tems should be expected to provide a drug output with about 50% of the particles below 5.0 μm mass median diameter. It is important to obtain an acceptable range of aerosol particle sizes because of the way in which these are deposited in the tracheobronchial tree.[1–5]

Practical definitions

Jet nebuliser: a nebulising chamber where an aerosol is generated from a flow of gas from an electrical compressor or from a compressed gas supply (air or oxygen). The gas passes through a very small hole (the jet or Venturi) resulting in liquid being sucked up through the small hole from the chamber base and atomised. The resultant large particles then impact upon baffles to generate small respirable particles.[6]

Ultrasonic nebuliser: an electrically driven system whereby a rapidly vibrating piezoelectric crystal vibrates the drug solution and produces aerosol particles of a respirable size.[6]

Flow rate through the nebuliser: the flow rate of gas, whether from a compressed source or from a compressor, that actually drives the nebuliser chamber. It is not the same as the flow rate from the compressor which will often be considerably higher.[7] It is obtained by producing a pressure-flow rate curve for the nebuliser. Recordings of circuit pressure are made from zero flow (maximum pressure) to maximum flow (minimum pressure) using a rotameter, a compressor unit (or flow generator), and pressure measuring device. By substituting the nebuliser chamber for the rotameter the pressure in the circuit can be obtained with a constant flow rate from the flow generator. From the pressure-flow curve the flow rate at the nebuliser can be obtained.[7]

Volume output from the nebuliser: the volume of solution leaving the nebuliser chamber. Whilst useful as a general guide to nebuliser performance, it does not give precise information about the actual drug output.[2]

Drug output from the nebuliser: the actual amount of drug that is released during nebulisation. Because of a variety of factors, including evaporation, a precise measure of drug output (as opposed to volume output) must be assessed using marker techniques.[8]

Residual volume: the volume of solution left in a nebuliser chamber once nebulisation has ceased and all of the aerosol particles have been generated and have left the nebuliser chamber. It is an important volume to take into account

Respiratory Department, Bristol Royal Infirmary, Bristol BS2 8HW, UK
A H Kendrick

Department of Medicine, c/o Respiratory Department, Bristol Royal Infirmary, Bristol BS2 8HW, UK
E C Smith

Department of Respiratory Medicine, Royal Shrewsbury Hospitals NHS Trust, Shrewsbury SY3 8XQ, UK
R S E Wilson

Correspondence to:
Dr A H Kendrick.

suggested that it should be at le
residual volume. It is important
of the desirable fill volume whe
nebuliser drugs in prepackaged an

The definitions of aerosol outp
particles, mass median diameter (
median aerodynamic diameter
respirable output, and respirable
given in the paper by O'Callagh
on page S35.

Factors affecting nebuliser pe

The general term "nebuliser" us
the combination of the nebuliser
the compressor. Jet nebulisers u
constant output, but to prevent
breath-enhanced nebulisers are av
the output is enhanced in the inh
Ultrasonic nebulisers are effectiv
robust and more expensive than
systems and are generally not us
domiciliary therapy.

The major use of nebuliser s
deliver bronchodilator therapy
cification of the nebuliser char
ministering bronchodilators is d
that required to deliver other d
antibiotics or pentamidine.

The output of a nebuliser is d
a combination of factors which n
into account, and will depend on
of the nebuliser chamber,[6] (2) th
driving gas and the performance
of the compressor,[7 10 11] (3) the volu
(fill volume) of the drug at the s
lisation,[9 12] (4) the time taken to
solution of drug,[7 9] (5) the viscosit
sion, and concentration of the dr
(6) the residual volume,[9] and (7)
nebuliser chamber during nebulisa

The volume output and particle
saline, salbutamol, terbutaline
tropium bromide are similar.[14] F
cous solutions the volume out
slower (fig 1).[13 15] The output of
be similar to salbutamol althoug
a suspension. However, the vo
from a nebuliser is not directly r
drug output,[8] and the drug ou
availability are different betwe
dilators, antibiotics, and steroid
volume output is simple and pro
to the performance of nebulise
combinations.[7 16]

solutions with a specific gravity of 1 have similar rates of output. The slightly more viscous antibiotic solution has a slightly slower rate of output. Data from reference 14.

