information can be re-evaluated over time, as more efficient or cheaper nebulizers emerge. Consideration can then be given to altering prescription convention and/or adopting alternative nebulizer systems whose nominal delivered dose and droplet size (available from the manufacturer using the same standard *in vitro* data) may be better suited to that given clinical application. However, as in step 1, any changes to SOP should be supported by appropriate follow-up of outcomes such as clinical benefits or side-effects.

It is recommended that the effect of significant changes to nebulizer usage be monitored by the appropriate follow-up of clinical outcomes (Grade C).

Future developments in nebulized drug delivery

The Task Force drafting these guidelines anticipates that technical advances in microtechnology and other areas will drive improvements in nebulizer design. At the very least, these improvements will offer a significant increase in efficiency in nebulized drug delivery. While these systems offer the potential to improve the quality of nebulized drug therapy, there are risks if they are adopted with insufficient consideration of the consequences of improvements in efficiency. However, if local practices adopted the recommendations of instituting and reviewing SOPs, new and improved nebulized therapies could be safely integrated with net benefits to patients requiring nebulized drug therapy. It is likely that newer, more efficient systems will deliver inhaled drugs more effectively and thus reduce the wastage and cost associated with inefficient systems.

Clinical uses of nebulizers

Nebulized treatment may be considered for three main reasons. 1) Where a patient is perceived to require very high doses of inhaled bronchodilator medication. 2) If a patient needs an inhaled drug such as recombinant human deoxyribonuclease (rhDNase) or an antibiotic which cannot be given by any other means. 3) It is sometimes considered for patients who are unable to use other devices or in situations such as acute severe asthma where patient cooperation with other devices may be problematic.

It is clear from the technical discussion that nebulized drugs can be divided into water-soluble drugs which behave like saline (*e.g.* bronchodilators) and drugs with individual physicochemical properties which may require unique nebulizer equipment (*e.g.* rhDNase). Therefore, the ERS Guidelines will discuss these applications (bronchodilator and nonbronchodilator) separately. The commonest application of nebulized therapy is to deliver bronchodilator drugs to patients with asthma or COPD.

Use of nebulized bronchodilator drugs in acute exacerbations of adult asthma and chronic obstructive pulmonary disease

Readers are referred to national and international guidelines for the overall management of patients with acute exacerbations of asthma and COPD. These guidelines will discuss only those aspects of care which are directly related to nebulizer use. There is strong evidence that for both adults and children with acute asthma, and for adults with COPD, equivalent bronchodilator effects can be obtained using multiple

doses from hand-held inhalers as can be obtained with presently available nebulized delivery systems (these studies have usually involved the use of large volume spacers by patients who have achieved a satisfactory inhaler technique with the spacer device). However, nebulizers continue to be used in most European hospitals because they may be regarded as more convenient for healthcare staff to administer and because less patient education or cooperation is required. This usage does not imply that nebulized therapy is superior and this should be made clear to patients and their relatives.

Hand-held inhalers (when used with spacer devices and a good inhaler technique) and nebulizers are equally effective in achieving bronchodilation in acute asthma or COPD exacerbations (Grade A). Nebulizers are widely used for the convenience of hospital staff and to overcome problems with inhaler techniques, especially with very breathless patients (Grade C).

Delivery system in acute asthma or chronic obstructive pulmonary disease. Where their use is indicated, nebulizer systems should be chosen and configured as described in the technical section of these guidelines. In hospital settings for asthma patients, the driving gas should be oxygen (O_2) (for acutely ill patients) or air (for stable patients). COPD patients should ideally receive monitored oxygen therapy while using an air-driven nebulizer system (to avoid increasing carbon dioxide (CO_2) retention), however, shorter nebulization periods (<10 min) may make this less of an issue with future nebulizer systems. Theoretically a mouthpiece may be better as it avoids nasal deposition of drugs, although no advantage has been found in two small clinical studies in stable asthma and COPD. Patients may prefer a face mask, especially when acutely breathless, a situation where patients are likely to mouth-breathe and thus diminish the theoretical disadvantages of the face mask. A mouthpiece may avoid the risk of ocular complication with anticholinergic agents.

A nebulizer system which is known to be efficient should be used (use CEN data). Face masks or mouthpieces are probably equally effective (Grade B) but breathless patients may prefer face masks (Grade B).

Selection and dosage of nebulized bronchodilator drugs. Acute asthma. Adult patients should be given a β-agonist equivalent to 2.5–5 mg of salbutamol or 5–10 mg of terbutaline (Grade B). There is evidence that additional benefit can be obtained by adding anticholinergic treatment such as 500 μg ipratropium bromide (Grade A).

Acute exacerbations of chronic obstructive pulmonary disease. COPD patients who require nebulized therapy should be given a β-agonist equivalent to 2.5–5 mg of salbutamol or 5–10 mg of terbutaline (Grade B).

In contrast to stable COPD and acute asthma, no additional benefit has been demonstrated when anticholinergic therapy has been added to β-agonist therapy for acute exacerbations of COPD (Grade A).

Frequency and duration of nebulized treatment in acute adult asthma and exacerbations of chronic obstructive pulmonary disease. Treatment may be repeated within a few minutes if the patient has a suboptimal response to the first dose of nebulized treatment or continuous nebulized therapy may be administered until the patient is stable (Grade B).

