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# Overview of nebuliser treatment

M F Muers

## Historical perspective

The word "nebuliser (from the Latin "nebula", mist) was first used in 1872 and was defined in 1874 as "an instrument for converting a liquid into a fine spray, especially for medical purposes".[1] The idea of producing a vapour or aerosol for the treatment of lung disease was by no means new even then since smoke and steam had been used in this way for centuries. Inhalation devices depending on mouth suction to draw air through a liquid were produced for essential oil treatment in the 18th century and similar devices were employed when antiseptic inhalations were advocated for the treatment of tuberculosis.[2] Although early inhalation devices depended on steam (fig 1), mechanical pumps to generate the gas flow for nebulisation were made in the 19th century and these were eventually supplanted by electrical compressors in the 1930s. Early nebuliser chambers were essentially simple atomisers – like the glass and hand bulb atomisers first introduced for asthma treatment in the 1930s (fig 2). These generated an aerosol with a wide range of particle sizes and much of the output was non-respirable. Modern jet nebuliser chambers use a combination of high gas flow, precise Venturi orifices, and baffles to restrict the size of the particles emitted more closely to those of respirable size (1–5 μm diameter) and thereby increase lung deposition and treatment efficacy. These designs depend upon the availability of precision engineering, originally of ebonite and perspex – for example, the Wright nebuliser of the 1950s (fig 3) – and now injection moulded plastics. By contrast, ultrasonic nebulisers which rely on high frequency sound waves induced by the vibration of a piezoelectric crystal were not introduced until the 1960s.[3] More recently, equipment development has focused on breath assisted chambers which generate an even higher percentage of respirable particles and can facilitate aerosol treatment with a wide variety of drugs, drug suspensions, and solutions with different physicochemical properties (fig 4). Progress towards the matching of specific equipment to particular types of drug delivery is likely to continue. Future treatment may well include a greater use of the products of recombinant gene technology – for example, rhDNase, $\alpha_1$-antitrypsin – as well as specific anti-inflammatory mediator drugs for both interstitial lung disease and obstructive air flow disease, and possibly cytokines and cell surface receptors for the treatment of endobronchial neoplasia.

Despite this expanding range of nebuliser therapies, there is a need for physicians to recognise that, for the foreseeable future, the principal use worldwide will be for bronchodilatation. By extrapolation from a regional study[5] it is possible to estimate that there are currently about 40 000 compressors in use for adult domiciliary treatment in the UK with an associated drug cost of approximately £40 million annually. A recent audit of a large Scottish teaching hospital revealed an annual use of 32 000 daily doses of nebulised bronchodilators.[6] Elsewhere in Europe usage may be even higher. Brandli[7] has reported a figure of 215 nebulisers per $10^5$ population in Switzerland compared with 70 per $10^5$ in the UK survey. Nevertheless, as so often happens with physical treatments in medicine, widespread use has preceded much needed, more fundamental work in optimising drug delivery. The reason for this is that modern compressors and nebulisers are efficient, large doses of drugs are used, and they are especially effective for emergency treatment. It is clear from Appendix 5 on pp S23–24 of the guidelines that much research still needs to be done to optimise even straightforward nebuliser treatment.

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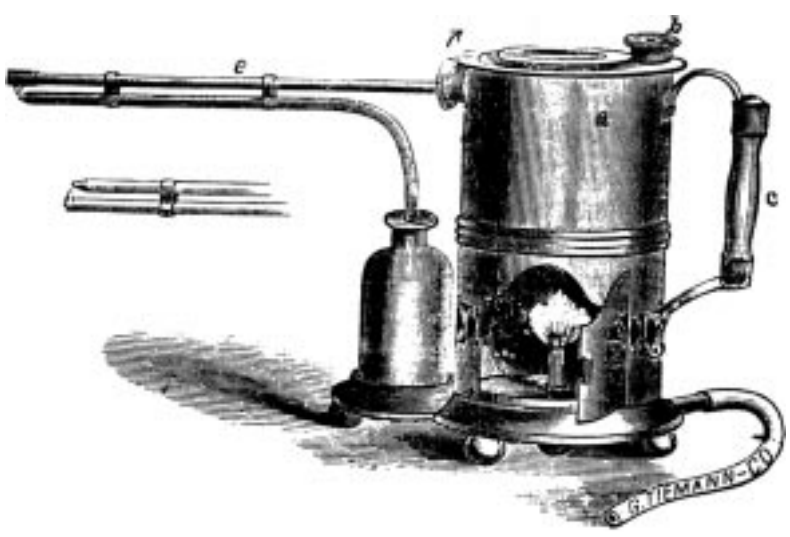