Selecting nebulisers and compressors

The choice of nebuliser and compressor depends on various factors including cost, ease of use and of maintenance, and overall performance. There are many nebuliser chambers and compressors available. Choice should be based on assessment of the systems and comments from other users. It is not advisable simply to pick a nebuliser chamber and a compressor at random. As will be discussed below, the matching of a nebuliser and compressor is important to achieve optimal performance. Furthermore, under certain circumstances par-

provide on the clinical use of the s
also be obtained.

Nebuliser/compressor combin

The performance of a given nebu
is closely linked to the flow of th
and, hence, the performance of th
chosen to drive the nebuliser ch
therefore important to use a
of nebuliser chamber and con
delivers an acceptable volume ou
with an acceptable range of respir
over an acceptable period of
patient.[7 12 16–23]

*Table 1 Examples of combinations of compressors and nebuliser chambers supplied for bronchodilator th
compressors have been divided into high, medium, and low flow rates and have been used with the nebu
indicated*

Flow rate	*Compressor*	*Nebuliser chambers sold with compressor unit*	*Multivolt*
High flow rate (>6.0 l/min)	AFP Classic	MicroMist	No
	AFP Aquillon	MicroMist	No
	AFP Ultima	MicroMist	Recharge
	AFP Tourer	MicroMist	Yes
	Flaem Nuova Combineb	Flaem Nuova Type 3	Yes
	Flaem Nuova Micelfluss Pro	Flaem Nuova Type 2	Yes
	Medic-Aid CR50	Medic-Aid Sidestream	No
	Medic-Aid CR60*	Medic-Air Ventstream	No
	Medic-Air Freeway		Yes
	Gast*†		?
	Inspiron*	MiniNeb, Incenti-Neb	No
	Medix M Flo	Medix A11	No
	Medix AC2000*	Medix A11	No
	Medix World Traveller	Medix A11	Yes
	Medix Econoneb	Medix A11	No
	Medix Minor*†	Cirrus	No
	Medix Turboneb	Cirrus	No
	Porta-Neb	Medic-Aid Sidestream Medic-Aid Ventstream	No
	Porta-Neb Multi	Medic-Aid Sidestream	Yes
	SunMist Plus	Perma Neb	No
Medium flow rate (4.0–6.0 l/min)	Aeroneb HP†	Cirrus	No
	Atomolette†	Own	No
	Flaem Nuova M70	Flaem Nuova Type 2	No
	NebuPump†	Acorn	No
	Novair II	Cirrus	No
	Pari InhalierBoy†	Own	No
	Pari TurboBoy	Pari LC Plus, LC Plus Junior	No
	Pari JuniorBoy	Pari LC Plus, LC Plus Junior	No
	Pulmo-Aide†	Own	No
	SunMist	Perma Neb	No
	DeVilbiss Traveller	Perma Neb	Yes
Low flow rate (<4.0 l/min)	Aeroneb Standard†	Own, Cirrus	No
	Pari WalkBoy	Pari LC Plus,	Yes
	Aeroneb HP†	Own	No
Others	Aerolyser CF1B†	Wright	Yes
	Aerolyser CF1R†	Respi-Neb	Yes
	Aerolyser 216†	Respi-Neb	Yes
	Flaem Nuova Travelneb	Flaem Nuova Type 3	Yes
	Henley HCU-1†	Hudson MK II	Yes

* Wilson and Steventon have tested these compressors with 19 nebuliser chambers: Acorn, Aerflo, Cirrus, De
Hudson II, Jet set, MicroCirrus, MicroNeb III, MiniNeb, Sandoz, Suremist, Turret Turbo, Unicorn, Unimist
and Wee Neb. With these compressors they all achieved flow rates at the nebuliser of >6.0 l/min.
† These devices may not be currently available but are included since they may still be in use.