A lack of response to repeated nebulized therapy indicates the need for review by senior clinicians and the possible need for additional treatment such as noninvasive ventilation or intensive care therapy (Grade C). In cases with a good response, the treatment should be repeated at 4–6-h intervals until recovery occurs (Grade C).

Patients should be changed to hand-held inhalers as soon as their condition has stabilized because this may permit earlier discharge from hospital (Grade B).

Use of nebulized bronchodilator drugs in chronic severe asthma and chronic obstructive pulmonary disease

The ideal prescription for inhaled therapy would use the simplest and most convenient device to deliver the lowest effective dose for each patient. For most patients using bronchodilator drugs, this will mean hand-held metered-dose inhalers (MDI) with or without a spacer or an alternative hand-held device such as a breath-activated inhaler or a dry powder inhaler. However, some patients benefit from higher doses of bronchodilator drugs which may be given more conveniently from a nebulizer. There is no clearly identified threshold dose where nebulized bronchodilator therapy becomes more effective or more convenient than hand-held inhalers. This "crossover point" is individual to each patient and will vary depending on which nebulizer system and inhaler are compared. The CEN data described will provide guidance in comparing the efficacy of different systems but the exact relationship between *in vitro* performance and *in vivo* clinical effect has not yet been well studied for most nebulizer systems.

It is recommended that hand-held inhalers should be used in increasing doses up to 1 mg salbutamol or equivalent. Doses >1 mg of salbutamol (2.5 mg of terbutaline) or 160 μg of ipratropium bromide or combinations of such therapy may be given more conveniently by using an efficient nebulizer system (see technical section). The exact cut-off point will depend on these technical factors and on patient related factors such as breathing patterns or different side-effect profiles. The availability and price of different hand-held inhalers in different countries may also influence the choice of device. Finally, for patients who require combined β-agonist and anticholinergic therapy, a combined nebulized solution (or combination MDI device) may be more convenient than multiple actuations from two separate hand-held inhalers. Clinical experience suggests that doses which require >10 puffs from hand-held inhaler systems tend to be unpopular with patients.

Most indications for bronchodilator therapy are best managed by the use of a hand-held inhaler device

(including a spacer device if appropriate) (Grade A). Doses of salbutamol >1 mg or ipratropium bromide >160–240 μg may be given more conveniently using a jet nebulizer device (Grade C). High-dose therapy should only be considered for patients with severe airflow obstruction as defined in asthma and COPD Guidelines (Grade C). Nebulized therapy may also be required for some adult patients who, after assessment, cannot use a hand-held inhaler device, even with appropriate spacer attachments (Grade C). If nebulized therapy is thought to be inappropriate for individual patients with asthma or COPD, it is recommended that the patient should be referred for "inhaled therapy optimization" as described below (Grade C).

Inhaled therapy optimization protocol for patients with chronic obstructive pulmonary disease or severe asthma. It is recommended that patients should be referred for "inhaled therapy optimization" rather than a "trial of home nebulizer". The latter terminology implies that the "trial" will have an outcome which will be judged as a "success" or "failure". Experience has shown that patients who have completed a protocol similar to that described in this section of the guidelines have almost always finished the protocol by using inhaled treatments or devices that were different to their previous treatments. About 50% of such patients have expressed a preference for nebulized therapy and 50% expressed a preference for a hand-held inhaler, usually at a higher dose than they had previously taken. Whatever the outcome of this process, most such patients have reported improved symptom control on their chosen therapy following the optimization protocol.

For most patients with severe symptomatic COPD or chronic asthma, the outcome of such a protocol may be judged as "successful" whether or not nebulized therapy is chosen (Grade B).

Step 1. Check diagnosis and confirm severity (exclude other treatable conditions such as heart failure). Assess patient's baseline level of symptoms and lung function and ensure that the patient can use their existing inhaler device effectively.

It is proposed that each of the assessments listed later should take place over 2 weeks. Shorter periods may be inadequate to assess response and longer periods would probably reduce patient compliance (Grade C).

At each stage of the process, the patient's subjective and objective response should be recorded using the scoring system given in Appendix 1 (or a similar locally devised scoring system for symptoms and lung function) (Grade C).

Step 2. Ensure that patients have tried other appropriate therapy (*e.g.* trial of steroid or theophylline or long acting β-agonist and, for COPD patients, consideration of long-term oxygen therapy, pulmonary rehabilitation *etc.* if appropriate). A number of patients may benefit from nebulized therapy in addition to the above strategies.

Nebulizer therapy has not been shown to prolong life but long-term oxygen therapy will prolong life for eligible hypoxic COPD patients (Grade A). Quality of life studies have shown little benefit with nebulized treatment but worthwhile benefits were obtained when patients with advanced COPD were entered into pulmonary rehabilitation programmes. Pulmonary rehabilitation should, therefore, be considered instead of or in addition to nebulized therapy for patients with advanced COPD (Grade A).

Step 3. Optimize existing asthma or COPD therapy using a hand-held inhaler which the patient is able to use (*e.g.* salbutamol 200–400 μg *q.i.d.* (terbutaline 500–1,000 μg *q.i.d.*) or equivalent or ipratropium bromide 40–80 μg *q.i.d.* or a combination of these agents).

Step 4. If these measures are not beneficial, try increasing further the dose of inhaled therapy *via* hand-held inhaler. (*e.g.* up to 1,000 μg salbutamol *q.i.d.* and/or up to 160–240 μg ipratropium bromide *q.i.d.*).

Patients may find it inconvenient to take a total of >10 sequential inhalations from ⩾1 hand-held inhalers devices (Grade C).

