Nebulizers in cystic fibrosis

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NEBULIZERS IN CYSTIC FIBROSIS

The use of nebulized drugs in cystic fibrosis concerns the science of inhaled particles and the physical properties of the equipment used to generate them. Bernoulli (1700–1782) made observations and mathematical calculations about the flow of liquids in channels at points of narrowing (Figure 1). He noted that at such points the velocity of flow increased, with a fall in pressure beyond the constriction. The presence of an accessory channel at this point of reduced pressure results in a flow into the main channel which is accelerated to a degree dependent upon the amount of negative pressure and velocity of flow. In effect, an accessory flow is sucked into the main channel. The rate of flow is also dependent on the density and surface tension of any such liquid so entrained. Venturi (1746–1822) utilized hollow tubes containing a constriction to estimate flow by measuring the pressure drop across it. A similar effect is achieved if the tube ends in a tiny outlet or nozzle. This is known as the venturi effect and is utilized in the design of jet nebulizers.

DEPOSITION OF PARTICLES IN LUNGS

The therapeutic aim is to deliver drug to the whole bronchopulmonary tree and alveoli, and this requires particles of an appropriate size. Particles or droplets in excess of 8 μm diameter do not pass the nose or oropharynx and are not respirable. Particles from 5–8 μm reach larger airways, and particles less than 5 μm penetrate the whole of the bronchial tree and the alveoli. Particles less than 2 μm diffuse freely and display Brownian movement. Thus, the optimal size of particles for penetration of and deposition in the respiratory tract is 2–5 μm (Table 1). Particles of any size tend to deposit in the nose during nasal breathing, which should be avoided. Oropharyngeal breathing via mouthpiece is preferred. Various studies have shown that no more than approximately 10% of nebulized drug will be deposited in the lungs, often less[1].

JET NEBULIZERS

A typical design (Figure 2) comprises the main tube conducting compressed air through a nozzle, around which is the concentric accessory tube, along which the solution

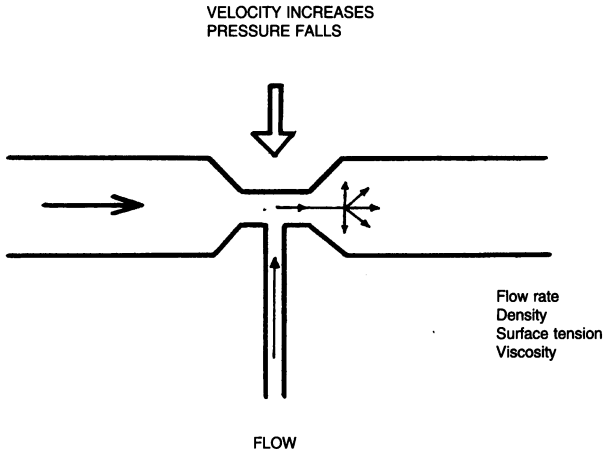

Figure 1 **The flow of liquids according to Bernoulli (1700–1782) and Venturi (1746–1822)**

flows from a reservoir containing the aqueous solution to be nebulized. This outer tube has a matching nozzle just distal to the compressed air tube. When physical conditions are appropriate liquid is sucked from the reservoir into the jet of air where it forms threads which collapse under surface tension, generating tiny droplets of various sizes, which are carried onwards in the main stream of compressed air. Baffles and filters may be placed downstream to filter out large unwanted particles, and the onward flow proceeds to the patient, entraining extraneous air through a supplementary side channel. The nozzles and baffles are contained within a chamber such that large particles 'rain out' and coalesce on all internal surfaces, falling back into the reservoir to be re-nebulized. The design and placement of baffles and filters affects the distribution of particle size contained in the aerosol.

During nebulization there is cooling of the reservoir caused by evaporation and adiabatic gas expansion downstream such that the temperature falls 10°–15°C at a flow of

Table 1 **Airway meteorology: droplet size and site of deposition**

Size (μm)	*Site*
>8	Oropharynx
5–8	Larger airways
<5	Respiratory bronchioles and alveoli
<2	Diffusion, Brownian movement

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8 l/min. Evaporation also results in gradually increasing concentration of the solute in the reservoir solution, and commonly the concentration will double by the end of nebulization. The outer concentric delivery tube sits just above the floor of the reservoir, and nebulization ceases when the liquid in the reservoir falls below this level, the nebulization time, leaving a residual reservoir volume, which can be reduced by design modification, in addition to a residuum on the walls of the chamber and the baffles. Thus, if the starting volume is 4 ml, the dead volume is 1 ml, and the initial concentration doubles it follows by simple calculation that 50% of the drug has been nebulized.