Flaem Nuovo Type 3	0.5	8.0	?	?	?
Hudson Neb MKII	?	?	50	57	82
Hudson UD I	2.3	17	?	?	82
Hudson UD II	1.4	10	25	33	79
Incenti-Neb	?	20	?	?	54
Jet set	?	?	?	?	?
MicroCirrus†	1.2	10	?	?	90
MicroMist	?	10	?	?	76
MicroNeb	0.9	13	28	59	78
MiniNeb	2.3	38	41	51	79
Pari Boy	2.0	9	50	64	64
Pari LC Plus	1.0	8	50	50	60
Pari LC Plus Junior	0.9	8	55	55	54
Perma Neb	1.2	9	39	75	70
Raindrop	?	?	?	?	?
Respi-Neb	?	?	?	?	?
Respirgard II†	1.3	9	?	?	?
Sandoz	?	?	?	?	?
Medic-Aid Sidestream	0.7	12	?	?	83
System 22 Mizer	2.0	15	?	?	73
Turret Turbo	?	20	?	?	73
Unicorn 1035	?	10	?	?	68
Unineb	?	?	?	?	?
Upmist	?	?	?	?	?
Venticaire	?	?	?	?	?
Medic-Aid Ventstream	1.0	10	?	?	86
Wee Neb	?	?	?	?	?
Wright	?	20	?	?	83

The data in this table have been compiled from various sources and provide a guide only. Whilst the residual volumes are accurate, the percentage of solution nebulised at 5 and 10 minutes is the best figure obtainab obtained for a fill volume of 2–2.5 ml and is generally taken from data obtained with its retail compressor. T under 5 μm is taken from various sources. Where a ? appears there are no data currently available from any kn
* Depends on configuration of nebuliser chamber (Type 2) and on type of compressor unit. Data are for diaphr compressors.
† Data with pentamidine.

BRONCHODILATOR THERAPY

We have divided some currently available nebuliser/compressor combinations into three bands based on the flow rate at the nebuliser (table 1). High flow rate combinations produce more than 50% of the particle size output less than 5 μm diameter and have an MMD of less than 5 μm.[7 16 19–21] The lower flow rate combinations have less than 40% of their particle size output below 5 μm diameter and an MMD of more than 9 μm. The performance of some of the nebuliser chambers is given in table 2. Particle size distributions may differ with different combinations of nebuliser and compressor (fig 2). Breath assisted nebulisers such as the Ventstream and Pari LC have been shown to have improved performance.[23]

An important point about nebulising bronchodilator drugs is whether or not there is a need for a specific combination or combinations. Whilst there are criteria for attaining an optimal performance, this may not matter in practice since subjective benefit and objective bronchodilatation are the most important factors. There are a number of nebuliser/compressor combinations currently available that do not achieve the standard criteria.[7] However, these systems are still being used and there have been no reports to suggest that long term use of a poor performance system has resu a reduction in the quality of life hospital admissions. Part of the r is probably that the doses of b drugs being administered are la even inefficient systems deliver en ensure maximal bronchodilatatio

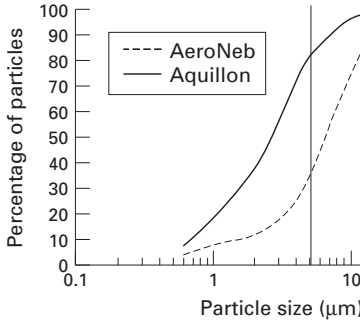

Figure 2 Two examples of particle distrib the cumulative percentage of particles with particle sizes for a high flow rate combina compressor with Neb MK II; flow rate 7 l flow rate combination (AeroNeb Standard Cirrus; flow rate 3 l/min). The fill volume was 2.5 ml of sterile water. For the Aquill of particles less than 5 μm was 83%, whil AeroNeb Standard it was 35%. Based on reference 7.

to be used with antibiotics.[16 24–28] A powerful, continuously rated compressor should be used (table 3). Various nebuliser chambers have been shown to be acceptable, although in some cases nebulisation times were longer than is perhaps ideally required by the patient.[29]

MUCOLYTICS AND SALINE

Where mucolytics such as acetylcysteine are used, standard delivery systems, as shown in table 1, can be used. The high and medium flow rate systems appear to be adequate,[30 31] especially since there appears to be little difference in the rate of output of saline and of bronchodilators.[14]

RHDNASE

Current recommendations are based on limited data.[32–35] rhDNase should be nebulised using a jet nebuliser since ultrasonic nebulisers may inactivate it or have unacceptable aerosol characteristics. Recommended combinations are given in table 4.