*Figure 1 Example of 19th century nebuliser equipment. Seeger's steam nebuliser from Geo. Tiemann and Co's Surgical Instrument Catalogue, New York, 1876.*

## Nebulisers in clinical medicine

Table 1 is a summary of the present uses of nebulisers in clinical medicine. Although the articles in this supplement concentrate on the use of nebulisers for treatment, it must be noted that, in parallel, much work has been done on their use – usually in a more precise way – in generating respirable aerosols for diagnostic purposes and for physiological measurement and basic lung research. For example, the use of radioactively labelled DTPA aerosols for the measurement of alveolar epithelial permeability depends critically on using a system able to generate large numbers of particles with a mass

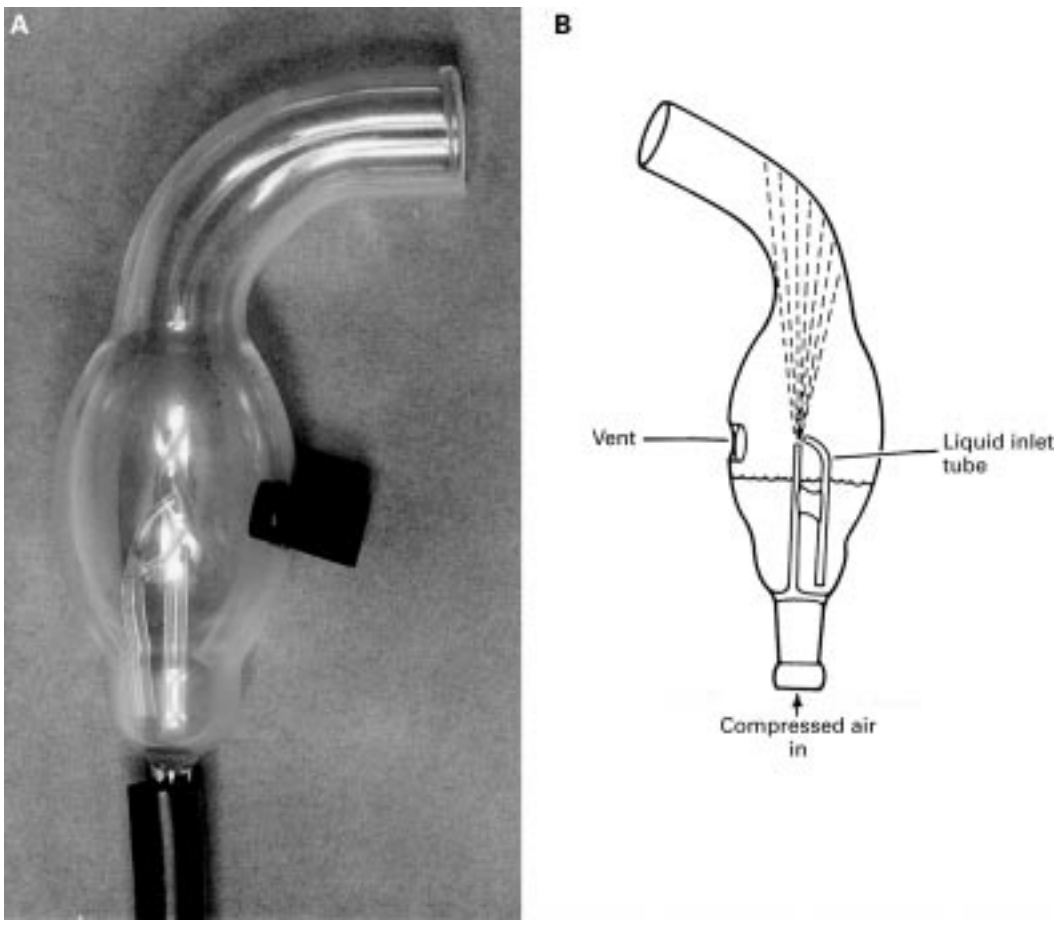


*Figure 2A and B The DeVilbiss No 40 glass nebuliser. Reproduced with permission from Mercer.*[3]