NEBULIZER OUTPUT

The conventional measure of nebulizer output is the mass median diameter (MMD), which defines a particle size at or below which half the aerosol mass is contained. Particle size distribution is a less satisfactory measure of output, because the amount of drug contained in any one droplet is proportional to r^3, e.g. a 10 μm particle contains 1000 times the amount of drug in a 1 μm particle. The MMD is chiefly influenced by flow rate through the system, being smaller at high flow rates and greater at low flow rates. The residual volume effect, mentioned above, causes the output of drug from a nebulizer to be greater for a given amount if it is contained in a larger starting volume. However, this has an adverse effect on the time taken to complete nebulization, which is longer for larger volumes and, conversely, shorter for small volumes. Nebulization time is important in clinical practice because it influences patient compliance. Solutions of high viscosity have adverse effects on output nebulization time and MMD, with opposite effects for solutions of low viscosity, e.g. bronchodilators.

DRUG OR PARTICLE LOSS

Other factors influence the amount of drug reaching the patient's respiratory tract (Table 2). Nebulization results in continuous delivery whereas the patient inhales for approximately half this time and half is lost. Very small droplets are lost in exhalation, large droplets rain out in the upper respiratory tract. Nasal breathing filters out most droplets, and oropharyngeal breathing is to be preferred. Within the lungs increased airways resistance and airway occlusion place limitations upon lung penetration. Residence time of particles in the lung is also important to allow deposition, and rapid shallow breathing has an adverse effect by exhaling particles too soon. Deposition is enhanced if patients are able to hold their breath at the end of inspiration, but this is less important in a continuous nebulization system as compared with other forms of inhalation such as metered dose inhalers. It has been demonstrated that rapid breathing at vital capacity volume is less effective than tidal breathing.

Table 2 **Some factors affecting net drug deposition in lungs**

Particle/droplet	*Nebulizer system*	*Patient*
Diameter	Residual volume	Reduced VC
Shape	Concentration effect	Airways obstruction
Density	Continuous delivery	Occluded airways
Charge	MMD	Respiratory rate
Hygroscopy	Baffle design	Residence time
Surface tension	Flow rate	Nasal breathing
		Nebulization time

MMD=Mass median diameter; VC=vital capacity

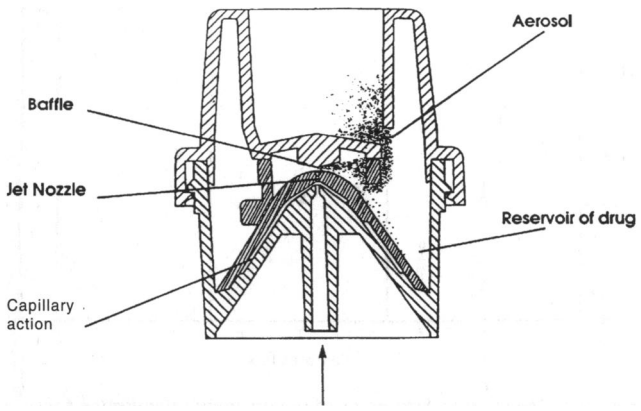

Figure 2 **A typical design for a jet nebulizer**

ULTRASONIC NEBULIZERS

Ultrasonic nebulizers are driven by a rapidly vibrating piezoelectric crystal. This is immersed in the solution to be nebulized, and at the high frequencies thus generated droplets form at the surface. These may be inhaled by the patient or driven by a supplementary flow of gas. In practice it has been found that they are less reliable in their function, with lower drug output than the jet nebulizers.