STEROIDS

These can be nebulised with medium or high power systems as shown in table 5.

Volume-time output and fill volume

Four criteria should be considered:

(1) The minimum initial fill volume is determined by the size of the residual volume of the nebuliser chamber. The larger the residual volume, the greater the initial fill volume will need to be.[9 17 22] The residual volume of the modern, small volume, nebuliser chambers is less than 1.0 ml (table 2) and for these a fill volume of 2.0–2.5 ml of drug solution is

Table 4 Recommended nebuliser/compressor combinations for rhDNase therapy

Compressor	*Nebuliser chamber*
Pulmo-Aide	Hudson T Up-draft II
	Airlife Misty
	A11
Pari InhalierBoy	Pari LL, Pari LC
Pari TurboBoy	Pari LC Plus
Aiolos	Aiolos
Medic-Aid Porta-Neb	Medic-Aid Sidestream
Medic-Aid CR50	Medic-Aid Sidestream
Medic-Aid CR60	Medic-Aid Sidestream
AFP Aquillon	MicroMist

Data from studies using Pulmozyme.

but in approximately half the time. Data Sidestream nebuliser under simulated tidal compressed air to drive the nebuliser. The is 0.5 ml. For a fill volume of 2.5 ml nebu "dryness" was six minutes which increased using the 4 ml fill volume. The 70% increa nebulisation time increased the drug output Data from reference 12. Reproduced from permission.

enough. Increasing the fill volume volume nebuliser (Sidestream) w same amount of drug but over a of time (fig 3).[12] Where the residu greater than 1.0 ml, a larger initi is required. Since many nebuliser available in prepackaged ampou or 2.5 ml, it is important to en nebuliser chamber used by a pati a small residual volume or that instructed to dilute the contents o with normal saline and to make fill volume to at least twice th residual volume. Table 6 lists s binations of nebuliser chambers poules.

(2) The time taken to delive important for patient complianc mum time for nebulisation is 5 Patients will generally not accept times (fig 4), especially if the tre quired several times per day.[29]

(3) The end point of nebul to be defined. There is some nebulising "to dryness" is confusi and is difficult for them to defi nebulisers nebulise continuously volume approaches the residual "spluttering" occurs.[36] At this po

Table 5 Examples of nebuliser/compresso suitable for corticosteroid therapy

Compressor	*Nebuliser chamber*
Medic-Aid Porta-Neb	Medic-Aid Vents
	Medic-Aid Sides
	Cirrus
	Hudson
	Turret
Medic-Aid Freeway	Medic-Aid Vents
Medic-Aid CR60/CR50	Cirrus, A11
	DeVilbiss 646
	Hudson Up-draf
	Turret
AFP Aquillon	MicroMist
AFP Tourer	Medic-Aid Sides
AFP Ultima	Medic-Aid Sides
Pari TurboBoy	Pari LC Plus, LC
Pari JuniorBoy	Pari LC Plus, LC

Data from various sources. This list is not ex devices may be suitable.

Sodium cromoglycate	Intal	2.0	As above for 2.0 ml
Dornase alpha	Pulmozyme	2.5	Hudson UD II, Acorn, M Sidestream, Medic-Aid Ventstream, Aiolos, Pari

It is taken that at least 50% of the drug solution should be available for nebulisation and without the need normal saline. Data from British National Formulary.
† Also available in 1.0 ml ampoules containing 250 µg/ml. The 2.0 ml ampoule contains 500 µg/ml. Use of th will need dilution as no nebuliser chamber has a residual volume of less than 0.5 ml.