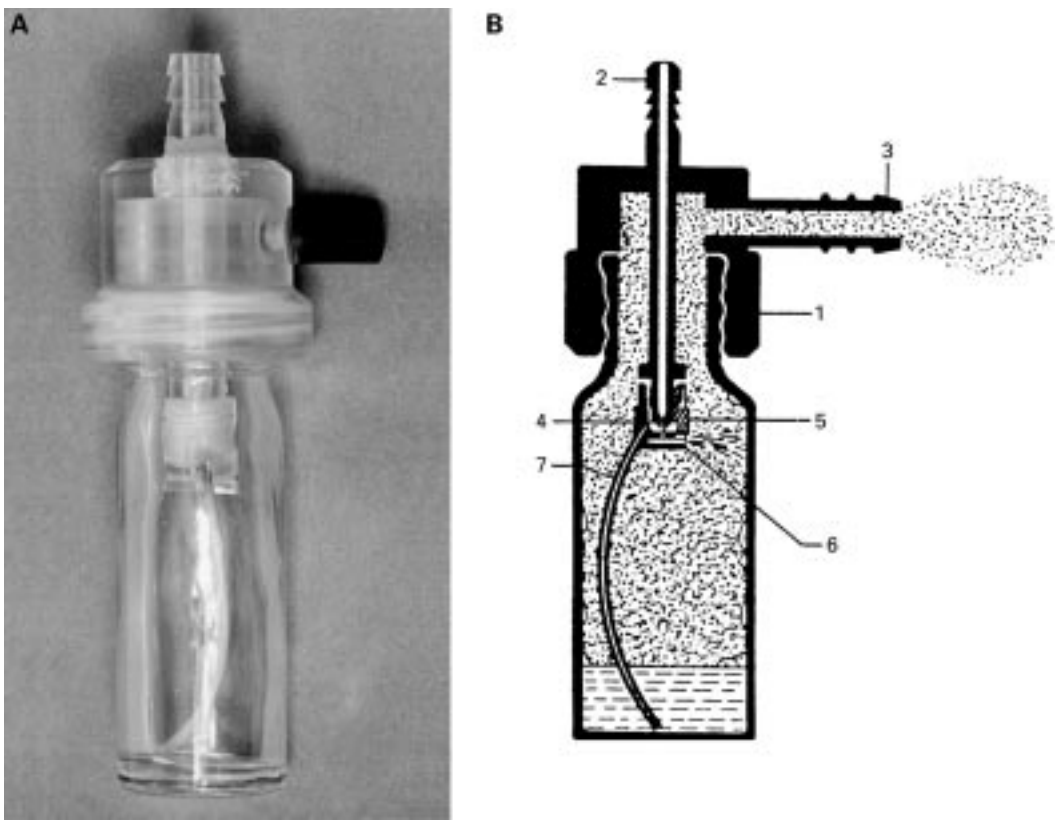


*Figure 3A and B The Wright perspex nebuliser. 1=cap; 2=inlet connection; 3=outlet connection; 4=jet; 5=knurled nozzle; 6=baffle plate; 7=flexible feeding tube. Reproduced with permission from Wright.*[4]