COMPRESSORS

Compressors pump air along tubes at varying flow rates. When resistance is introduced, i.e., the compressor is connected to a nebulizer, resistance and pressure rise within the system but flow diminishes. The crucial characteristic is the 'dynamic' flow rate during operation which is inevitably less than the 'static' flow rate which pertains during operation with an open tube. In practice, a dynamic flow rate of 8–12 l/min or more is necessary for the nebulization of relatively viscous solutions such as antibiotics and corticosteroids. Bronchodilators have favourable molecular size and properties, and are nebulized at lower flow rates

and pressures; they are also pharmacologically active at all times.

NEBULIZATION SYSTEMS: PERFORMANCE

Newman has reviewed nebulizers previously[2]. We have studied 3 compressors against 2 jet nebulizers. Measurements of dynamic pressures and flow in the various combinations are depicted in Table 3. The relative power of each compressor is readily compared and it can be predicted that the least powerful compressor (Portaneb 50) would have a long nebulization time, and possibly a poor MMD at lower flow rate. These predictions are broadly confirmed by the data in Figures 3 and 4, which show the measurements made in the various combinations against solutions of antibiotics (colomycin, gentamicin and ciprofloxacin). The MMD measurements were made by passing the output through a laser particle analyser (Malvern Instruments 2680 SD). For MMD the results show that the Portaneb 50 device is not satisfactory for the administration of gentamicin, ciprofloxacin or colomycin via the System 22

Table 3 **Mean (standard error of mean) dynamic pressure and flow values of the compressors when coupled with either the Microneb III or System 22 Acorn nebulizers (*Arch Dis Childhd* 1994; 71: 335–8)**

	Microneb III		*System 22 Acorn*	
Compressor	***Pressure (psi)***	***Flow (l/min)***	***Pressure (psi)***	***Flow (l/min)***
Turboneb	34 (0.04)	9.1 (0.08)	35.1 (0.03)	8.3 (0.04)
CR 60	26 (0.06)	7.8 (0.03)	27.2 (0.02)	7.3 (0.01)
PortaNeb 50	17.1 (0.05)	6.1 (0.08)	17.7 (0.49)	5.4 (0.59)

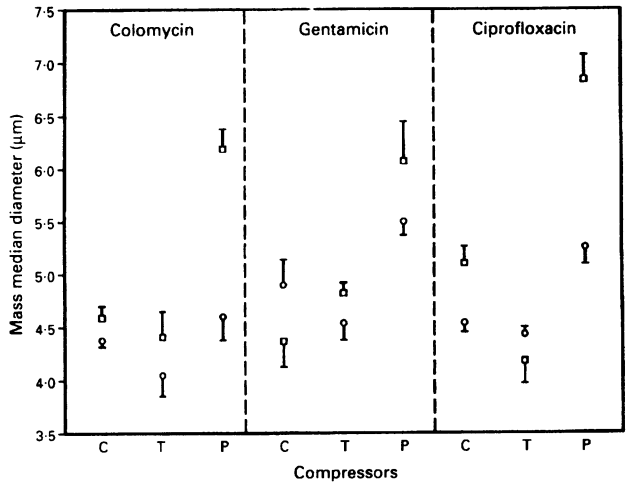

Figure 3 **Mean (standard error of mean) mass median diameters for different combinations of compressors (C=CR 60; T=Turboneb; P=PortaNeb 50) and nebulizers (□=System 22; ○=Microneb III) (*Arch Dis Childhd* 1994; 71: 335–8)**

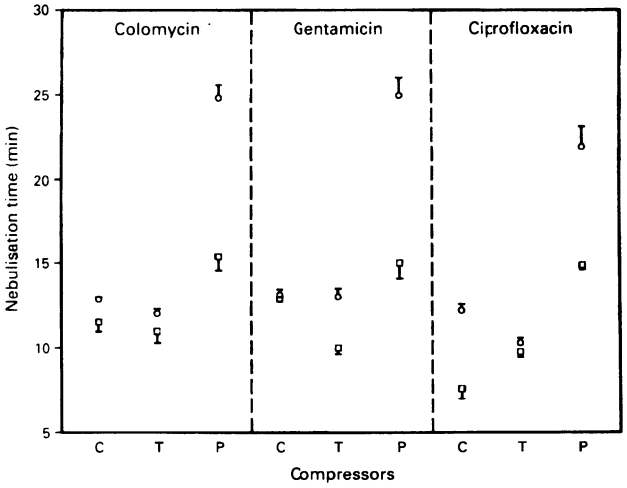

Figure 4 **Mean (standard error of mean) nebulization times for different combinations of compressors and nebulizers (See Figure 3 for key to abbreviations) (*Arch Dis Childhd* 1994; 71: 335–8)**