Step 5. If the patient responds poorly to the measures described earlier, consider a period of home nebulizer therapy with careful evaluation of the patient's response (ideally using loaned equipment).

Laboratory tests cannot predict who will benefit from nebulized therapy or which medication or dosage will be optimal for each patient (Grade A). Home assessment protocols such as those described in Appendix 3 are more valuable than laboratory-based studies (Grade B).

Step 6. Assess the patient's response to 2 weeks of therapy with nebulized β-agonist (salbutamol 2.5 mg *q.i.d.* or terbutaline 5 mg *q.i.d.* or equivalent).

Assess response as shown in Appendix 2 (Grade C).

Step 7. If the response to monotherapy is poor, consider one or more of the following: nebulized salbutamol 5 mg *q.i.d.* (terbutaline 10 mg *q.i.d.*) (Grade B); nebulized ipratropium bromide 250–500 μg *q.i.d.* (Grade B); mixture of salbutamol (2.5 or 5 mg) or terbutaline (5–10 mg) with ipratropium 500 μg *q.i.d.* (Grade B).

Step 8. Decide with the patient which of these therapeutic interventions was most beneficial, use the evaluation system given in Appendix 2. The programme may be terminated at any step if the patient reports a good response at that treatment step.

Assessment of response to nebulized therapy or altered hand-held inhaler therapy. There is no universally agreed system to assess each patient's response to inhaled bronchodilator treatment. It is suggested that the patient should keep a record of peak expiratory flow rate (PEFR) and symptoms twice daily but it is not known which symptom score (or quality of life

score) should be used. It may also be helpful to measure spirometry at each visit (at completion of 2 weeks therapy with each type of treatment). However, these single measurements may be difficult to interpret. Exercise tests and placebo-controlled evaluations have also been suggested but improvements in exercise tests tend to be small or nonreproducible and these assessments can prove difficult in clinical practice outside of clinical trials. Future trials will evaluate more subtle and patient-centred quality of life issues.

Deciding on outcome of nebulizer assessment/optimization of inhaled therapy. There is little agreement about what constitutes a "positive" response to inhaled bronchodilator treatment. Approximately 20–30% of patients report definite subjective benefit associated with clear-cut objective benefit during periods of home nebulizer therapy. These patients are likely to benefit from long-term nebulizer therapy. Approximately 30% of patients report varying degrees of subjective benefit but little objective benefit during periods of home nebulizer therapy. Planning long-term therapy for these patients remains a difficult clinical problem. The choice of therapy is usually negotiated between the patient and their doctor on the basis of magnitude of symptomatic benefit and whether side-effects are acceptable. A longer period of assessment may be appropriate in these circumstances. Other patients (~35–50% of those assessed) report a preference for hand-held inhalers either because of lack of benefit from nebulized therapy or because of increased side-effects. These patients should not be commenced on home nebulizer treatment.

It is recommended that the protocol described in Appendix 1 and 2 should be used to assess a patient's response to each new inhaled therapy (Grade C).

Choice of device for home nebulizer therapy. For bronchodilator drugs, any efficient nebulizer system which meets CEN standards could be used in accordance with the manufacturers instructions.

Patients should be allowed to choose whether they prefer a face mask or a mouthpiece to administer their nebulized treatment, unless their therapy specifically requires a mouthpiece (*e.g.* nebulized pentamidine) (Grade C).

Occasional use of nebulized therapy for severe attacks. Many patients request a nebulizer for occasional use during sudden exacerbations. The Task Force felt that most such patients should be treated with high doses from hand-held inhalers or spacer devices but there are some situations (*e.g.* panicking patient) where a nebulizer may be easier to use than a hand-held inhaler. The theoretical risks (*e.g.* failing to take corticosteroids or failing to call for medical help) and the theoretical benefits (*e.g.* improved patient confidence or reduced hospital admissions) have not been confirmed in randomized clinical studies. The consensus view of the Task Force was that there was no good evidence of benefit or harm but some patients felt safer with this "back-up therapy" and even a small reduction in hospital admissions would make such therapy cost-effective. However, there is strong published evidence that patient education involving self-management and the issuing of written action plans can reduce morbidity and the use of health-service resources by asthmatic patients. For this reason, the Task Force felt that the self-management of acute exacerbations should be guided by an agreed self-management plan.

"Emergency nebulizers" should only be used in accordance with a self-management plan agreed with an appropriate specialist (Grade C).

Use of nebulizers by ambulance staff and paramedics. The Task Force felt that it was appropriate for ambulance staff and paramedics to institute bronchodilator treatment as early as possible in acute asthma, using nebulized bronchodilator therapy driven by O_2. For short urban ambulance journeys, COPD patients could be treated in a similar manner, but for journeys >15 min or for patients who are known to be vulnerable to CO_2 retention, a controlled O_2 system may be required (it is acknowledged that it may be difficult for ambulance staff to identify individual patients for whom the risk of hypercarbia and acidosis may be greater than the risk of hypoxia). Ambulance staff should be instructed to stop nebulized therapy and administer controlled low-dose O_2 if a patient with COPD should become drowsy during nebulized treatment using O_2 as a driving gas.

Ambulance staff should commence nebulized bronchodilator therapy (*e.g.* salbutamol 2.5–5 mg or Terbutaline 5–10 mg) as early as possible for patients with acute asthma or acute exacerbations of COPD (Grade B).