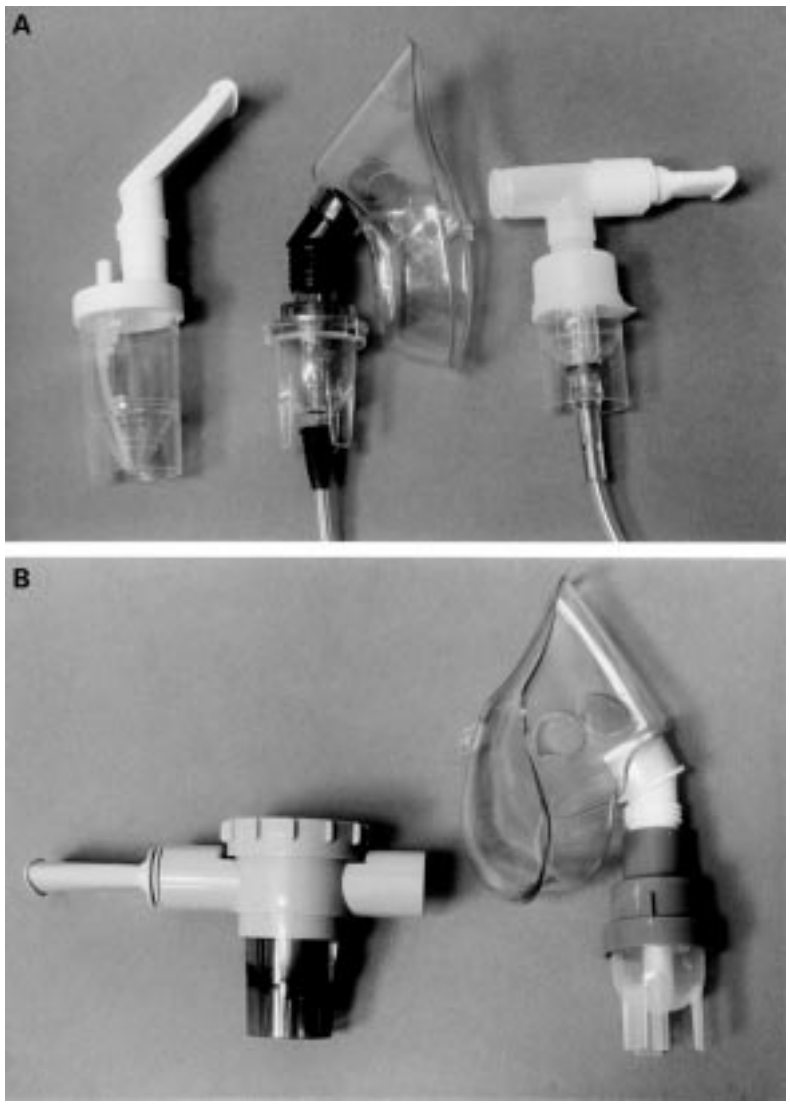


*Figure 4 Examples of modern nebuliser chambers. (A) Simple jet nebulisers: Unimed; Lifecare; Hudson Up-draft II. (B) Breath assisted nebulisers: Ventstream (left); Sidestream (right) (Medic-Aid).*

*Table 1 Uses of nebulisers in clinical medicine*

| | | *Reference* |
|---|---|---|
| Diagnosis: | | |
| Lung physiology | | |
| Ventilation | $^{99m}$DTPA <3 μm MMAD | 8 |
| Mucociliary clearance | Albumen microspheres >5 μm MMAD | 9 |
| Epithelial permeability | $^{99m}$DTPA 0.5–3 μm MMAD | 10 |
| Airway reactivity | Histamine, methacholine | 11 |
| Airway reversibility | | |
| Cough threshold | Citric acid, capsaicin | |
| Lung cell sampling | | |
| Sputum induction | 3N NaCl ultrasonic | 12 |
| Treatment: | | |
| Airway obstruction | Bronchodilators, steroids | |
| Infection | Antimicrobials | |
| Abnormal secretions | Mucolytics (saline, acetylcysteine, rhDNase) | |
| Cough | Local anaesthetics | |
| Breathlessness | Opiates | |

MMAD = mass median aerodynamic diameter.

median aerodynamic diameter (MMAD) of 0.5–2 μm.[10] By contrast, delivery of therapeutic aerosols is often far less precise. "Shell" analysis of the distribution of inhaled particles generated by different commonly used nebuliser chambers has shown elegantly how drug distribution to different generations of bronchi can vary enormously.[13]

## INDICATIONS FOR TREATMENT WITH NEBULISERS

The absolute indications for treatment with nebulisers are relatively few (table 2). They have to be used (1) where the drug is not available as a hand held inhaler, (2) where drug delivery to the alveoli is needed (for example, pentamidine for the prophylaxis or treatment of pneumocystis pneumonia), and (3) when a patient is too ill or is incapable of using a hand held inhaler.