nebulizer. The CR60 and Turboneb compressors generally performed well. However, Turboneb performs consistently better, as might be expected from its pressure/flow rate characteristics. Concerning the particular antibiotics, there is a slight trend in the data to indicate that ciprofloxacin is more difficult to nebulize than gentamicin, with colomycin the least problematical. The relationship between dynamic flow rate and nebulization time is well seen in Figure 4, with Portaneb requiring longer than 15 min in all test situations. Many patients would find this somewhat unacceptable. As expected Turboneb gives the shortest nebulization times.

Of crucial importance are the data relating to residual volume and drug output obtained by weighing before and after, coupled with osmolarity measurements, which assess the concentration effect of the respective systems. These data are shown in the Figures 5 and 6. It can be seen that the Microneb 3 nebulizer has a consistent advantage over System

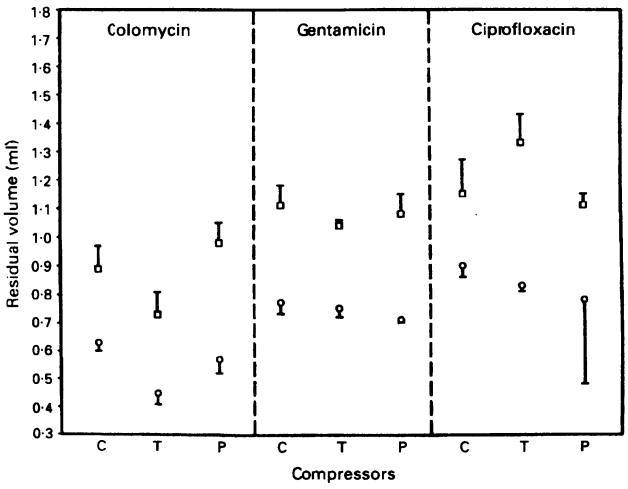

Figure 5 **Mean (standard error of mean) residual volumes for different combinations of compressors and nebulizers (see Figure 3 for key to abbreviations) (*Arch Dis Childhd* 1994; 71: 335–8)**

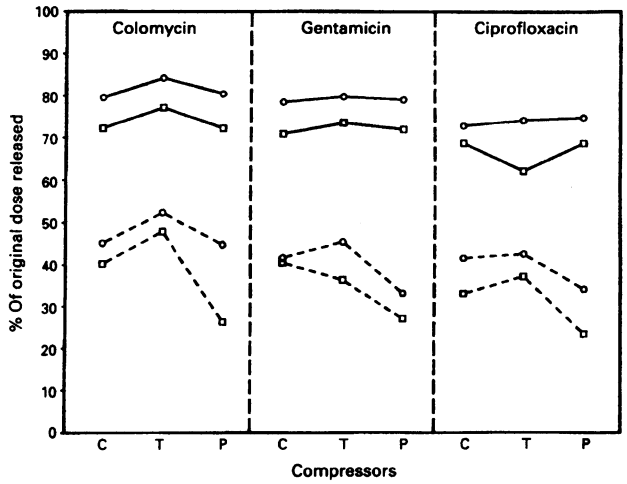

Figure 6 **Mean percentages of dose released (solid lines) and dose in < μm droplets (dashed lines) for different combinations of compressors and nebulizers (see Figure 3 for key to abbreviations) (*Arch Dis Childhd* 1994; 71: 335–8)**

22 in its volume output. It also performs better in terms of the dose released whether measured in droplets less than 5 μm or calculated total dose release. It must be remembered that much of the latter is lost and that only 40–50% of the drug is released as respirable particles, somewhat less with the Portaneb compressor.