Ambulance staff should make peak flow measurements whenever possible before administering nebulized drugs (Grade C).

Use of nebulizers in paediatric asthma

Children differ from adults in more than just size, they have, for example, different breathing patterns, tidal volumes and airway geometry. Most paediatric use of nebulized therapy occurs in the management of acute asthma. Because of the earlier considerations, careful attention to detail is important if nebulized therapy is given to children and infants. The findings of the Task Force were as follows. 1) As with adults, most patients can be treated just as well with hand-held inhalers and spacers (Grade A). 2) Nebulizers are frequently used for convenience or to overcome problems with inhaler technique (Grade C). 3) Adding anticholinergic therapy in severe asthma is beneficial (Grade A). 4) For long-term treatment of asthma, hand-held inhalers are as effective as nebulizers so it is very unusual for a child to require long-term, high-dose nebulized therapy for asthma (Grade B). 5) In the past, nebulizers were widely used to treat young children who were unable to use hand-held inhalers. The development of spacers with face masks has reduced this indication for nebulizer use in childhood (Grade B).

Use of nebulizers in other paediatric conditions

In bronchiolitis, nebulized β_2-agonists or ribavarin have not consistently been shown to be beneficial and nebulized corticosteroids are ineffective in this condition. It is recommended that these treatments should not be used pending further trial data (Grade B).

In the management of croup, oral dexamethasone and nebulized corticosteroids are equally effective; corticosteroids from a hand-held inhaler with spacer device have not been shown to be effective in this condition (Grade A).

In surfactant deficient respiratory distress (hyaline membrane disease), nebulized surfactant is still the subject of investigation. Intratracheal instillation is the recommended route of administration (Grade C). There is conflicting evidence concerning the possible benefit of nebulized surfactant in older children with respiratory distress syndrome (Grade C).

Nebulized DNAse and N-acetyl cysteine have been used in paediatric intensive care units for sputum retention. There is no evidence of benefit from either agent but N-acetyl cysteine may cause bronchoconstriction. It is recommended that these treatments should not be used pending further trial data (Grade C).

There is conflicting evidence of possible benefits of nebulized prostacyclin (iloprost) in pulmonary hypertension in childhood (Grade B).

Use of nebulizers in cystic fibrosis

Nebulizers may be used to administer bronchodilator therapy, mucolytic therapy or antibiotics to patients with cystic fibrosis. However, nebulized therapy is time consuming and should be reserved for situations where it has been shown to be the best or only way to administer a given drug. The use of nebulized therapy should be evaluated and re-assessed regularly. A change in the treatment programme does not always show improvements of pulmonary function parameters but a successful regimen may prevent a fall in lung function over a long period of time. Other outcomes should also be considered, for example; weight gain/maintained weight, reduced exacerbation frequency, improved physical function, reduced tiredness, reduced breathlessness, shortened time spent on daily airway clearance therapy or improved quality of life. Long-term studies are required to show these effects.

There is evidence that selected patients with cystic fibrosis benefit from nebulized antibiotics (Grade A). There have been few controlled trials to determine the optimal dose and delivery system for such a treatment. Nebulized rhDNase has shown benefit in selected patients during medium-term treatment (Grade A). Long-term benefits of nebulized rhDNase are controversial (Grade B).

Some controlled trials of nebulized mucolytics of other kinds have shown little or no benefit. Objective effects on pulmonary secretion viscosity have so far been difficult to measure, subjective effects are difficult to interpret. However, these different kinds of nebulized mucolytics or saline are frequently used in some cystic fibrosis centres and not at all in others. There is a great need for long-term controlled trials with expanded parameters on the effects of nebulized mucolytics (Grade C). Careful attention to technical detail is required for special applications such as nebulized rhDNase and antibiotics (Grade C).

Choice of an appropriate nebulizer system is essential for the quality of the aerosol produced and the drug output. Other factors of importance are treatment strategy and inhalation technique. Theoretically, these patients may require more than two nebulizer systems to administer, for example, rhDNase, antibiotics or bronchodilator drugs. But a situation like this might have negative effects on adherence with the treatment and/or cleaning of the nebulizer systems.

A high capacity nebulizer system including a high output should be considered to keep down the time spent on nebulizer therapy. However, the drugs should be administered separately as it may be hazardous (and ineffective) to mix these agents except when safety and efficacy data are available concerning the particular mixture (Grade C).

Nebulized antibiotics and nebulizer use in bronchiectasis

Most nebulized antibiotic use occurs in patients with cystic fibrosis or bronchiectasis. As discussed earlier, much of this treatment is not evidence-based (there are no randomized controlled trials comparing different antibiotic regimens showing clear superiority of any particular regimen). Furthermore, the CEN data cannot be applied directly to antibiotics and other viscous solutions but would require separate assessment. When such treatment is considered desirable, the clinician should use a drug-nebulizer combination that has been reported to be efficacious in at least one published study (even if nonrandomized). The end-points of "success" are difficult to define in a relapsing condition such as bronchiectasis, perhaps exacerbation rate should be a key measurement. The use of nebulized bronchodilators and nebulized mucolytic agents in bronchiectasis have not been the subject of any large randomized trials and the advice given in the COPD and cystic fibrosis sections of the guidelines should be applied to bronchiectasis also. A nonrandomized trial has shown enhanced mucus clearance when nebulized saline or terbutaline was given as an adjunct to chest physiotherapy to patients with bronchiectasis.