All other indications for nebuliser treatment are relative. Dose escalation can be achieved with multiple actuations of a hand held inhaler, even in emergency treatment,[14 15] although patients may prefer the relative ease of a nebuliser to taking 12–50 actuations of a hand held inhaler for an equivalent drug dose. Thus, although in theory hand held inhalers may be substituted for nebulisers in acute treatment (and this is increasingly so in paediatric practice), most adult patients and emergency services will continue to prefer nebulisers for their convenience and the reassurance that, even with unrestricted tidal volume breathing, the drug is being inhaled. Otherwise it remains a reasonable principle that, where drugs are available both in hand held inhalers and in nebuliser solutions, compliance with treatment, technique with hand held inhalers, and the benefit from them should be carefully checked before regular nebuliser treatment with all its complexity and expense is advised.

## EFFICACY

If the purpose of nebuliser treatment is to obtain a response from the interaction between drug molecules and lung cell receptors, it follows that the most straightforward way of assessing efficacy is by physiological measurement.

The treatment of acute airflow obstruction may be measured by simple physiological responses with a clear correlation between these and symptom relief. Nevertheless, criteria for establishing what is an unequivocal bronchodilator response have evolved and are not yet well established (table 3). The assessment of response in patients with chronic airflow obstruction when airway disease is much less reversible is quite different. There may be poor correlation between measurements of exercise capacity, validated symptom scores, and measurements of bronchodilatation.[26] Furthermore, there is no well validated criterion as to what is an unequivocal physiological response in terms of peak flow changes (table 3).[23 24] Increasing attention is being given to the use of other measures such as the six minute walk,

*Table 2 General indications for treatment with nebulisers*

| |
|---|
| Absolute indications: |
| (1) Too sick or incapable of managing hand held inhalers. |
| (2) Drug not available in hand held inhalers. |
| (3) Need to target treatment to particular generations of bronchi or the alveoli. |
| Relative indications: |
| (1) Need for a large drug dose. |
| (2) Patient preference. |
| (3) Practical convenience. |

*Table 3 Criteria for identifying bronchodilator responses*

| | | *Reference* |
|---|---|---|
| Repeat measurements on one day | | |
| $FEV_1$ | >15% of baseline | 16 |
| $FEV_1$ | >9% of baseline | 17 |
| $FEV_1$ and FVC | >200 ml | 18 |
| $FEV_1$ and FVC | >12% of baseline and >200 ml | 19 |
| $FEV_1$ and FVC | >12% of predicted and >200 ml | 20 |
| | PEF >60 ml | 21 |
| Repeat PEF measurements over several days | | |
| Corticosteroid trials | >20% baseline, mean 7 days | 22 |
| | >15% baseline, mean 7 days | 23 |
| Nebuliser assessments | >15% baseline, mean 7 days | 24 |
| Reproducibility (PEF) | | |
| Best two measures within 20 l/min | | 25 |

$FEV_1$ = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow.

symptom relief, and quality of life questionnaires[26] as more valid criteria to judge the efficacy of treatment in chronic disease. The same caveats apply to the use of nebulisers for antimicrobials and palliative drugs where, apart from a few studies in cystic fibrosis, well conducted trials of treatment are sparse and end points for judging benefit are not precise (table 4). As discussed in the following papers, this is an area where emphasis on major research is long overdue.

In this context it is perhaps salutary to note that these unmet needs have been recognised since 1929 when a London general practitioner, Dr P W L Camps, wrote *A note on the inhalation treatment of asthma*![27]

## Equipment

The in vitro measurement of the output characteristics of nebuliser systems is an important corollary to the measurement of clinical efficacy. The development of national (UK, BS 5724) and international (European, IEC 601–1) standards should act as a stimulus in this direction. Examples of how establishing standard methodologies could affect this field are the recent recommendation that a multistage impinger rather than a two stage device should be used to measure drug particle size distribution,[28] the increasing realisation that direct drug output estimates rather than gravimetric methods are superior for assessing nebuliser chamber performance,[29] and the recognition that quality control in the manufacture of chambers is important to ensure that there is a low unit to unit variation in output characteristics.[30] Consideration probably ought to be given to the suggestion that there should be reference laboratories using standardised methods and able to publish reliable and comparable data on the function of compressor/nebuliser combinations. At present much of this information is difficult to obtain and comes from several disparate sources. Direct comparisons between equipment are relatively sparse, and are themselves difficult to compare because of different methods and criteria for assessment.[29 31]