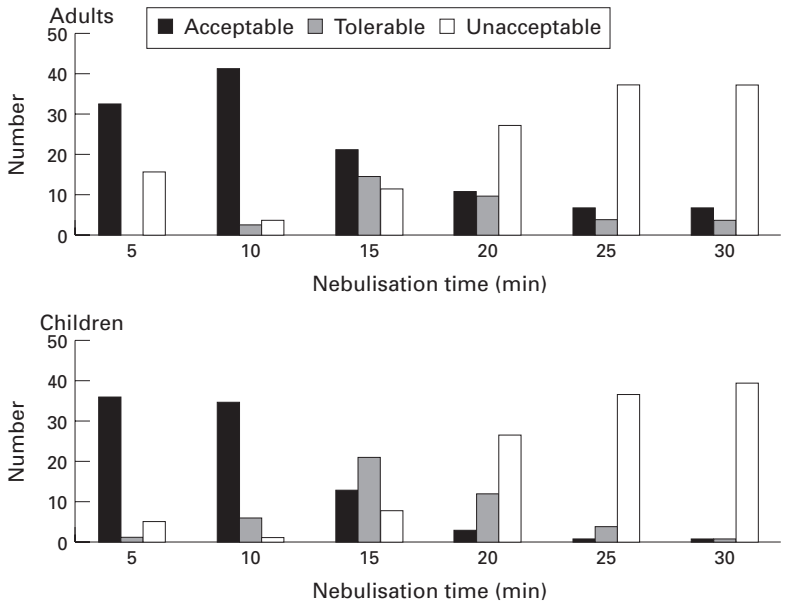

Figure 4 Patient acceptability of different durations of nebuliser treatments. Most patients preferred a treatment time of 10 minutes or less. Unpublished data from R S E Wilson.

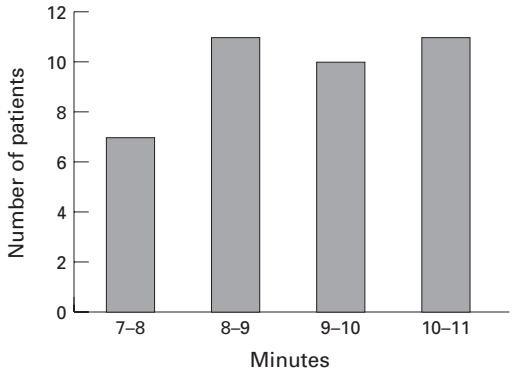

Figure 5 Recognition by patients of "dryness" at the end of nebulisation. The combination of a Charles Austen compressor with a MiniNeb nebuliser would usually reach residual volume in 10 minutes with a fill volume of 2.0–2.5 ml. Following explanation of the meaning of "dryness", patients timed the system to "dryness" with a stopwatch in minutes and seconds (n = 39 episodes). Unpublished data from J Pugh and R S E Wilson.

volume output is reduced beca oration, drug output remains hig period of time (fig 6). This patients should be told to nebuli tering occurs and then to continu minute. Previous tests should hav with the fill volume used, the sy this point in 10 minutes or less. that the compressor/nebuliser co working efficiently and has no fa

(4) During nebulisation (particu units) large particles tend to adhe of the nebuliser. Adherence becon nebuliser ages. These large particl couraged to fall back into the well c by tapping the side of the nebu once the nebuliser begins to "splu evidence that this may improve ou 50% over a given period of time (

Ease of use

The choice of nebuliser chamb some extent, be based on its ea general, chambers should (1) not ponents that can be easily swallo children (ideally, all nebulisers s of a removable top and the singl chamber); (2) be easily disassem assembled by patients of all ages ticularly important in the elderly a whose manual dexterity is sign paired); and (3) employ a chamb left connected to the compressor, surface, or be mounted on the itself, and so be filled easily.

Mouthpieces/face masks and circuits

Lung deposition is the same in a children, when either a mouthp mask can be used.[37 38] Face mas for infants and younger children, gencies. Mouthpieces are recomm steroids or anticholinergics are bei

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.