The recommendations for cystic fibrosis also apply to patients with bronchiectasis where there is less experimental evidence of benefit from nebulized therapy (Grade C). It is recommended that individual patients should have a "n of one" trial (*i.e.* a trial including only one person) to determine if nebulized antibiotic therapy or other nebulized treatments are beneficial in their case (Grade C).

Use of nebulizers in acquired immune deficiency syndrome, including Pneumocystis carinii *pneumonia*

In summary, the Task Force found that nebulized therapy in human immunodeficiency syndrome-infected patients can place patients and staff at risk of nosocomial infections including multi-drug resistant tuberculosis. For this reason, elaborate precautions are necessary if nebulized agents are used for diagnostic or therapeutic purposes in this patient group (Grade B).

Nebulizers are widely used to deliver hypertonic saline for sputum induction. This has a lower yield than bronchoscopy with bronchoalveolar lavage but, if positive, it may avoid the need for bronchoscopy. It is recommended that bronchoscopy is used in preference to sputum induction for safety reasons and because of the superior yield (Grade B).

Nebulized pentamidine is more effective than placebo but less effective than oral co-trimoxazole in the prophylaxis and treatment of *Pneumocystis carinii* pneumonia (Grade A). The effectiveness of nebulized pentamidine is highly dependent on the equipment and dose used and on the dosing schedule. Some non-randomized studies with more intensive regimens have given results equivalent to those obtained with oral co-trimoxazole (Grade C).

Nebulized corticosteroids

Nebulized corticosteroids have been used as a substitute for oral corticosteroids in moderate exacerbations of adult and paediatric asthma and to reduce the dose of oral steroid therapy in chronic asthma. Nebulized steroids have also been given to lung transplant recipients (see later). However, in each of these situations, an equivalent dose of inhaled steroid could be given more easily by the use of a hand-held inhaler. There is no clinical data to suggest superior benefit from nebulized corticosteroids (compared with steroid from hand-held inhaler with spacer device) in acute or chronic asthma.

Inhaled steroids delivered by hand-held inhaler and by nebulizer have been shown to have an oral steroid-sparing effect (Grade A). There is evidence that some conventional jet nebulizers and most ultrasonic nebulizers may deliver a lower dose of inhaled steroid to the lung than the same nominal dose from a hand-held inhaler. However, advanced breath-activated nebulizer systems have been shown to deliver equivalent lung doses compared with an effectively used hand-held inhaler system with spacer device (Grade B).

It is recommended that inhaled steroids should preferably be given by hand-held inhaler devices (using a spacer device) because of lack of evidence for any advantage from the nebulized route which is more time consuming and more expensive (Grade C).

Nebulizer use in the intensive care unit

MDI and nebulizers are used in intensive care units to deliver bronchodilator medication to mechanically ventilated adults and children. It is not yet known which treatment modality is more effective because it is difficult to undertake studies which are sufficiently large to permit the measurement of meaningful outcomes such as morbidity, mortality and duration of mechanical ventilation.

Some trials have suggested that MDI in combination with an in-line spacer device may be more efficient in delivering aerosolized drugs to the lungs in ventilated patients, where practical (Grade B).

No randomized trials exist today to prove the efficacy of aerosolized antibiotics for the treatment of nosocomial pneumonia or long-term benefit for the prophylaxis of nosocomial pneumonia (Grade C).

Trials of nebulized surfactant in acute respiratory distress syndrome (ARDS) are at an early stage at present. The optimal dosage is unknown and there may be a problem in achieving adequate drug delivery to the alveoli because some current nebulizers may denature the drug. It has been demonstrated that nebulized or intratracheally instilled surfactant does improve gas exchange in ARDS patients (Grade B), but randomized trials failed to prove beneficial in outcome measures (Grade A).

Trials of nebulized Prostacyclin (iloprost) in ARDS are at an early stage at present but physiological benefits on pulmonary hypertension have been demonstrated in some studies on patients with this condition (Grade B).

Use of nebulizers in bronchoscopy units

Nebulized bronchodilators may be given before bronchoscopy in patients with airflow obstruction or afterwards if bronchospasm occurs. It is likely that high doses from a hand-held inhaler would be equally effective (Grade C).

Some operators give nebulized anticholinergic treatment before bronchoscopy but this has not been proven to be clinically beneficial (Grade C). Nebulized lignocaine may be administered before the procedure as an alternative to lignocaine administered *via* the bronchoscope. If this is done, the clinician should select a nebulizer which delivers most particles to central airways (Grade B).

Treatment of airflow obstruction in patients with tracheostomy

Many patients with laryngeal cancer requiring laryngectomy also have co-existing COPD which is difficult to treat using conventional MDI. Nebulizers are frequently used to treat these patients. However, recent case reports indicate that MDI-spacer devices can be used with appropriate adaptors. This permits quicker treatment with lower doses of bronchodilators. For patients with an open tracheostomy, a 750 mL spacer with a baby sized face mask can be placed over the tracheal stoma to deliver bronchodilator therapy (Grade C).

For intubated patients or patients with permanent tracheostomy tubes, the MDI-spacer can be connected

to the patients tracheostomy tube by means of an appropriately sized adaptor (Grade C). No controlled trial has compared these treatments with nebulized therapy but case reports suggest that patients may find MDI-spacer therapy quicker to administer (Grade C).

Use of nebulizers in palliative care

Nebulized bronchodilators may be used for the treatment of severe co-existing COPD in lung cancer patients (as described in the COPD section of these guidelines) (Grade B). The use of nebulized saline or mucolytics to loosen airway secretions in patients with advanced cancer remains of unproven value (Grade C).