## Reviews of nebuliser use in clinical practice

Few reviews or audits of nebuliser use in institutions or communities have been published but even this small literature has shown a disturbing picture. Caldwell *et al*[6] found that more than 50% of treatments in a large Scottish teaching hospital were incorrectly prescribed (inefficient gas flows, small fill volumes, etc) while more than 20% of prescriptions used water rather than saline to dilute bronchodilators and 30% of equipment was not cleaned daily. Similarly, only 7% of nebuliser prescriptions reviewed on five medical wards of an English teaching hospital were correct.[32] The circulation of fairly simple directions can change technique abruptly, and both studies reported improvements after such procedures. However, only 30% of prescriptions in the English study were subsequently correct and this emphasises the point that patient and staff education has to be a continuing process and a single directive is not adequate.

Similarly, both national and international comparisons have shown an unreasonable variation in nebuliser treatment use and, by implication, unreasonable differences in clinical practice. In a UK regional survey,[5] for instance, compressor use for domiciliary treatment varied between districts from four to 213 per $10^5$ population. The European 1992 international asthma survey[33] showed a similar variation in reports by physicians on their use of nebulisers for airway disease (fig 5). Such variations may represent, in part, varying access by patients and doctors to funding, but almost certainly they also reflect inconsistencies in the interpretation of present evidence about the suitability of nebuliser treatment. In contrast, in situations where there is a clearly restricted and detailed clinical indication and care has been taken to specify the details of nebuliser technique, they are likely to be approached in a much more uniform way. Examples are

*Table 4 Measuring the efficacy of nebuliser treatment*

| *Drug* | *Problem* | *Objective* | *Usual measurements* | *Agreed criteria for response* |
|---|---|---|---|---|
| Bronchodilators | Acute airway obstruction | Rapid bronchodilatation | PEF<br>$FEV_1$ | + |
| Bronchodilators | Chronic air flow limitation | ↓ disability | PEF, ? exercise test, ? validated questionnaires | ± |
| Steroids | Chronic air flow limitation | Bronchodilatation, ↓ oral dose | PEF, oral dose | ± |
| Antimicrobials | Chronic infection | Fewer exacerbations, less secretions | ? | − |
| Mucolytics | Abnormal secretions | Better physiology, ? patient comfort | ? | − |
| Local anaesthetics | Cough | ↓ frequency | Cough count | − |
| Opiates | Breathlessness | Palliation | VAS or questionnaire | ± |

PEF = peak expiratory flow; $FEV_1$ = forced expiratory volume in one second; VAS = visual analogue scale.