Nebulizer design is much more difficult for clinicians to assess. It is interesting that the System 22 Acorn which performed less well had a flat base and a large umbrella shaped baffle. This comparatively larger surface area, visible by eye, might be predicted to result in a larger residual volume due to fluid trapping. Interestingly, in a subsidiary pilot study using the surfactant Curosurf we found a reduced droplet formation on the interior surfaces and a reduced residual volume, indicative of a greater drug output. However, predictably, this was associated with a prolonged nebulization time. We have not yet had opportunities to assess some newer nebulizers which incorporate an extra venturi effect to enhance volume output. The manufacturer's data for the 'sidestream' nebulizer indicates MMD of 3 μm at a dynamic compressor flow rate of 6 l/min. The supplementary venturi effect generated by the patients inspiratory effort boosts the outflow rate to 16 l/min without affecting MMD, and nebulizes at a rate of 0.37 ml/min, or 4 ml in 10–11 min. The 'ventstream' nebulizer uses the same base and produces a net flow of 22 l/min, giving a nebulization rate of 0.55 ml/min or 4 ml in 7–8 min. In addition, the venturi is valved so that flow shuts down in expiration, thereby reducing drug loss and environmental contamination.

As newer compressors and nebulizers become commercially available there remains a continuing need to assess performance as outlined in this article. Provided manufacturers give information about dynamic flow rates, it seems relatively straightforward to select suitable compressors. However, the performance of nebulizers is much more difficult to predict, and it is important to know the MMD which is produced at various pressures and flows. From the patient's point of view, the nebulization time is the most important characteristic, and clinical experience suggests that this should be no longer than 10 min.

We have also studied jet nebulizing systems used for administration of inhaled recombinant human DNASE 1[2]. We compared the manufacturer's recommended systems with our own commonly used systems, and demonstrated comparable efficiency of delivery. Output was assayed directly by measuring enzyme activity. The results (Table 4) show that more powerful compressor systems are satisfactory, with no evidence that there is any significant degradation of the enzymatic activity of DNASE 1.

IDEAL NEBULIZING SYSTEM

The desirable features required for a clinically successful and effective system are summarized in Table 5. The patients prefer short nebulization times, using apparatus which is lightweight and portable and easy to use and maintain. Nebulization time is shortened by more powerful compressors, but these tend to be heavy, and by smaller starting volumes which tend to reduce drug output. Thus, the selection of compressor, nebulizer and starting volume

Table 4 **Comparison of six jet nebulizing systems for the nebulization of rhDNASE (2.5 mg in 2.5 ml)**

	Recommended systems		*RMCH systems*		
Compressor+nebulizer	***Pulmo-aid+updraft***	***CR50+sidestream***	***CR60+sidestream***	***CR60+MicroNeb III***	***Turboneb+MicroNeb III***
Median mean diameter (μm)	5.19	5.23	3.83	4.89	4.87
Nebulization time (min)	6.57	2.9	3.85	6.83	5.88
Residual volume (ml)	0.5	0.6	0.4	0.6	0.7
Per cent of activity in the released aerosols*	73	71	65	64	65

RMCH=Royal Manchester Children's Hospital
*The activity of 2.5 mg (in 2.5 ml) with rhDNASE is taken as 100%

Table 5 **Ideal nebulizing system**

Short nebulization time 5–15 min
High drug output
MMD $\leqslant 5\ \mu m$
Portable, lightweight
Easy to use and maintain
Bronchodilators—any system
Antibiotics, dornase—adequate compressors

must be a compromise between desirable and practical characteristics. In practice, clinicians should use compressors which produce at least 8 l/min 'dynamic' flow, nebulizers with MMD $< 5\ \mu m$ at the operating flow rate, and a start volume of 2–4 ml. Improved nebulizers (see above) may be effective at dynamic flow rates of 6 l/min with nebulization times acceptable to patients. The more viscous drug solutions require more powerful compressors to satisfy these requirements. A patient's complaint that nebulization takes too long suggests that the system is either inadequate or faulty or in need of overhaul. Mouth breathing is the preferred mode of delivery, masks should be avoided, although this is less critical for bronchodilators. Nose clips may be helpful in some children.

Maintenance requires daily washing and drying of nebulizer and mouthpiece and cleaning of the compressor's air filter. Tubing and nebulizer should be sterilized weekly and dried. Manufacturers should provide detailed instructions and recommendations for their products. The most crucial and delicate part of a nebulizer is the Venturi nozzle which may be easily damaged with consequentially adverse effects on its performance. Disposable nebulizers may have an effective life of 2–3 months if carefully maintained.

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