Nebulized opiates have been shown to be ineffective in the treatment of breathlessness and this therapy is not recommended (Grade B). The use of nebulized lignocaine in lung cancer has not been subjected to any controlled study (Grade C).

Use of nebulized mucolytic therapy in chronic obstructive pulmonary disease

Nebulized mucolytic agents are used to treat COPD patients in some countries but there is very limited clinical trial evidence to support such use. Further controlled trials are needed. In the meantime, it is recommended that such treatment should be restricted to cases where benefit has been shown in "n or one trials" (Grade C).

Use of nebulizers in lung transplantation

Nebulized steroids and nebulized cyclosporin have been used as preventive therapy in lung transplant patients who are at risk of developing obliterative bronchiolitis because of frequent episodes of rejection in the first 3 months post-transplantation. This use is presently the subject of further research studies (Grade B).

Use of nebulizers in fungal lung diseases

There is evidence of modest benefit from nebulized amphoteracin-B in the prophylaxis of fungal pulmonary infections in neutropenic leukaemic patients (Grade A). However, drug intolerance due to airway side-effects (cough and bronchospasm) was a major concern, causing discontinuation of therapy in ~20% of patients.

There is evidence from nonrandomized trials that nebulized amphoteracin, when given to lung transplant patients with positive cultures for aspergillus or candida, may prevent the development of invasive fungal pneumonia (Grade B). A randomized trial of nebulized bronchopulmonary aspergillosis failed to show any benefits. This treatment is not recommended (Grade A). However, clinicians should consider the use of oral itraconazole which has been shown to produce clinical benefits in two recent randomized studies (Grade A). There is limited evidence of lack of benefit for the use of nebulized amphoteracin in the treatment of tracheobronchial fungal infections (Grade C).

Use of nebulizers in the treatment of pulmonary hypertension

There is evidence of long-term clinical and physiological benefit from nebulized prostacyclin (iloprost) in pulmonary hypertension in adults (Grade A). The relative benefits of parenteral and inhaled prostacyclin are still the subject of ongoing research protocols, the inhaled preparation had given superior physiological outcomes in some trials (Grade B).

Upper airway uses of nebulizers

Nebulized treatment has been used for a variety of nasal, pharyngeal, laryngeal and sinus conditions but there are limited controlled trial data to support such use (Grade C). Warmed humidified air has been shown to produce symptomatic benefit in patients with chronic rhinitis (Grade B).

Diagnostic uses of nebulizers

Nebulizers are used for a number of diagnostic purposes, most of which are highly specific (allergen or occupational challenge in asthma, reversibility testing in COPD, hypertonic saline for sputum induction, radioisotopes in ventilation studies or clearance studies). The majority of such uses are highly dependent on the use of specific equipment which has been validated in previous studies.

It is recommended that investigators should use equipment and solutions which have been validated in at least one published study or validated in their own laboratory (Grade C).

Service issues

Selection and purchase of nebulizer systems

The choice of nebulizer system will depend on the drug prescribed, the patient and disease being treated and on availability and price in each country. The background papers in the *European Respiratory Review* include a table describing present usage in various European countries. It is recommended that the CEN data should be used to guide the choice of system (see technical section). The final choice of system may depend on local factors but should be guided by the principles described earlier.

Running a local nebulizer or inhaled therapy optimization service

There is increasing evidence that the understanding of the use of nebulizers by patients and health

professionals is poor, leading to inappropriate and suboptimal use. It is recommended that an appropriately trained specialist such as a chest physician, paediatrician, physiotherapist or respiratory nurse specialist (or a primary care physician with a special interest in respiratory diseases) should assess whether nebulizer therapy is indicated. Assessments should be undertaken using standard protocols as described earlier (Grade C). If nebulizer therapy is prescribed, the patient should have access to an appropriately run nebulizer service providing equipment, advice and support for patients who require long-term nebulizer therapy (Grade C).

The "local nebulizer service" should include the following: assessment and advice for patients who might benefit from home nebulizer therapy; loan or hire of nebulizer equipment; advice for healthcare professionals; access to servicing of equipment; audit of all aspects of nebulizer use in the locality. Patients should be provided with training (including practical demonstration) and clear written instructions in how to use and maintain their equipment (Grade C). The different healthcare professionals who may care for an individual patient need to communicate effectively with each other and with the patient (Grade C).

Cleaning, maintenance, and replacement of equipment

Cleaning nebulizer equipment involves getting rid of drug residues as well as dirt and microbes. The ideal standards and methods for such cleaning (and the optimal intensity and frequency of cleaning) have not yet been well established. It is important that nebulizer chambers, tubing and masks should not be re-used for multiple patients unless they have been sterilized (and are capable of withstanding sterilization) (Grade C). All other usage should be for individual patients with careful cleaning and disinfection of the whole nebulizer system on a regular basis (Grade C). The driving source should be cleaned and checked for safety and efficiency in accordance with the manufacturer's recommendations or at least once per year and the whole nebulizer system should be brought for this check-up (Grade C). Filters should be changed at intervals specified by the manufacturer (Grade C). Nebulizer chambers, tubing and masks should be changed regularly (Grade C).

It is recommended that the person in charge of the local nebulizer service should provide patients with advice and support to ensure that all nebulizers are used safely and efficiently including details of disassembly and cleaning (Grade C). It is suggested that manufacturers should undertake appropriate tests and trials to permit the production of evidence-based instructions.