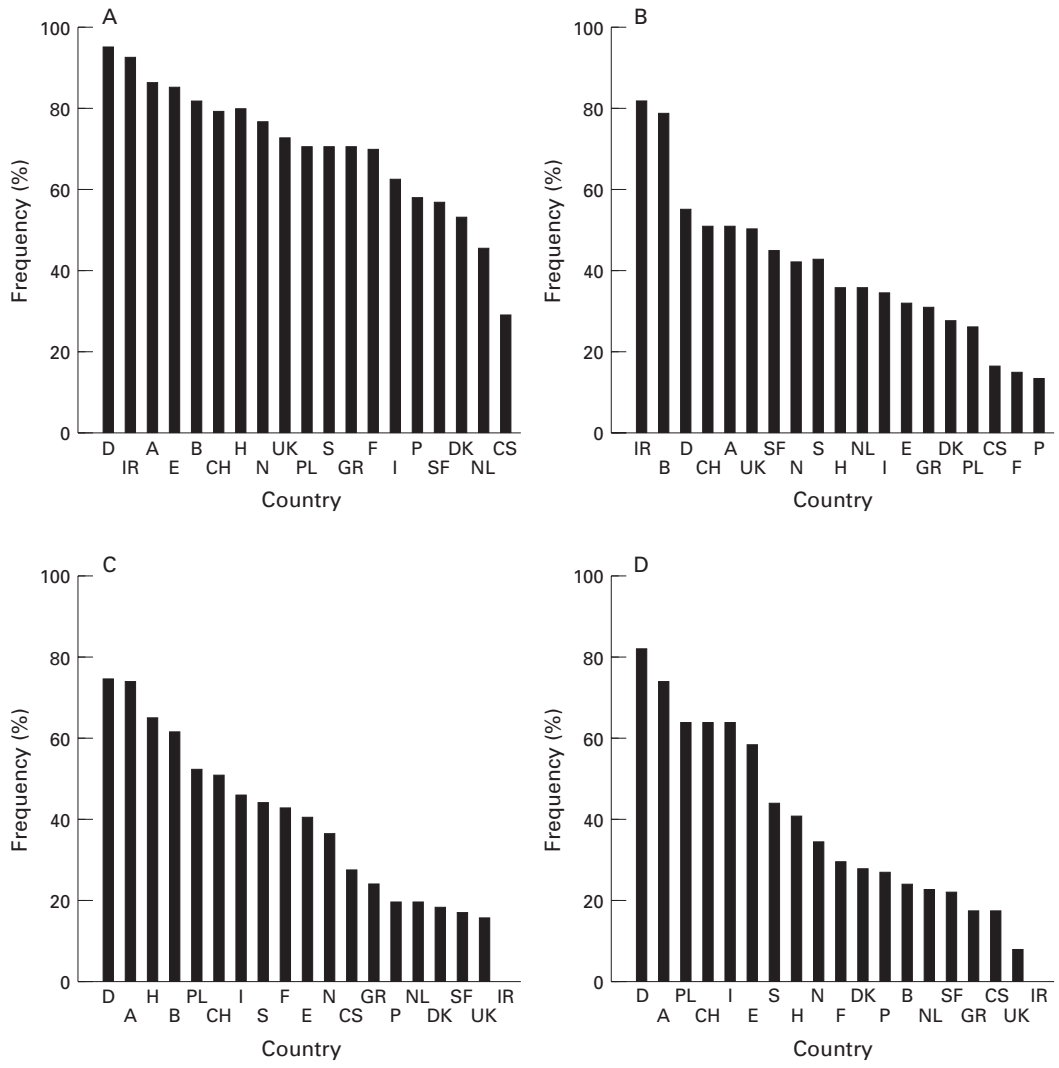


*Figure 5 Percentage of pulmonologists from 19 European countries using nebulisation often or always for (A) β agonists in adults; (B) anticholinergics in adults; (C) cromoglycate in children; (D) steroids in children. Reproduced with permission from Vermiere.*[33]

the use of particular nebuliser chambers for pentamidine and the US Food and Drug Administration (FDA) recommendation of the small particle aerosol generator (SPAG) to nebulise ribavirin.

There has been little concerted effort, either national or international, to pool experience, examine details of practice, and establish a consensus of best clinical practice. A 1991 US aerosol consensus statement[34] has general recommendations regarding hand held inhalers and nebuliser use but details were restricted to recommended precautions by health care workers for the administration of pentamidine and ribavirin. A Dutch group has recently produced specifications for nebuliser equipment[35] and these have been mirrored by the published UK and European equipment standards. However, good nebuliser treatment requires more than equipment specifications.[36] Details of indications, drugs, timing, etc are also all relevant. To improve the situation more collaboration is needed between health service administrators, the medical profession, and the pharmaceutical and equipment manufacturing industries. National and international respiratory societies are in a good position to take the lead in establishing such ventures and the benefits both to health services and to patient care should be large.

## Conclusions

The purpose of this document is (1) to gather together authoritative reviews of the evidence for nebuliser treatment in different clinical situations; (2) to provide clinicians with accessible information on the scientific basis of nebuliser treatment and the factors to be considered in using and choosing equipment and running a domiciliary service; (3) to present a summary of recommendations – as guidelines – on treatment with nebulisers for physicians, together with a short precis for general practitioners and example information sheets for patients and nursing staff; and (4) to highlight the particular areas where future research on nebuliser treatment can usefully be directed. It is hoped that improvements in the provision of nebuliser treatment will ensue and that patients will correspondingly benefit.

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