Education of clinical staff and patients

It is recommended that a local "inhaled therapy coordinator" (doctor, nurse or physiotherapist) should be made responsible for the production and implementation of local policies for the use of inhaled therapy, including nebulizer therapy (Grade C). This will improve efficacy and patient safety and it is likely to be cost-effective as the inappropriate use of expensive nebulized drugs should be minimized (Grade C). This person should provide education for other healthcare professionals and patients in addition to running an assessment and support service for patients. This should include support and advice for physicians who prescribe nebulized drugs, although the prescriber remains responsible for the patient's treatment and safety (Grade C).

Follow-up of patients

It is suggested that long-term nebulizer users should have the support of a local service, as described earlier. Patients should be re-assessed soon after treatment starts (at ~1 month) and then re-assessed regularly (at least annually) to determine whether their treatment is still necessary and effective and to ensure that the patient continues to use the nebulized treatment safely and effectively (Grade C). This evaluation should include lung function testing, assessment of symptom control and breathlessness and sense of well-being. The clinician should also ask about side-effects of treatment and check that the treatment is still judged by the patient to be working (Grade C).

It may also be helpful to ask the patient to demonstrate their technique by using their own nebulizer system. The local nebulizer support team should maintain good communication with the patient's primary care physician, especially with regard to dose and frequency of nebulized therapy.

Implementation and dissemination of the European Respiratory Society Nebulizer Guidelines

There is a great need to improve technical standards and present clinical practice. Because of the complex ways in which inhaled therapy is used in different countries, the Task Force has tried to provide information and recommendations rather than rigid prescriptions or instructions which might not be applicable to many users. The ERS would encourage national and local dissemination of these guidelines (translated into local languages where necessary).

It is especially important to target healthcare professionals such as doctors, nurses and physiotherapists who may be involved in administration of nebulized treatment and the local purchase of nebulizer devices.

It is hoped that specialists in each country or region will initiate local programmes to implement the ERS Guidelines. The ERS will not issue any formal guidance on local implementation, this will be the responsibility of national and local respiratory societies. In some cases it may be necessary to prepare short abstracts, tables and wall charts or to tailor the guidelines to meet the needs of users and healthcare staff in different parts of Europe. The ERS will

encourage such use of the guidelines by healthcare professionals throughout Europe.

National and local respiratory societies, pharmaceutical companies and equipment manufacturers will be encouraged to promote and distribute these guidelines or selected abstracts from the guidelines for the use of local clinicians and patients. It is hoped that clinicians will initiate local audit of practice before and after the introduction of these guidelines. Feedback from these clinicians to the ERS will be much appreciated by the Society.

A complimentary copy of the *European Respiratory Journal* paper which contains the guidelines will be circulated by the ERS to the editors of all major respiratory journals, general medical journals and pharmacological journals with a recommendation that editors should insist on the description of a standard operating practice in all papers which involve the use of nebulized drugs (this information should be circulated to referees and associate editors). The guidelines will be made available on the World Wide Web in the future. The guidelines will be reviewed and updated as the need arises.

Areas of uncertainty and future research needs

There are many areas of uncertainty where future research is needed. 1) The relationship between *in vitro* studies and *in vivo* effects needs further investigation. This issue will be especially important as newer, more efficient nebulizer systems are introduced into clinical use. 2) Matching nebulizer systems to individual drugs and to individual patients (*e.g.* width of "therapeutic windows" (see technical section of this paper)). 3) For patients who could receive a similar dose of the same drug from a hand-held inhaler device or from a nebulizer, are there specific situations where one system or the other might have advantages? 4) Cost-effectiveness and health resource utilization studies comparing nebulizers and hand-held inhaler therapy. 5) Methods to identify which patients with asthma and chronic obstructive pulmonary disease might benefit (or not benefit) from nebulized therapy using clinically relevant assessment systems. 6) How to decide whether or not a patient with asthma or chronic obstructive pulmonary disease has derived definite benefit from home nebulizer therapy. 7) Value (and possible risks) of nebulized bronchodilator therapy in chronically hypoxaemic patients with severe but stable chronic obstructive pulmonary disease. 8) Physiological effects of nebulized saline and mucolytic agents in chronic obstructive pulmonary disease and bronchiectasis. 9) Controlled comparisons of different nebulized antibiotics given by specific nebulizer systems and evaluation of the indications for the use of nebulized antibiotics and the effectiveness of this treatment. 10) Relative value of nebulized therapy and metered-dose inhaler therapy in mechanically ventilated patients using clinically meaningful end-points. 11) Role of mucolytic agents other than recombinant human deoxyribonuclease in cystic fibrosis. 12) Long-term benefits of nebulized antibiotics and recombinant human deoxyribonuclease in cystic fibrosis. 13) Clinical comparisons of nebulized corticosteroids with the equivalent dose of inhaled corticosteroid given by hand-held inhaler. 14) Best practice for cleaning and servicing of nebulizers. 15) Role of nebulized prostaglandin analogues in pulmonary vascular disease. 16) Role of nebulized therapy in palliative care. 17) Role of nebulized therapy in upper airway diseases.

Appendix 1: Assessment of subjective and objective response to therapy

Suggested tools to measure response to each treatment modality during "inhaled therapy optimization protocol" (to assess response to therapy with hand-held inhalers or nebulized therapy).

Objective response (compared with two weeks on usual treatment):

PEF worse	Score -1
PEF unchanged or rise of 0–10%	Score 0
PEF rise of 11–20%	Score 1
PEF rise >20%	Score 2 (but reconsider diagnosis of COPD)

Subjective response: ask the patient to respond to the following question: "compared with your previous therapy, how was your condition overall during this period of therapy?" (and record what symptoms have improved).

Worse	Score -1
Same or no definite change	Score 0
Definitely better	Score 1
Definitely much better	Score 2 (and ask the patient to state which symptoms have improved)

Appendix 2: Evaluation of outcome following each period of treatment during "inhaled therapy optimization protocol"

Possible outcomes for each period	Suggested action
Subjective Response +1 or +2 Objective Response +1 or +2	Consider continuing this treatment long-term (depending on side-effects and patient preference *etc.*)
Subjective Response +1 or +2 Objective Response 0	Consider longer reial of this treatment modality

Subjective Response -1 or 0 Objective Response -1 or 0	Stop this treatment (and proceed to next step of assessment if appropriate)
Subjective Response -1 or 0 Objective Response +1 or +2	Reconsider diagnosis and consider longer trial

If objective response is +2, reconsider diagnosis of COPD.

Appendix 3: Summary of recommendations for optimization of inhaled therapy in severe chronic obstructive pulmonary disease and severe chronic asthma

1. Check diagnosis and confirm severity and baseline disability and ensure that the patient can use their existing inhaler device effectively. Assess response to each treatment as shown in Appendix 1.
2. Ensure that patients have tried other appropriate therapy including consideration of nondrug therapy such as a pulmonary rehabilitation programme.
3. Optimize existing asthma or COPD therapy using a hand-held inhaler which the patient is able to use (*e.g.* salbutamol 200–400 μg *q.i.d.* (terbutaline 500–1,000 μg) or equivalent or ipratropium bromide 40–80 μg *q.i.d.* or a combination of these agents).
4. If these measures do not achieve benefit, try further increasing the dose of inhaled therapy *via* hand-held inhaler (*e.g.* up to 1,000 μg salbutamol *q.i.d.* and/or up to 160–240 μg ipratropium bromide *q.i.d.*).
5. If the patient responds poorly to the above measures, consider a period of home nebulizer therapy (ideally using loaned equipment).
6. Assess the patient′s response to 2 weeks of therapy with nebulized β-agonist (salbutamol 2.5 mg *q.i.d.* or terbutaline 5 mg *q.i.d.* or equivalent).
7. Consider ⩾1 of the following: nebulized salbutamol 5 mg *q.i.d.* (terbutaline 10 mg *q.i.d.*); nebulized ipratropium bromide 250–500 μg *q.i.d.*; mixture of salbutamol (2.5 or 5 mg) or terbutaline (5–10 mg) with ipratropium 500 μg *q.i.d.*
8. Decide with the patient which of these therapeutic interventions was most beneficial: use the evaluation system given in Appendix 2.

Acknowledgements. The authors would like to thank the following Task Force Consultants: J. Denyer (Medic Aid), M. Knoch (Pari), M.T. Lopez-Vidriero (Boehringer Ingelheim), O. Nerbrink (AstraZeneca), J. Pritchard (GlaxoWellcome).

In addition to the Task Force members and consultants, the following experts have contributed to the preparation of these guidelines or the background papers on which the guidelines are based: M. Bainbridge, P.W. Barry, T. Benfield, H. Bisgaard, P. Bonfils, G. Braunstein, P.H. Brown, A. Bush, G. Chantrel, H. Chrystyn, G. Crenona, G.K. Crompton, D.W. Denning, C.F. Donner, A. Dyche, J. Efthimiou, R. Escamilla, F. Faurisson, B. Fouroux, G.A. Ferron, D. Geddes, R. Harkawat, C. Hermant, A. Hopkins, C. Janson, E. Lemarie, L. Lores, R. Miller, M.F. Muers, S.P. Newman, K. Nikander, C. O′Callaghan, J. Pagels, M. Partridge, D. Pavia, M.G. Pearson, S. Pederson, C.A. Pieron, J.N. Pritchard, C. Roussos, I. Sampablo-Lauro, P.L. Sayers, R.K. Sharma, E. Sommer, S.C. Stenton, C.J.P.M. Teirlinck, A. Torres, J.A. Wedzicha, A.M. Wilson, B. Zierenberg.

References

1. Boe J, Dennis JH. European Respiratory Society Nebulizer Guidelines: Technical Aspects. *Eur Respir Rev* 2000; 10: 72, 1–237.
2. Boe J, Dennis JH, O′Driscoll BR. European Respiratory Society Nebulizer Guidelines: Clinical Aspects. *Eur Respir Rev* 2000; 10: 76, 495–583.
3. Petrie GJ, Barnwell E, Grimshaw J, on behalf of the Scottish Intercollegiate Guidelines Network. Clinical Guidelines: criteria for appraisal for national use. Edinburgh Royal College of Physicians, 1995.
4. Agency for Healthcare Policy and Research. Acute pain management, operative or medical procedures and trauma 92–0032. Clinical practice guideline. Rockville, Maryland, USA, Agency for Healthcare Policy and Research Publications, 1992.
5. Rudolph G, Kobrich R, Stahlhofen W. Modelling and algebraic formulation of regional aerosol deposition in man. *J Aerosol Sci* 1990; 21: 5306–5406.